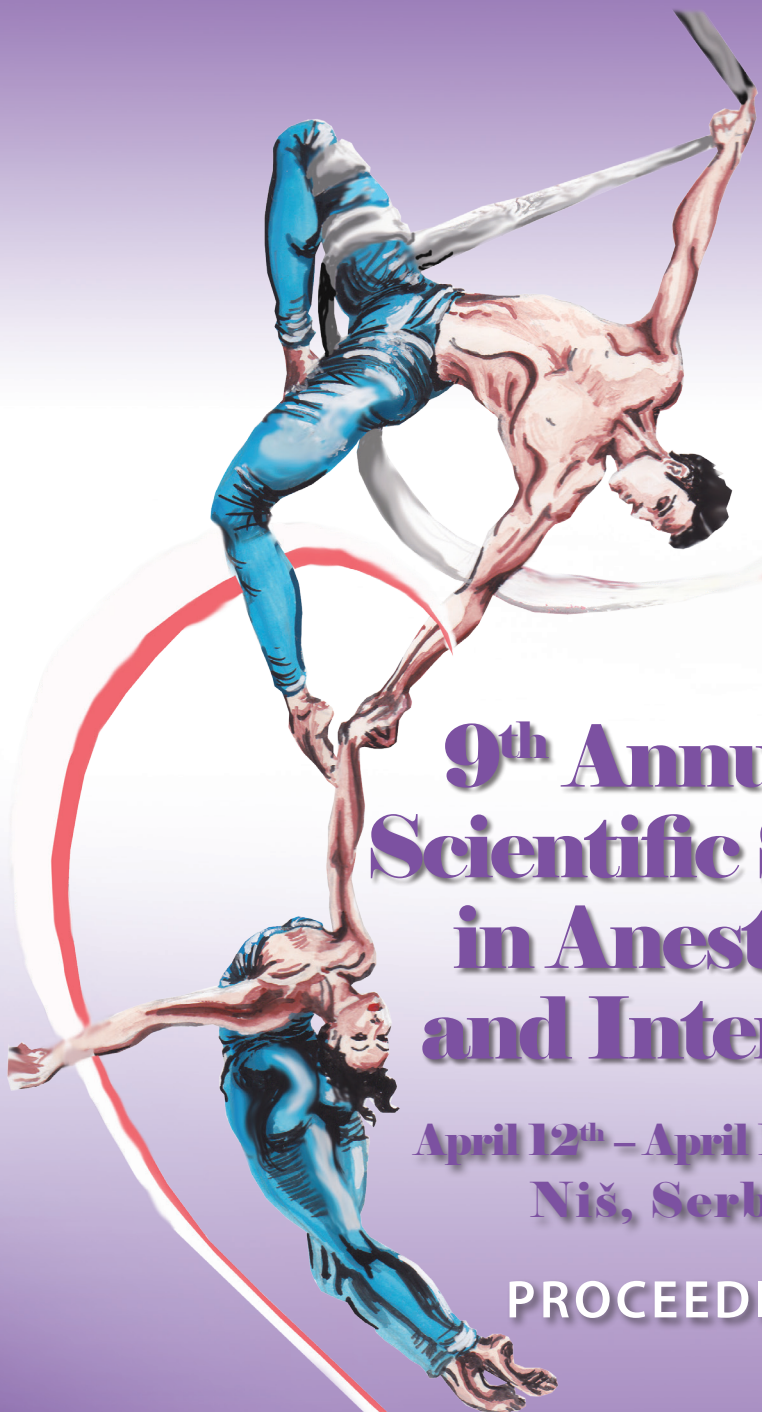

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April 12th – April 14th 2019
Niš, Serbia

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10th ANNIVERSARY

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PROCEEDING

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AIRWAY MANAGEMENT IN EMERGENCY DEPARTMENT. STANDARDS AND PROTOCOLS

Biljana Kuzmanovska
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Airway management is a cornerstone of resuscitation. Managing the airway of acutely critically ill or severely injured patients is challenging, whether in prehospital setting, emergency department or in the ICU due to acutely decompensated and rapidly deteriorating patient's health, limited recourses and health care provider's skills, as well as limited time.

There is lack of standardization and often, emergency departments rely on individual experiences of the health care providers and generally accepted knowledge when it comes to emergency airway management. Important issue in emergency airway management is who is the healthcare provider; anesthesiologist, anesthesia resident, emergency medicine specialist, emergency medicine resident or paramedics. Suboptimal airway management performance has been reported in intensive care settings and emergency departments .[1,2]

Patients undergoing airway management and endotracheal intubation (ETI) during emergency circumstances are at increased risk for adverse events (25-30%)[3] compared to patients treated in elective circumstances (0.2%).[4]

Limited time for preparation and a patient in distress, as well as difference in expertise levels of airway management may explain this safety gap, yet, there are expectations that practitioners should be able to demonstrate mastery performance.

Main characteristics of the emergency airway management are urgency and unpredictability. Lack of informations about the patient's medical history and short time for physical examination, urgent decision to establish artificial airway with short preparation time as well as difficulties with patient's cooperation on one hand, and very often, lack of equipment for managing difficult airway in emergency departments and prehospital settings, arose the need to develop a standardized airway management protocols. The guidelines for airway management written by anesthesiologists (ASA guidelines – Practice Guidelines for Management of the Difficult Airway) are not wholly applicable or appropriate in emergency clinical conditions. So far, several strategies in emergency airway management have been suggested. More notable are Clinical consensus of emergency airway management, authored by Chinese Collaboration Group for Emergency airway management, published in Journal of Thoracic Disease in 2017 [5] referring to general emergencies, and specifically for trauma patients; Adult Trauma Clinical Practice Guidelines, Emergency Airway Management in the Trauma Patient, JE Ollerton, 2007 NSW Institute of Trauma and Injury Management (www.health.nsw.gov.au),[6] and more recent Updates in emergency airway management, and NICE (The National Institute for Health and Care Excellence, www.nice.org.uk)[7] guidance, trauma quality standard, quality statement airway management, published 2018. These strategies were based on retrospective reviews, randomized clinical trials and case series. Also, in the past year, several large randomized clinical trials were completed informing key aspects of emergency airway management and advocating use of techniques such as bougie, video laryngoscopy and supraglottic airways.[8]

The Clinical consensus of emergency airway management by Chinese Collaboration Group for Emergency airway management, focuses on four principles:

1) Priority to ventilation and oxygenation
2) Evaluation before intubation
3) Higher level of preparation (de-escalation)
4) Simplest (and least potentially harmful) form of intubation.

This policy aims to standardize the management of the emergency airway.

Step 1: ensure ventilation and oxygenation, and assess airway conditions on the basis of the "CHANNEL" principle:

Crash airway

Crash airway refers to patients who can't maintain ventilation and oxygenation. A crash airway should be managed quickly (BVM ventilation and rapidly moving to laryngoscopy).

Hypoxemia

A primary goal of emergency airway management is to correct hypoxemia. In patients with stable spontaneous respiration, nasal cannulas and high-flow oxygen devices (such as non-rebreather masks or venturi mask) are common means of oxygen therapy. In patients with unstable spontaneous respiration as well as hypoxemia despite the above treatment, BVM ventilation is demanded.

Persistent hypoxemia despite using the above oxygen therapies should be managed as an urgent airway. In these cases, an artificial airway should be built immediately according to the urgent airway process, and invasive airway devices should be ready.

Artificial airway:

Endotracheal intubation - Indications for endotracheal intubation include: inability to protect the airway or maintain airway patency, failure to adequately achieve ventilation or oxygenation, and anticipation of a deteriorating

clinical course that will eventually lead to the above-mentioned situations.

Supraglottic techniques-[laryngeal mask airways (LMAs)

Tracheotomy, needle or surgical cricothyroidotomy

Neck mobility:

Neck mobility is essential for positioning the patient for optimal direct laryngoscopy. Neck stiffness/injury/fixation increases the difficulty of endotracheal intubation.

Narrowing

Decreased endotracheal diameter, such as extratracheal compression (tumor, local abscess, hematoma, etc.), intratracheal foreign body, tracheal diseases (local radiotherapy, scar healing, etc.) would increase the difficulty of intubation.

Evaluation

It is required to adjust mouth axis, pharynx axis and larynx axis to be aligned as much as possible when conducting orotracheal intubation. The 3-3-2 Rule is used to evaluate the correlation of these three axes. Use the modified Mallampati scale to evaluate the structure of the pharynx (Class 1: soft palate, fauces, uvula, and tonsillar pillars visible; Class 2: soft palate, fauces, and uvula visible; Class 3: soft palate, and base of uvula visible; Class 4: Soft palate not visible.). The higher the grade, the more difficult it is to view under direct laryngoscopy. Grades 3 and 4 suggest a difficult airway.

Look externally to examine for signs of a potentially difficult intubation, such as a short neck, obesity, a receding mandible, long canine teeth, traumatic deformities,

Laryngoscopy

After proper analgesia, sedation as well as muscle relaxation (rapid sequence induction), the upper airway can be further evaluated by the laryngoscopic view grading system (Grade I: visualization of the entire laryngeal aperture; Grade II: visualization of only the posterior commissure of the laryngeal aperture; Grade III: visualization of only the epiglottis; Grade IV: visualization of only the soft palate). Both grade 3 and grade 4 indicate a likely difficult airway.

Difficult airway management

If a difficult airway is encountered, start the difficult airway management algorithm: ensure ventilation and oxygenation by BVM, and concurrently seek help from an experienced operator. An alternative airway approaches should be ready.

Visualization technology

Common devices include video laryngoscopes, fiberoptic bronchoscopes,etc.

Supraglottic airway devices

Supraglottic airway devices are used to keep the upper airway open. to provide unobstructed Contraindications for use of supraglottic airway devices include obstructive airway diseases, traumatized airways, etc. Supraglottic airway devices should be used under sedation to reduce pharyngeal spasms.

The LMA (laryngeal mask) is a common supraglottic airway device used as an aid for intubation of the emergent airway . The LMA can be used for intubation when a difficult laryngoscopic view or difficult BVM ventilation. In terms of safety, the LMA does not increase the risk of aspiration but is easier to dislocate compared with endotracheal intubation, therefore, careful fixation should be guaranteed.

Other assisted intubation devices

Include gum elastic bougies, lighted stylet, intubating LMA, esophagotracheal combitubes, and others.

Percutaneous cricothyroidotomy

Cricothyroidotomy is indicated when oral or nasal intubation is impossible. It is faster and easier to perform than a tracheotomy in terms of requiring less surgical skill and in its ease of learning.

Tracheotomy

Equivalent to endotracheal intubation, tracheotomy could establish both a definite and permanent airway when oral or nasal intubation is impossible. In emergency setting, percutaneous tracheostomy is recommended as it is much more rapidly performed.

Post-intubation management

Confirmation of endotracheal intubation placement

It is recommended to use $ETCO_2$ detectors as the primary choice to verify the position of the endotracheal tube, aside from traditional methods such as bilateral chest auscultation.

Guidelines for emergency airway management in trauma patients don't differ much. The Adult Trauma Clinical Practice Guidelines, Emergency Airway Management in the Trauma Patient, NSW Institute of Trauma and Injury Management, suggest the following steps:

1. Airway assessment : Assess for deformity from maxillofacial, neck or tracheal trauma and airway debris such as blood, vomitus and loose teeth. Consider the likelihood of encountering a difficult airway at intubation, eg small chin, protruding dentition, large body habitus, facial hair, pregnancy.

2. Airway management: Basic airway maintenance techniques:

Tongue and soft tissue obstruction of the hypopharynx in the unconscious patient can be corrected by the chin lift or jaw thrust manoeuvre.

Suction the airway with a rigid suction device to remove any blood, vomitus or debris.

On review of the airway, if it remains obstructed and/or patient remains unconscious, insert an oropharyngeal or nasopharyngeal airway to attain and/or maintain a patent airway (nasopharyngeal airway insertion is contraindi-

cated in patient's with suspected base of skull fractures).

A definitive airway is defined as a cuffed tube secured in the trachea. This is required if the patient is apnoeic ,inability to maintain a patent airway using the basic airway maintenance techniques , impending or potential airway compromise, closed head injury with GCS ≤ 8, inability to maintain adequate oxygenation with a face mask.

Definitive airway interventions include: orotracheal tube insertion, nasotracheal tube insertion and surgical airway (surgical cricothyroidotomy).

Both NSW Institute of Trauma and Injury Management and NICE guidelines recommend rapid sequence induction and intubation in trauma patients.

Clinical trials

In 2018, four randomized clinical trials regarding emergency airway management were published in JAMA.

1. Effect of use of a bougie vs endotracheal tube and stylet on first-attempt intubation success among patients with difficult airways undergoing emergency intubation: a randomized clinical trial. Driver BE, Prekker ME, Klein LR, et al. JAMA 2018; 319:2179–2189.
   This randomized clinical trial found improved first-attempt success rates were higher in bougie-facilitated intubations compared with traditional styletted intubation in emergency department patients.
2. Effect of bag-mask ventilation vs endotracheal intubation during cardiopulmonary resuscitation on neurological outcome after out-of-hospital cardiorespiratory arrest: a randomized clinical trial. Jabre P, Penaloza A, Pinero D, et al. JAMA 2018; 319:779–787.
   This randomized clinical trial found similar rates of neurologically intact survival between adult out-of-hospital cardiac arrest patients treated with intubation compared with bag-valve-mask ventilation; however, complication rates were higher in the bag-valve-mask group.
3. Effect of a strategy of initial laryngeal tube insertion vs endotracheal intubation on 72-hour survival in adults with out-of-hospital cardiac arrest: a randomized clinical trial. Wang HE, Schmicker RH, Daya MR, et al. JAMA 2018; 320:769–778.
   This randomized clinical trial found higher rates of 72-h survival in adult out-ofhospital cardiac arrest patients treated with supraglottic airways compared with intubation. Other outcomes (return of spontaneous circulation, survival to hospital discharge and neurologically intact survival at discharge) also favored supraglottic airways.
4. Effect of a strategy of a supraglottic airway device vs tracheal intubation during out-of-hospital cardiac arrest on functional outcome: the AIRWAYS-2 Randomized Clinical Trial. Benger JR, Kirby K, Black S, et al. JAMA 2018; 320:779–791.
   This randomized clinical trial, comparing supraglottic airways to intubation, found similar rates of neurologically favorable outcomes either at hospital discharge or 28 days in adult out-of-hospital cardiac arrest patients.

The findings of these and further clinical trials should be incorporated in the guidelines for emergency airway management, since the guidelines are not a definitive statement on the correct procedures, but rather a general guide to be followed , helping the clinicians judgement in each case.

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7. Updates in emergency airway management, NICE (The National Institute for Health and Care Excellence, www.nice.org.uk)

8. Updates in emergency airway management, Wolters Kluwer Health, Inc. 2018 (www.co-criticalcare.com).

PSYCHOLOGY OF ERRORS IN AIRWAY MANAGEMENT

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Airway management is a core skill for anesthesiologists, and it still remains today, despite the many technological advances and guidelines availability, one of the most important sources of anesthesia related morbidity and mortality.

We might ask why this happens, any device and technique being available to manage almost any airway. The weak point of the system, remains the doctor, as human component of the system, dealing with an airway, and particularly with a difficult one.

For better understanding of this phenomenon we should step back to the way we learn or lessons and to the concept of error.

Human beings learn by the *attempt and mistake* process: we learn how to walk just falling, and the learning process is based on developing all countermeasures necessary to avoid falling down (and hurting ourselves). Once we repeat and repeat the process, our brain fixes memory of the whole process, turning it from a conscious and continuously controlled series of behaviors (*type 1 reasoning*, rational) into an automated unconscious sequence (*type 2 reasoning*, automatic).

This process develops equally when we learn how to drive, when we learn a fitness exercise and even when we perform airway management maneuvers as anesthesiologists.

In evolutional perspective, these processes are vital for learning and for survival; not a case they have been evolutionary developed to deal with high stress conditions, such as during the *fight or flight response*, so to optimize performance, our brain using pre-determined neuronal circuits and pre-ordered schemata.

Whenever we deal with a new situation, we unconsciously try to pick from the type 2 reasoning any pre-existing behavior to save time and to be more effective, type 1 reasoning requiring more time, resources and attentions.

Whenever the automatic process over-rides the rational one during a crisis, we might experience a so-called *cognitive bias*, which we commonly call *error*.

Human beings do normally experience cognitive biases, they are physiological part of the learning process. Whenever they occur in crisis, it is typical situation when the over-ride is taking us away from reasoning, so that the bias turns into an error.

There are many cognitive biases described, and a large body of literature is now supporting the evidence that many of the medical errors are the result of cognitive biases. The largest example of such findings was the National Audit Project 4, developed in UK in 2011, clearly showing that behind the many accidents occurred in ICU, OR and Emergency department, the main causes were identified in errors in judgment, lack of communication, lack of planning before technical issues as missing device or misused device.

Many of these biases are absolutely well known and categorized:

- *Fixation error*: that is reiterating laryngoscopic attempts, carelessly of number of attempts, elapsed time, ongoing desaturation, the physician *fixed* on the target of intubation. Whereas it is ell known, if not obvious, that no patient dies because of missed intubation, but because of missed oxygen delivery to the lungs and the vital organs.
- Anchoring bias: Failure to consider reasonable alternatives after primary diagnosis or opinion is reached, remaining anchored to the original one. Some studies suggest this is between the most common biases.
- Overconfidence bias: that is overestimating our competencies and capacities in front of crisis. This bias is strictly linked with consequential biases such as the hero complex, the god complex, the authority gradient and it is depicted in the Dunning-Kruger effect.
- Yerkes-Dodson law, regulating the optimum of performance whenever stress level and awareness are in medium level.
- Confirmation bias: The tendency to search for, interpret, favor, and recall information in a way that confirms one's preexisting beliefs or hypotheses, ignoring alternatives. Rather than looking for disconfirming evidence to refuse it, despite the latter being more persuasive and definitive.
- Apophenia: Is the tendency to attribute meaning to perceived connections or patterns between seemingly unrelated things (Visual form of Confirmation bias). Apophenia has come to imply a universal human tendency to seek patterns in random information, such as gambling (Gambler's fallacy).
- Loss aversion bias: one of the strongest demonstrable biases in human decision making is the preference to behave differently depending on whether the decision is viewed as a gain or a loss.

Modern research is aiming to develop effective tools to deal with cognitive biases, with many lessons learnt from the aviation. In this perspective, checklists, easy diagrams, tools for optimal communication are developed daily with brilliant examples in recent DAS 2018 ICU guidelines, reporting diagrams of personnel positioning around the patient bed for airway management, or with the Australian Vortex approach, designed to provide a bias-free communication and behavioral sequence during the airway crisis.

In this perspective, also teaching is getting new directions, highlighting the role of human factors and non-technical skills. These topics become object of new teaching models, and simulation turns out to be the most powerful didactic tool to develop and improve the bias prevention and the no-blame culture. Further, participation in a simulated or real experience can trigger a range of emotions in those participating in the event. Emotions can profoundly influence a learner's retention and activation of knowledge (a so-called heuristic process), as a core affect that is highly activated can help anchor knowledge, skills and abilities newly gained through experiential-learning cycle.

As biases are physiological part of the learning process, we should therefore accept the idea that we normally commit errors. In other words, we should not blame on errors, but getting them back to their original learning function, that is using them as a lesson.

This means focusing on the process and not on the outcome, it calls for different approaches with teamwork and with audits, so to turn any accident, near miss or error into a powerful tool to prevent further errors and to optimize individual and team performance.

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AIRWAY MANAGEMENT, VENTILATION AND COMPLICATIONS IN PAEDIATRIC ENT ANAESTHESIA

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One third of all surgical interventions in ear, nose and throat surgery (ENT) are performed on paediatric patients [1]. The main concerns of an anaesthesiologist in ENT surgery are: preoperative assessment of a child in preanaesthetic visit, patient premedication, adequate anaesthetic technique, ensuring sufficient oxygenation and ventilation of the patient by choosing the adequate airway management device for maintaining previously uncompromised airway, planning adequate postoperative analgesia and preventing the postoperative nausea and vomiting (PONV) [2]. In children scheduled for an ENT surgery, the airway patency can be established and maintained in two ways: with the use of an endotracheal tube and by applying supraglottic devices. The choice of devices for establishing the airway depends on: anatomic characteristic of the upper airway concerning the child's age, presence of instruments in the oral cavity, presence of secretions, blood and tissue detritus, the fact that the airway is being shared by the anaesthesiologist and the surgeon, and the experience of the anaesthesiologist and the surgeon [3].

Characteristics of the paediatric airway anatomy

The paediatric airway anatomy differs from the one in adults. Several anatomic differences have been identified between airways in childhood and those in adulthood: 1. position of the larynx, 2. size of the tongue, 3. shape of the epiglottis, 4. arytenoid cartilages, 5. vocal cords, 6. mucosa and 7. cricoid ring [4,5]. The larynx of a term newborn is located in the level between the third and the fourth cervical vertebrae, which enables the newborn to swallow and breath at the same time [6]. In older children, the hyoid bone and epiglottis are located in the level of the third cervical vertebra (C3) [7]. The tongue is relatively larger compared to the oral cavity, and in the conditions of general anaesthesia it may easily cause obstruction of the upper airway [5].

Epiglottis is situated more cranially, and is narrower, stiff, longer and omega or V-shaped [8]. The epiglottis axis deviates from the trachea axis: it projects posteriorly above the glottis at a 45-degree angle. The hyoid bone is in close contact with the thyroid cartilage, so the base of the tongue extrudes and protrudes the epiglottis into the pharyngeal space. For that reason, it is more difficult to lift the epiglottis with the tip of the laryngoscope blade [4-6]. The vocal process of the arytenoid cartilage is inclined downwards into the trachea. This way, the vocal cords with their remaining ligamentous part have a concave position which results in restriction of the glottic opening [5]. The cylindric epithelium is loosely tied to the submucosal tissue, so there is a bigger tendency towards the oedema occurrence [5]. The mucosa of the cricoid ring lacks submucosa, and therefore even a moderate trauma of mucosa and perichondrium of the cricoid cartilage results in laceration, infection and creation of granulation tissue that may later bring to airway obstruction [9]. The cricoid lumen is oval, with rigid, V-shaped posterior part [7,10].

Endotracheal intubation

Endotracheal intubation is a "gold standard" in the airway management in paediatric surgery[(11)]. In surgical interventions in the head and neck area, it is recommended to use reinforced (flexible) endotracheal tube which is elastic but also resistant to kinking [12,13]. In literature overview, one may find different recommendations for determining the size and the length of the endotracheal tube used in children. However, during the ENT surgical intervention we have to think of repositions of the child's head (flexion or extension) since this may lead to dislocation of the endotracheal tube [6]. Therefore, the endotracheal tube should be inserted below the cricoid ring and above the carina of trachea, regardless of the head position change and movement of the endotracheal tube when changing the head position. When choosing the cuffed endotracheal tube, one needs to think about another anatomic characteristic in children i.e. distance between the vocal cords and the edge of the cricoid. This distance is surprisingly big in children i.e. 1.1 cm in neonates, 1.3 cm in one-year-olds and 1.4 cm in two-year-olds. After introducing the endotracheal tube, it is necessary to measure the cuff pressure which should not exceed 20 cm H_2O [14].

Insertion of supraglottic devices – flexible laryngeal mask airway (fLMA)

Unlike the classic laryngeal mask, in flexible laryngeal mask the tube is made of silicon and is reinforced by a spirally positioned wire which prevents it from kinking when manipulating the tube or inserting the surgical instruments into the oral cavity. In addition, the silicon tube in fLMA is longer and has a smaller diameter compared to the classic LMA. Such structure of the fLMA enables better access to the surgical field and prevents dislocation of the cuff during the ENT surgical interventions [15,16]. The insertion of fLMA's represents an efficient

alternative to endotracheal intubation during the adenotonsillectomy in children with regards to fewer respiratory complications, less postoperative pain during immediate postoperative period and better operating room efficiency [17]. fLMA can be also safely used in paediatric surgery in the field of rhinology, laryngology and otology as well [18-20]. When applied, it provides airway protection but avoids stimulation of the airway, trauma to the vocal folds, and possibly damaging coughing and straining while waking from anaesthesia, which is particularly important in surgical interventions on the middle ear.

fLMA cannot be used in children who did not adhere to preoperative fasting guidelines, for whom it is impossible to obtain reliable data on preoperative fasting, in those with lower lung compliance, in those with mechanical obstruction of the upper airway with a foreign body, in extremely obese ones, in those with multiple and massive head and neck injuries, and in children with acute abdominal or thoracic injuries [18,21].

Complications of endotracheal intubation

When performing endotracheal intubation, it is possible to cause minor or major injures of the airway. The incidence of upper airway injuries in patients during the endotracheal intubation is low. The most common injuries that occur upon endotracheal intubation are: lip lacerations or hematomas (63%), teeth injuries (25%), tongue lacerations or hematomas (6%), throat lacerations (4.5%) and larynx lacerations (1.5%) [22]. By turning the neck of an intubated child, it is possible to dislocate the endotracheal tube, which may result in bronchial intubation on one or extubation of the child on the other side[(1)]. The presence of instruments in the oral cavity may result in dislocation of the endotracheal tube [23].

The endotracheal intubation may cause numerous respiratory compilations in patients, like hoarse voice, laryngospasm while waking from anaesthesia, cough and sore throat [24].

Typical postextubation injuries of the airway in children before they are 8, could be indirect and direct. Indirect postextubation injuries include: oedema, mucosa ulcerations, granulations of mucosa, creation of scar tissue between the vocal cords and postextubation stridor. Direct larynx traumas occur in 5% of cases and they include: injuries of the glottic structure - front commissure injury, right vocal cord rupture or laceration of the posterior part of the larynx entrance. Direct injuries of the larynx heal either without or with minor sequele [25].

Complications associated with the use of the flexible laryngeal mask

The occurrence of complications and problems related with the use of laryngeal mask is inversely proportional to the degree of experience of the anaesthesiologist who is placing it. Most complications that occur when applying the laryngeal mask are the result of its misuse or inappropriate selection of the patients [26].

The use of laryngeal mask may result in the injuries of the structure of oropharynx: mucosa, pharyngeal and laryngeal soft tissue, salivary glands, nerves and blood vessels of the neck, laryngeal cartilage and bone structures of the neck. Hypoglossal nerve paralysis and lingual nerve or recurrent laryngeal nerve injuries are less common but more difficult complications when using the laryngeal mask. However, even besides such injuries, a spontaneous recovery of a patient is expected within 6 months [27].

Possible complications are the injuries of epiglottis as a result of poor positioning of the laryngeal mask and the occurrence of epiglottic oedema which closes the entrance to the larynx [28]. The paralysis of the vocal cords after the application of the laryngeal mask is also one of the severe complications that may require later surgical care [29]. The pressure on lingual venous blood vessels leads to lingual cyanosis and paraesthesia [30].

Respiratory complications relating to airway management

Postintubation stridor

Postintubation stridor occurs as a result of airflow restriction because of the present oedema caused by mechanical damaging or ischemia of the mucosa resulting from endotracheal intubation. The incidence of postextubation stridor in children is from 0.1 to 1% [31]. The risk from occurrence of the postextubation stridor increases when the pressure in the cuff exceeds 25 cmH_2O, in children under 4, in multiple endotracheal intubation attempts and airway trauma during intubation [32]. Clinical, postextubation stridor may develop immediately after the tracheal extubation and up to 24 hours after the extubation, which requires child observation and monitoring [31].

Laryngospasm

Laryngospasm is a reflective and continuous closure of the vocal cords which consequently completely obstructs the airway [33]. The incidence of laryngospasm in children's population is from 0.04 to 14%, and its occurrence depends on a series of factors, where some of them relate to the anaesthetic techniques, some to the patient himself, and some to the type of surgical intervention [34]. Obese children and those with OSA, show greater tendency towards laryngospasm compared to other children [34]. The biggest incidence of postextubation laryngospasm, which sometimes reaches 26%, occurs after tonsillectomy and adenoidectomy [35]. The occurrence of laryngospasm is possible during the anaesthesia induction, maintance, while it occurs far more often (up to 54%) during awakening of the patient [36,37].

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PAIN AS A FIFTH VITAL SIGN: DO WE REGRET?

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Pain has always been a matter of interest for physicians, from ancient era to present time. Historically, the pain was first mentioned, perceived and treated by Homer, Hippocrates and Celsus in ancient documents before 5th century. Understanding the meaning of pain varied from century to century, and was associated with either emotional or sensational aspect of life. [1] At the end of 1960s and in the beginning of 1970s, International Association for the Study of Pain (IASP) defined pain as: "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

American Pain Society in mid 1990s promoted the concept of "pain as the 5th vital sign" to elevate the awareness of pain treatment among healthcare professionals. A half decade later, Joint Commission emphasized the need for pain to be regularly assessed in all patients. Pain is the only vital sign that is not objectively measured. [2] Different subjective pain intensity scales such as Numeric Rating Scale (NRS), Wong-Baker Faces Pain Rating Scale, and Visual Analogue Scale (VAS) are used for assessing the pain.

While these remain the generally accepted assessment paradigm, and while we all agree that these pain scores are highly subjective entity, we nevertheless rely to make judgments about the effectiveness of treatments and/or procedures that we provide to our patients. Misinterpretation of pain complaints can lead physicians to underestimate or overestimate the patients' medical condition, thus misguiding them in providing appropriate therapies.

NRS or VAS are reliably used to assess acute pain, both at rest (important for comfort) and during movement (function and risk of postoperative complications). Dynamic pain provoked by deep breathing, coughing, and getting out of the bed is more important for reducing the risks of cardiopulmonary and thromboembolic complications after surgery. Besides pain scores, other indirect measures might be used to assess acute postoperative pain such as opioid consumption, length of stay, discharge readiness, etc. However, in chronic pain conditions, assessing pain is more complex and requires using additional, more sophisticated scales/questionnaires and other parameters.

The Brief Pain Inventory (BPI) was developed in the late 1970s, and is the most widely used measurement tool for assessing clinical pain. This scale assesses for different levels of pain such as "worst", "least", "average", and "current". Furthermore, rates how much pain interferes with 7 daily activities (general activity, walking, work, mood, sleep, relations with others and enjoyment of life) within the last 24 hours.[3]

Pain Castrophizing (PC) scale was developed between 1979-1987 by multiple authors. It contains 13 questions regarding pain experience that patients are grading on a scale from 0 to 4, with a possible total score from 0 to 52. It contains 3 subscales: rumination, magnification and helplessness. This scale has been shown to be one of the strongest psychological predictors of pain outcomes. A systematic review of 11 randomized controlled trials (RCTs) with 2,269 patients with low back pain showed that baseline PC score was predictive for disability and pain at follow-up in 6 studies.[4] Decrease in PC score during treatment was found to be linked with better outcomes in all studies. Another systematic review of 85 observational studies that included 13,628 patients with chronic musculoskeletal pain showed an association between PC and pain intensity/disability in these patients.[5]

The short-form McGill Pain Questionnaire 2 (SF-MPQ-2) contains 22 questions that describe different qualities of pain and pain-related symptoms in the past week such as shooting/ stabbing/sharp/aching pain, etc. and patients are asked to grade each of them on a 0-10 scale. Furthermore, it has 2 additional questions; one regarding current pain intensity and another one to rate the total pain experience. The SF-MPQ-2 assesses the major symptoms for both neuropathic and non-neuropathic pain, and was found to have an excellent validity for patients with low back and radicular leg pain.[6]

Neuropathic pain requires the use of additional scales specific for neuropathic pain such as: Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale, Douleur Neuropathique en 4 questions (DN4), and PainDetect. The simplest one is DN4 that contains 4 questions to estimate the probability of neuropathic pain; patients respond to 2 questions, while physicians give answers to the remaining 2 questions after examining the patient.

Functionality scales such as Oswestry Disability Index (ODI), Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC), and Neck Disability Index show how much pain affects patients' everyday functions. The ODI questionnaire targets patient's activities and physical limitations plus patient's ability to manage everyday duties (sitting, standing, sleeping, etc.). A patient is asked to answer each of 10 questions on a 0-5 scale and total number of points can range from 0-50 (0-no effect at all, 50-completely disabled).

A study by Knezevic et al. was conducted on 100 patients with radicular low back pain that were followed for one year. All patients were asked to complete pain scores on an 11-point numeric rating scale (NRS) both at rest and during movement, as well as ODI questionnaire,

and to do so 10 times during a 12-month period. Results showed that pain scores at rest correlated well with ODI in 65% of patients. Mild, moderate or severe discrepancies in pain during rest and functionality were present in 30%, 4% and 1% of patients, respectively. Comparisons between ODI and pain scores during movement showed normal correlation in only 39% of patients. Mild, moderate and severe discrepancies during movement and functionality were present in 42%, 14% and 5% of patients, respectively. Furthermore, patients taking opioids showed more discrepancies in reporting pain intensity scores than did patients taking non-opioid analgesics or not taking medications for low back pain. "Negative discrepancy" meant that patients graded their pain scores higher than their functional ability (exaggeration of pain), while "positive discrepancy" meant that patients graded their pain scores lower than their functional ability (underrating their pain). A very high percentage of patients (58%) unknowingly exaggerated their pain during movement. There was a highly statistical significant correlation between morphine equivalent doses and the level of discrepancy ($p<0.0001$). There was a negative correlation between patients' satisfaction and the degree of inconsistency in reporting pain scores. It was concluded that a special emphasis on patients' education regarding accurate report of their pain level must be paid to avoid inconsistencies between patients' pain intensity scores and their functional levels.[7]

For the assessment of the treatment effectiveness we, as physicians, are using either the difference in NRS/VAS pain scores pre- and post-treatment or asking the patients to express pain reduction in percentage of pain relief (patient-reported percentage of pain reduction - PRPPR). Knezevic et al. performed another study evaluating the correlation between PRPPR and calculated a percentage of pain reduction (CPPR) in 803 patients with different chronic pain conditions that were followed up for at least 12 months. The majority of patients (69.6%) had low back pain. The mean follow-up duration was 30±11.7 months, and the mean NRS score before and after treatment was 8.1±1.4 and 4.1±1.9, respectively. Results have demonstrated significant pain improvement in all patients via NRS scores regardless of demographics and pain etiology ($p<0.001$). The mean PRPPR was 62±20.9 and CPPR was 49.8±21. Almost half of the patients had more than 30% discrepancy between PRPPR and CPPR. Intraclass Correlation Coefficient (ICC) between CPPR and PRPPR was moderate (0.52, 95% CI 0.24-0.68) and the same applied to Concordance Correlation Coefficient (CCC) (0.52, 95% CI 0.48-0.56). This study showed a need for adoption of a multidimensional measurement of pain to periodically assess treatment effectiveness.[8]

To be clinically significant, minimal difference in pain reduction varies across the range of pain severity (e.g. a 30% of pain reduction may be more or less meaningful depending on the starting level of pain). Patients should be asked to rate how much pain they consider manageable because some patients might be satisfied with improved functioning despite a relatively small reduction in pain intensity.[9]

A systematic review that included 19 studies describing 15 different devices and techniques to objectively measure patients' pain showed that electrical stimulators had high validity, reliability and feasibility. Other devices/stimulators that are using pressure, ultrasound, sound, thermal stimulation require future research prior to possible clinical implementation.[10]

Due to complexity of chronic pain patients, other factors such as age [11], genetic polymorphisms [12], sex and gender [13], race and ethnicity [14], socioeconomic factors, lifestyle (diet and physical activity), medical comorbidities etc. should be taken into consideration when assessing and treating these patients.

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EVOLUTION OF PAIN COMPREHENSION (ONTOLOGICAL AND PHENOMENOLOGICAL FACE OF PAIN)

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Summary

Pain is the basic evolutionary mechanism and one of the oldest stressors known. Nevertheless, unlike other medical problems, today, in the 21st century, the pain remains on the margin of interest of healthcare professionals and society in general. A person usually does not think about pain until it happens to him or until someone from his close environment suffers from pain. And then, the pain becomes a terrifying master of life. He seizes the whole personality, seizes all attention and changes life from its foundations. In the practice of today's medicine, the dominant role belong to a scientific concept over three centuries old, whose roots can be found in the ancient era. Recognizing physical signs and symptoms and treating them, alongside suppression of mental problems that cause pain, more than any other illness, is still the primary form of treatment for patients with pain. Such an approach has its own evolution that we are often unaware of. Only by its deliberation we become aware of the significance of this problem and the relative inability to deal with it. Even today, when medical knowledge is on a high level, we are not able to fully control the pain. Although science has long been viewed comprehensively, doctors in practice have not found a way to apply such a comprehensive systemic approach on the patient. The first step towards the solution is certainly the change in the attitude of professionals who deal with pain, which includes: extended pain education, raising awareness about the importance of the problems and treatment options, as well as the need to engage those who are not having a professional task, but who certainly, at some point in their lives, become aware of how nice painless life is.

Key words: Chronic Pain, Ontology, Phenomenology, Psychosomatic, Pain model

Introduction

The International Association for the Study of Pain (*IASP*) defines pain as: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or expressed by terms of such damage" [1].

Defining pain in this way has enabled over 50 years of significant progress in fundamental pain research and understanding of the numerous phenomena that accompany it.

What we know for certain from the definition of pain is the fact that pain usually occurs in the body, but it is shaped by brain activity. That the pain is an unpleasant subjective experience, that's what the patient tells us to feel. Therefore, it is necessary to distinguish painful sensations (noxious stimulus awareness) from painful experience (the general subjective experience of suffering due to pain), which makes it primary and secondary components of pain. Primary includes the following: sensation, perception, discrimination and recognition of the noxious stimulus, while secondary involves suffering and reactive aspects (anxiety, depression, and other emotional-affective and cognitive-discriminatory pain responses). The emotional component is inextricably involved in all aspects of painful experience [2,3].

Pain is probably one of the oldest phylogenetic stressors, as old as the life itself. At the same time, it is also the most comprehensive form of stress and suffering that follows man from the very beginning. Despite the long-lasting awareness of the pain and suffering caused by him, as well as the effort to eliminate it, pain is not fully understood today and can not be controlled comprehensively.

We can agree we are living and working in the time of medical miracles. While it is quite easy to break down molecules, mark receptors, affect the genome, or even go to the Moon, we can not say that we have simple, safe, universal and effective options for treating pain conditions and pain.

The evolution of the knowledge of pain

Our knowledge of pain, its causes and consequences, was not always the same. In accordance with the knowledge and understanding of pain in a certain time, the principles of its treatment were set. It can be said that understanding of chronic pain is a process that reflects the sole understanding of disease and treatment. Understanding of pain is a typical function of knowledge and science in general. Therefore, today we can, historically, recognize more pain theories, whose significance is that they have influenced the way of assessment, monitoring and treatment of pain, as well as the level of priority given to this treatment in practical life.

Even the emergence of medicine itself can be linked to attempts to remove pain. Seeking adequate help and making efforts to explain the pain, a man gradually discovers a vast field of medical science since ancient times. Chronic pain today, in the 21stcentury medicine, is a consequence of the historical and epistemological construction. Developing knowledge and thinking about pain is a reflection of the prevailing biomedical approach and understanding of the disease.

In the beginning, medicine was reduced to magical rituals with elements of witchcraft. Pain itself is per-

ceived as a punishment of gods or the action of ghosts. This has ceased to be the dominant form of pain perception when a person has been able to explain the causes of the disease and has come to know the initial ways and purposes of healing.

The first attempts at rational explanation of pain occured in Greece (Hippocrates) and Rome (Galen) [4,5]. The attitudes of the rationalistic approach initiated by Galen extend to the Middle Ages, complemented by the teaching of Avicenna [6]. Pain receives significant attention as an important factor in the prognosis of the disease, and not only of the resulting damage. At the end of the Middle Ages, there were significant discoveries in chemistry, the substances that can affect the pain are identified, and we recognized power of opium.

However, the concept of understanding the disease, even the pain, did not change significantly in relation to the ancient understanding. It was necessary to identify a new scientific model that, on the basis of new starting points, methods and goals, would change the basics of knowledge, both in science in general and in medicine in particular. During the Renaissance period, new facts about the material of the human body were learned. In the 18th and 19th centuries, new medical knowledge accumulated. A person gets acquainted with microorganisms and the advancement of the technique allows the discovery of the microscope. The significance of the antiseptic is recognized, and the need for the discovery of drugs is also required to provide for analgesia and anesthesia. The new scientific concept, whose outlines originated at the end of the Middle Ages, defines its attitudes in a new, classical era, trying to reject occult beliefs and nominal explanations of previous periods.

The psychic component of the pain has been recognized by the Greeks in the ancient world (Homer), yet in the first records of health and disease that date 500-300 years before the new era, the mind and body are observed separately. Hippocrates advises doctors to treat what can be spotted and palpated [4].

Such a scientific concept (supported by works of Galen and Avicenna) had a decisive influence until the first half of the 17th century. In the 17th century, the philosopher and mathematician René Descartes (1596-1650) laid the foundations of a new understanding of science, and his teaching probably had the greatest impact on science in the next three centuries, even today [7]. The views of Descartes and his followers laid the foundations of modern rationality. He experienced man as a symbiosis of two substances: soul (abstract, spiritual, thinking and indivisible) and body (physical components, concrete and divisive). For Descartes, the soul was so different from the body that it could exist completely independently. The only connection between the soul and the body is seen in the pineal gland (epiphysis), as the place where our soul is hiding or where the gate of our mind is. To understand Descartes as a true philosopher, a mathematician, and above all a thinking man, one needs to understand the context of the time and relations he lived in. The influence of religion was crucial at that time, both to everyday life and to scientific thought. By defending its position and attitudes, religion suppressed scientific thought for centuries. Since the interest of religion was primarily related to the human soul, from the moment when Descartes presented his philosophy, the conditions have been created for science and religion to develop independently without compromising one another.

The obsession of the Descartes with immortality produced one of the most significant outcomes of his opus. It can be said that this is a new look at medicine, a medicine that has been curing the diseases and delaying death. Descartes dealt with the methodology of body dissection, seeking to understand its functioning. He concluded that the body can be seen as a machine whose various parts perform different functions. As a consequence of such an attitude, that is, a human body separated from its life, a Cartesian metaphysical and scientific form of research emerged [8,9]. That way, Descartes could preserve the "soul" ("Mind") in the field of theology, and legitimately deal with scientific research of the body. This Cartesian dualism enabled a materialistic scientific approach, removing the mind (soul) from clinical practice for almost three following centuries.

Leder quotes a fine example of how Cartesian dualism of Descartes was rooted in the development of medicine and was kept until today: "Medical education still begins with the dissection of a cadaver, just as the clinical case ends in the pathologist's lab" [10].

The medical thought, based on the newly established scientific concept, sees the human body as a complex machine, composed of parts that, like in a musical ensemble, work synchronously. The concept of medical evidence-based conclusion begins to prevail. In this period, new substances that can be used for the treatment of pain are also discovered. The discovery of ether and the discovery of anesthesia in 1846 provide conditions for the incredible progress of surgery, which still happens. A better knowledge of the anatomy of the central and peripheral nervous system, the discovery of receptors and the understanding of nerve conduction also affects the treatment of pain. Pain is seen as a purely biological phenomenon that can be explained by physiological processes.

This approach to science, especially medicine, has led to significant success. In the 19th and 20th centuries, numerous revolutionary discoveries in medicine were emerging. More and more diseases are being treated more effectively. A curative approach leads to the prevailing of the paternalistic attitude of most physicians and becomes a form of our action. Priority place in the education of a doctor takes an exact, practical way of thinking, based on evidence only. From the place of priority, during the last two centuries, former important scientific disciplines such as ethics have been slowly suppressed, and there is less and less space for compassion in contemporary life and the work of doctors.

The most relevant theories of pain

In this concept of understanding of health and illness, the first theories of pain arise [11]. They are best illustrated through the Specificity theory and the Pattern theor. The Specificity theory implies the existence of painful receptors, which are projected from the periphery of the body to the pain centers in the brain. Despite apparent simplicity, this theory explicitly points to the evolution of specialized physiological processes, and implicitly implies the assumption of the significance of psychological process-

es associated with pain. The discovery of pain receptors (free nerve endings), pathways of transmission, and the observation of brain parts that could correspond to pain centers, confirm the physiological explicitity of the Specificity theory, in which lies its strength and significance for the further development of pain medicine. However, the assumption and implicitness of the psychological component are the essential weakness of this theory.

In reaction to this weakness, new pain theories are emerging that can be grouped under one common name: The Pattern theory. The basis for this group of theories is set by Goldscheider in 1894, assuming that the intensity of the stimulus and the central summation are basic determinants of pain. From this concept, two types of pain theory have developed, which in their basis carry the model of the sample as the essence of explaining painful phenomena, but while one group ignores the fact of physiological specificity, other theories put a central summation at the central spot. Weddell and Sinclar base their theory on the assumption that all the qualities of the skin stimulus are formed by a special spatio-temporal pattern rather than specialized pathways for pain.

Evidence of the existence of specialized receptors and pathways of pain has undermined this theory. The other Pattern theories seek an explanation primarily in central summation mechanisms (Livingston) and recognize evidence in clinical phenomena. According to these theories, special control systems usually prevent the formation of a summation, and the disorder of these systems causes pain.

Without going into details of these theories (which marked a long period of pain management based on them) it should be pointed out that the override of the Pattern theory over the Specificity theory (Nordenbos) led to one significant change. It distanced itself from the psychological quality of the pain as such, which also led to the treatment of pain. For decades, in clinical practice, pain treatment has been approached from these points of view, and the dominant therapeutic attempts involved numerous neurosurgical techniques, specific drugs, and the personality of the patient remained at the margin of the priorities that the clinicians dealt with.

Different theories failed to provide unique attitudes about the view and understanding of pain. It should be stated that the amount of experimental data that would confirm such concepts was insufficient. Over time, accumulated physiological knowledge enabled the emergence of a new theory: *Gate Control Theory of Pain* [12].

Without dealing with the details of this theory, the work of Melzack and Wall brought about a revolution, both in understanding pain and in the possibilities of clinical ways of pain relief. The basic benefit of this theory is the fact that it shifted the focus of our attention from the periphery to the central nervous system. Introducing new terms and accenting processes in the back horns of the spinal cord as well as descendent pathways, and at the same time directing our attention to the neuromatrix located in the brain, this theory also provides significant clinical transformation. In addition to the dominant surgical pain management techniques, new methods of healing are introduced in practice: behavioral therapy, work therapy, psychological techniques, hypnosis, placebo and a long series of techniques that return the long-pressed, psychological component of pain to the center of attention. Today it all seems a little odd. Young doctors arising from the clinical practice in the 21st century are surely wondering what the debate is all about, or how it is possible to neglect the mental component of the pain entirely. This can be understood if one knows the epistemological-ontological aspect of the evolution of knowledge of pain, which has followed the prevailing scientific-philosophical concepts of the time in question [13].

Towards ontology of pain and pain phenomena

Epistemologically speaking, contemporary attitudes about pain are the result of understanding the knowledge of the pain accumulated over centuries and caused by numerous successes and failures in its treatment. Over time, numeorus data has been accumulated that were only ontologically classified, analyzed and integrated in the form of various biomedical data. Such an approach has made great success in numeorus medical fields. Progress in most of the medical opus has not been adequately monitored in the area of pain medicine. Certain problems have been identified when we are faced with the pain and other symptoms of the disease whose main characteristic is subjectivity. Specifically, there is a certain physical component of the pain, which is reflected in the damaged structure of the painful area. Sometimes this disorder is manifest and can be explained by the changed architecture of the painful area, and sometimes it is not visible, which does not mean that it is not present. The disorder can be at the level of nerve membranes, receptors, nucleotides, within a genome, but it certainly does exist. Symptoms that we recognize (pain, agony, disgust, anxiety, sleepiness) are just a part of the phenomenon that we see as doctors. There are also changes that relate to behavior and some qualities of the body that we can see and recognize. But we are not able to adequately measure the qualitative/quantitative aspects of these symptoms. For these reasons, we must rightly trust a patient when he says he is in pain. The patient's experience of pain is interpreted in his words and the clinician is to accept it, sincee he is not in a position to judge that experience, except in the case of a clear simulation.

In order to better understand the language of pain used by patients, the types of pain and the phenomena that result from it can be classified [14] (Table 1).This ontologically based approach enables better integration of data obtained from the patient relating to its pain. It helps especially in categorizing patients and analyzing different types of pain data. Because pain has complex characteristics, its examination may have a heuristic value for ontological consideration of symptoms in general. The individual pain experience obviously imposes different approaches to the study of this phenomenon, which are not based solely on a complex scientific method, but also correlated, with the domain of experiential collaboration in a scientific approach.

Modification of paradigm

The subjective feeling of pain is still an unknown fact for science. Over time and through different cultures, understanding and expressing of pain reflects the contem-

Table 1. The types of pain and the phenomena that result from it

	Symptom	Signs (= Objectively Observable Features)	Physical Basis	Examples
CP: Canonical Pain				
PCT: Pain with Concordant Tissue Damage	Pain	Manifestation of tissue damage Report of pain concordant with stimulus sufficient to cause this tissue damage Protective response	Activation of nociceptive system through peripheral tissue damage	Primary sunburn Pain from strained muscle Pain from fracture Pulpitis
VP: Variant Pain				
PNT: pain with peripheral trauma but no concordant tissue damage	Pain	Report of pain associated with stimulus intensity insufficient to cause tissue damage	Activation of pain system through cognitive mechanisms regarding threat of tissue damage, the latter often based on peripheral non-nociceptive input to the CNS	Secondary sunburn without tissue damage Myofascial pain disorder Tension-type headache Chronic back pain
NN: neuropathic nociception (pain with no peripheral trauma)	Pain	Report of pain No identifiable pathological peripheral stimulus History of probable causes	Disordered nociceptive system Neuropathic (for example in result of demyelination of nerve fibers)	Trigeminal neuralgia Post-herpetic neuralgia Diabetic neuropathy
PRP: Pain-Related Phenomena Without Pain				
PBWP: pain behavior without pain		Sick role behaviors accompanied by normal clinical examination Report of pain discordant with physical signs Grossly exaggerated pain behaviors Identified external incentives	Description of pain relates to mental states such as anxiety, rather than peripheral tissue locus Misinterpretation of sensory signals by the emotional or cognitive systems Deception by patient	Factitious pain Malingering Anxiety-induced pain report
TWP: tissue-damage without pain		Manifestation of tissue damage normally of the sort to cause pain No reported pain	suppression of pain system by one or other mechanism	Stress associated with sudden emergencies Physiological damping of the pain process caused by adrenalin Placebo induced opioid analgesia Genetic insensitivity to pain

porary spirit of the epoch. Usually, the human experience begins with a painful birth and during ones lifetime this painful experience is repeated and exists in its physical, emotional and spiritual form. It is an integral part of life in every sense of the word. It is followed by the universal experience of suffering.

A compartmentalized view of a man from Greek times, enhanced by dualism of Descartes, created the conditions that in the treatment of pain the focus is on the damaged part of the body, without significant attention to individual identity. Such a biomedical paradigm of pain could not survive because it neglected individual experience and other non-physical aspects of pain. The turning point was enabled by Freud's theory, with which he put unconsciously to the focus of our attention and its effects on the perception of pain and behavior [15]. The consequent expansion of the understanding of the importance of psychological and social factors in the disease is presented in psychoanalysis, and later through psychosomatics. The explanation of the relationship between unconscious and physical sensations in hysteria has served as a basis for explaining psychogenic pain. In 1970, George L. Engel explained the link between chronic pain and psychiatric illnesses [16]. Depression and anxiety, alongside physiological basis of pain, became the focus of our attention, and since the 1980's, cognitive-behavioral approach to pain and consequently the way of treatment has been associated with this.[17] Such therapy, by learning the methods of coping with stress and avoiding a catastrophic scenarios, became the basic component of the interdisciplinary treatment of pain that we have today [18].

Nevertheless, the holistic, biopsychosocial model of pain described above did not give revolutionary advances in the field of chronic pain treatment. It must be acknowledged that this model of pain theory contains Cartesian dualism and the positivistic premise of seeking a unique reality based on scientific methods. This is also reflected in the definition of the pain that we are using today. In addition to the still existing division of body and soul, which is present in this concept, it must be said that such an approach nevertheless made significant progress, pointing to the fact that pain is a completely private, individual experience. When living with the painful expe-

rience, the individual's life is attacked to the extent that his previous experience intertwines and defines both the origin and the expression of one's own pain. The patient's experience now includes pain, but from the perspective of a physician, the patient himself remains divided, compartmentalized.

Phenomenological aspects of pain

In the situation in which we are today,and in the way of perceiving the pain that is dominant in today's medicine, one should not dismiss the phenomenological view of pain [19,20]. Phenomenology seeks to master the essence of a painful experience, trying to understand a person (individual) who, in his characteristic, overcomes a simple sum of different parts (compartmentalism). A man is not the product of the world in which he lives – it is a part of it. The body, mind and the world surrounding them are in constant interaction and influence [21]. This makes human life an integral function, rather than a set of simple mathematical equations.

The phenomenological view of the pain is based on the concept of intentionality, derived from Brentano's scholasticism, elaborated in the works of Husserl and other authors who attempted to propose a different view of a man from Cartesian [22, 23]. The principle of intentionality, according to Huserel, implies that consciousness is an unambiguous consciousness of something, and that consciousness is conscious only if it is directed at an object. Conversely, an object can only be defined if it is in relation to the consciousness of it. Intentionality is the relation of the individual and its world, and not just the individual or individual object, that is, the relation that the subject and object are creating. Intentionality is the meaning that arises from the contact of a man with the world in a constant dialectical relation, whereby the dichotomy of that relationship transcends. The singularity of the relationship between the body, the mind, and the world was most reminiscent of Merleau-Ponty, saying: "I am conscious of the world through my body" [24].

Thus, the term *lived body* emerged (the body that lives), which leads to a new understanding of the body, because man through such a body opens itself to the world and thus experiences the world and oneself together.

As part of this thinking, to understand the pain through the anatomo-pathological perspective, as something that happens in some part of the body, means not to understand the experience, feeling of pain, from a human perspective. The body that hurts is the expression of the relationship between the individual and the environment and under the influence of both of them all the time, taking such specific characteristics, which, if neglected, limit the therapeutic possibilities.

When pain occurs, person's attention is directed to a damaged place, and pain can control this attention as no other experience. All past and present experiences of a person change in pain. It focuses on the moment in which it experiences painful sensations, as well as the place where the sensation originates. The appetite is lost, the interest of any kind is limited, insomnia occurs, the libido is lost and the movement is limited. It is interesting to say that a person in pain completely loses interest for the future, and only needs to end the pain, but at the same time he wants to forget everything from the past, which reminds him of that pain. Very often, catastrophic scenarios are formed in the patient's head, and life without pain can simply not be imagined. For such pain, as a disease, which chronic pain certainly is, it can be said that it is a special form of life. Pain is not just a simple reflection of the site that causes it. Pain comprehensively takes on the man and the person he represents. It involves the whole man, with all his individual characteristics, physiologically, socially and psychologically. Pain seizes attention, causes new questions and re-examinations, causes suffering, changes the role of the sick person in the family and society in general, affects working abilities and prevents leisure and rest.

For this reason, it is simply impossible to experience pain only according to the number on the scale, as it is impossible to overcome and treat the chronic pain alone by intervention based on experience in numerous scientific discoveries. It is impossible to help a patient with pain without getting to know him. The patient's word must be heard to understand his pain.

Chronic pain does not exist isolated from the person who feels it. In order to understand it, we have to understand it from the perspective of a patient who is completely unique and is never the same in different patients. People understand in different ways, give a different meaning or express their pain experience. Suffering in pain, a patient creates a certain experience, which then influences and creates an ill person. Brain in pain teaches, constantly analyzes received imputes, processes them and shapes into an affect, through a significant emotional-affective and cognitive-discriminatory experience.

Madjar describes this nicely:

"To understand pain we need to understand the person in pain and a phenomenological gaze can help us to do that. The key is our attentiveness to the lived experience of the person in pain, and our willingness, individually and as members of health care teams, to work as much with as on our patients. The cognitive and technical work of pain diagnosis and treatment needs to go hand in hand with the supportive, and the affirming acts that make possible for the patient's voice to be heard and to be valued" [25].

In today's circumstances of the fragmented concept of health and treatment, a positivistic view of science (and medicine) is predominant and continues to be fostered, ignorant of ethical, moral, social and psychological aspects of chronic pain. It is safe to say that on the scale of our interest and practice, a notion of mutual influence and interweaving of all these factors is far behind. The psychological and social component of the pain is most often not considered, if the physiological component (cause of pain) can be affected. Only if the cause is impossible to treat or define, the socio-psychological aspects of pain start to be considered. This maintains and often deepens the gap between the perceptions and the starting point of the healthcare professionals in terms of the patient's understanding and expectations. Doctors often unconsciously make artificial division of pain from anxiety, depression, suffering, and other emotional reactions of the patient. Patients, however, do not experience pain as a mere sensation, but rather as a painful sensation package upgraded by suffering, anxiety, depression, etc. [26]

In the light of the comprehension of total, personalized pain, it becomes increasingly clear that a simplistic positivistic approach to the treatment of such a complex phenomenon is not sufficient [27]. The question is just how to upgrade such an approach, taking into account the individual psycho-social context. The combination of modern treatments and significant empathy and attention to the underestimated personalized features of a painful experience can offer a possible step forward. Whether it is a possible solution remains to be proven by complex scientific methods which, in addition to the numbers obtained by the scale of the measurement of pain, must include other aspects of the monitoring of the painful behavior.

Someone once said, "give me a specialist, I'll tell you a disease". In practice, patients are treated by different specialists, who are not trained to step out of their everyday work patterns. There are few or insufficiently trained healthcare professionals whose primary interest is the treatment of pain. It is even more difficult to understand that in the 21st century the need for such healthcare professionals is not sufficiently recognized. When considering that the total cost of treating pain exceeds the cost of treating malignancies, cardiovascular diseases and AIDS all together, the dilemma is even greater [28].

Concluding remarks

What is the possible solution to such an unusual situation where"we know a lot" and still,"we do not succeed sufficiently"? Today, with great conviction, I believe that the first step towards solving the problem of pain lies in education: education of healthcare professionals, patients, and the general population where we live in. Healthcare professionals need to learn about the pain especially during their undergraduate studies, and postgraduate studies need to be improved and aligned with modern learning programs in the world. Patients should be educated in order to deal with pain more easily. Raising awareness of the general population about the significance of this problem will alleviate the conditions of work of healthcare professionals and the possibilities of treating patients. A comprehensive first step such as this one would make it possible to deal with pain more effectively, as an integral part of life in each of its manifestations [29].

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MANAGEMENT OF CHRONIC POSTOPERATIVE NEUROPATIC PAIN

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Chronic postoperative pain (CPOP) is a major health problem which affects millions of patients every year [1]. The number of surgical procedures is large and continues to grow in all economic environments. It was estimated that between 266.2 and 359.5 million operations took place in 2012, and surgical volume increased 33.6% over 8 years [2]. Also, it is estimated that 10 – 50% of patients underwent surgery develop CPOP, and pain is severe in 2 – 10% of them [3,4]. Although CPOP is a serious health issue that directly interfers with the quality of life of affected patients and results in occurrence of disability [5], the first paper on CPOP was published by Crombie et al. only 20 years ago [6,7].

Definition was serious problem when investigating CPOP. Finally, the World Health Organization (WHO) released its new the International Classification of Diseases, 11th Revision (ICD-11) in June 2018, according to which CPOP is defined as chronic pain developed after a surgical procedure and persisting beyond the healing process, i.e. at least 3 months after surgery; pain is either localized to the surgical field, projected to the innervation territory of a nerve situated in this area, or referred to a dermatome (after surgery/injury to deep somatic or visceral tissues); other causes of pain including infection, malignancy etc. need to be excluded as well as pain continuing from a pre-existing pain problem [8]. Depending on the type of surgery, CPOP is often neuropathic pain (on average 30% of cases with a range from 6% to 54% and more) [8,9]. Neuropathic pain resulting from surgical trauma is still the most common expression of CPOP [10]. Differentiation of neuropathic from non-neuropathic causes of postoperative pain is essential for the design of effective strategies to prevent and treat the conditions [11].

The development of chronic neuropathic postoperative pain (CPNP) involves key mechanisms such as ectopic afferent nerve activity, peripheral sensitization, central sensitization, impaired inhibitory modulation, and pathologic activation of microglia. Treatments aimed at reducing neuropathic pain are targeted at one or more of these mechanisms [12]. For prevention of CPNP, appropriate perioperative analgesia is essential, techniques that avoid nerve damage are recommended and should be used whenever possible, because the management of CPNP, in general, is difficult [13]. Interventions are predominantly pharmacological, but other interventions, including acupuncture, exercise, postamputation limb liner, spinal cord stimulation, further surgery, laser therapy, magnetic stimulation, mindfulness-based stress reduction, mirror therapy and sensory discrimination training, are also present in the management of CPNP [14,15].

The recently published systematic review of available literature in order to provide an evaluation of evidence-based interventions for the management of CPOP, included 66 randomized trials with data from 3149 patients. Trials to date have focused on pharmacological interventions, and no trials have been conducted to evaluate multimodal interventions matched to pain characteristics for the management of CPSP. In the current clinical setting to treat CPNP, commonly used drugs are: N-methyl-D-aspartate (NMDA) receptor antagonists, antiepileptics, antidepressants, opioids, capsaicin and neurotoxins [16].

NMDA receptors are excitatory receptors in neurons that play a fundamental role in neuronal development, synaptic transmission, and synaptic plasticity [17]. Also, NMDA receptors are important in the pathophysiology of central sensitization after surgery, and their blockade by NMDA receptor antagonists has been shown to prevent its development and reduce both acute and chronic postoperative pain [18,19]. The role of NMDA receptor antagonists in the management of CPNP was evaluated in seven trials, including 122 patients [16]. Ketamine was evaluated in three studies [20-22] and results of all trials provided evidence that ketamine was effective in the management of CPOP [16]. In contrast, the results of four memantine trials [23-26] showed that memantine was ineffective in the treatment of CPNP [16].

Antiepileptics reduce nociceptive neurotransmission through their potent blockade the α2β subunits of voltage-gated calcium channels [27,28]. Also, antiepileptics are recomanded as a first-line treatment for chronic neuropathic pain, and they are commonly used as part of multimodal analgesic regimen [29]. The effects of antiepileptic medications on CPNP was evaluated in eight randomized trials including data from 338 patients [16]. Gabapentin was evaluated in six randomized studies including 293 patients [30-35], and all of them demonstrated positive therapeutic effect of gabapentin in current pharmacotherapy for CPNP. Pregabalin was examined in a small (18 women) placebo-controlled trial which results demonstrated statistically significant improvement in pain control in pregabalin group, but the trial was terminated early by the industry sponsor [36]. Levetiracetam was evaluated in a small (27 women) placebo-controlled study without differences in pain relief between levetiracetam and placebo over 4 weeks of treatment [37].

Antidepressants are known modulators of serotonin or noradrenaline signaling, which are critical neurotransmitters in the modulation of nociceptive transmission in the spinal cord. Also, antidepressants represent the first recommended line of the management for chronic neuropatic pain [28,29]. Such drugs include selective serotonin reuptake inhibitors, seronin-norepinephrine reuptake

inhibitors and tricyclic antidepressants [28]. The role of antidepressants on CPNP were investigated in four studies, initially including 177 patients [16]. Amitriptyline was evaluated in three randomized placebo-controlled studies with conflicting results for CPNP intensity or relief [38-40]. Venlafaxine was examined in a small study (13 patients), which results showed no difference was found between venlafaxine and placebo [41].

Opioid receptors belong to the super-family of G-protein coupled receptors (GPCRs), which are the most abundant class of cell-surface receptors, and also the targets of about one-third of approved drugs [42,43]. There are three major subtypes of opioid receptors: δ receptor, μ receptor, and κ receptor, which are activated by endogenous peptides [43]. Furthermore, opioid receptors are widely studied due to their crucial role in pain management [44]. The impact of opioids for the management of CPNP was evaluated in six trials including data from 297 patients [16]. Morphine was evaluated in five trials, included oral morphine [45-47], morphine infusion [48] and epidural morphine [49]. Results demonstrated that oral morphine and morphine infusion was effective in the management of CPNP, although a common side-effect was constipation [16]. Tramadol was examined in a study incuding 94 patients that received individually titrated doses of tramadol, placebo or amitriptyline, which results demonstrated considerable effectiveness of tramadol and amitriptyline in the management of CPNP with no major adverse events [50].

Capsaicin, a compound found in chili peppers and responsible for their burning and irritant effect, can also be used to relieve pain [51,52]. Capsaicin selectively stimulates nociceptive neurons by activation of transient receptor potential cation channel subfamily V member 1 TRPV1 receptors and has been widely used to study pain-related events [52,53]. Capsaicin importance is corroborated by the varied pharmaceutical formulations available and clinical applications, such as the capsaicin 8% patch to treat neuropathic pain [52]. Also, low-concentration creams, lotions, and patches containing capsaicin (0.025%–0.1%) intended for daily topical application have beneficial effects against various pain syndromes, including post-herpetic neuralgia, diabetic neuropathy, and chronic musculoskeletal pain [52,54]. The use of capsaicin in the management of CPNP was evaluated in three trials with a total of 174 patients [16]. Two studies investigated the efficacy of low-dose (0.075%) capsaicin topical cream applied four times daily for 6–8 weeks and both of them showed lower the intensity of CPNP, with caution that the usual side effect was local skin reaction [55,56]. However, a recent study that examined the efficacy of a single 60-minute application of capsacin 8% cutaneous patch in 46 patients, showed no significant difference in CPNP relief at 3 months after the application patch [57].

Botulinum toxin type A (BoNT/A) is a type of neurotoxin that causes focal chemo-denervation and has been shown to be effective in management of several pain conditions. BoNT/A injections have anticholinergic effect which responsible for muscle-paralyzing action, and also an independent antinociceptive effect [58,59]. The effectiveness of BoNT/A injections on CPNP was evaluated in three trials with a total of 91 patients [60-62], and all of them were showen positive effects in the management of CPNP [16].

In conclusion, trials to date that evaluated the management of CPNP focused on pharmacological interventions. Gabapentin has evaluated in the most number of trials and all of them demonstrated positive therapeutic effect of gabapentin in current pharmacotherapy for CPNP. Also, the use of morphine (oral and intravenous infusion), ketamine, and botulinum toxin A has been shown to be effective in the management of CPNP. The recently therapeutic interventions as low-dose capsaicin topical cream and botulinum toxin A has demonstrated the promising results, but the larger number trials of these interventions are needed to provide evidence base to guide the management of CPNP. Given the complexity of pain that extends or emerges after surgery, individualized interventions should be developed and evaluated. High-quality trials of these interventions are needed to provide a robust evidence base to guide the management of CPSP.

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TWO POST-ICU SECRETS THAT STILL NEED TO BE REVEALED: CHRONIC PAIN AND OPIOID DEPENDENCE

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Background

For the last sixty years improvements in critical care medicine led to increased survival rate of patients hospitalized in the intensive care unit (ICU) [1]. ICU is specific environment for patients who suddenly experience deterioration of their health and therefore stay in ICU leads to physiological, psychological and ethical problems with longterm consequences summarized under the term "post ICU syndrome"(postintensive care syndrome (PICS)) [2]. It was found that one or more symptoms such as sleep deprivation, fatigue, weakness and chronic pain, can be present in 88.5-97% patients after four months of ICU treatment [3]. Additionaly, deterioration in mental processing speed, memory, executive functioning, attentiveness, and IQ can persist up to two years [4,5]. It is noticed that 22% of ICU survivors depends from help of others, and in 80% of cases the support comes from family members [6]. Post ICU syndrome can have serious consequences on patient's everyday activity and indirectly can cause economical burden for a family and society in general [6]. Recently, the chronic pain in the post discharge ICU period became more apperent as possible problem. On the other side, despite the story of chronic opioid use, opioid dependence after ICU treatment is rarely explored in literature.

Chronic pain after intensive care unit

No definition of chronic pain after ICU exists. In recently published review, the authors defined the chronic post ICU pain (CPIP) based on the definition of chronic pain from ICD 11 classification and its application on the chronic pain described in patients after their treatment in ICU,as "pain persisting or recurring three months"after patient's discharge from ICU [7,8].

In literature incidence of CPIP ranges from 33% to 73% [8]. Moreover, CPIP was recorded in 57% of ICU survivors even six years from ICU treatment [9]. From the point of pain localization, one study recorded shoulder pain in up to 22% of studied ICU survivors [10]. The CPIP intensity ranges from moderate to severe [8].

CPIP origins are complex, including the inflammation and nerve injuries from multiple sources like patient position in the bed, necessary movement of patient by medical staff and different procedures that are performed in critically ill patient (central venous line or thoracic drain plaments). Risk factors for CPIP development are still under investigation and conclusions from different studies are controversial, including increased patient age, diagnosis of sepsis, longer hospital stay and longer time of ventilation, surgical or trauma diagnosis and patient age [8-12].

Post-ICU neuromuscular complications as critical illness polyneuropathy and myopathy are studied distinctively from chronic pain, but might aggravate painful state. The prevalence of post-ICU neuromuscular complications is 57% (range 9-87%), with the most frequent presentation at lower extremities [13]. Diffuse symmetric sensorimotor axonal neuropathy is clinically presented as critical illness polyneuropathy [13]. Several mechanisms of axonal degeneration are described and they include microcirculation dysfunction compromising oxygen and nutrition delivery, endoneuronal edema caused by cytokines increased microvascular permeability and mitochondrial dysfunction [13,14]. Additionally, cytokines and neurotoxic factors have direct influence on nerve [13]. Long term immobility causes changes in the muscle cell metabolism, like reduced protein synthesis, increased catabolism resulting in muscle mass reduction [13]. Additionally, reduction of microvascular circulation with reduced oxygen delivery and insulin resistance causes further changes in muscles leading to critical illness myopathy [13]. Critical illness polyneuropathy and myopathy contribute to ICU-acquired weakness and consequences are seen as muscle mass reduction and loss of strenght [15].

The longterm consequences of CPIP are functional capacity deterioration and low quality of life [16-18]. The chronic pain is "highly comorbid with anxiety and depression" [19]. There is a correlation of pain presence with severity of sleep disorders, fatigue and weakness [20]. One study analyzing the data from ICU survivors after severe accidental injury, found that CPIP was present in all patients with posttraumatic stress disorder [21]. Additionally, the high distress score was found in family members involving in care of ICU survivors with moderate and severe pain [6].

Opioid dependence in ICU survivors

ICU-acquired opioid dependence is relatively new term used to denote opioid dependence in post-ICU discharge period in ICU survivors [22]. Dependence presents physiological and biochemical neuronal adaptation after longterm opioid use. Clinically, opioid dependence is described as a „physical effect, characterized with abstinence syndrome, seen upon abrupt drug withdrawal" [22,23]. As defined by Van Korff and adopted by Chou, chronic opioid therapy is "daily ornear-daily use of opioids for at least 90 days, often indefinitely" [24,25].

One of the rare studies investigating chronic opioid use among ICU survivors, found that 12.2% patients

used opioids in postdischarge period with decreasing to 4.4% after 48 months (26). Studies analyzing opioid use habits in ICU survivors from surgical and nonsurgical diagnosis and one trauma population noticed "discrepancy" between reported high incidence of chronic post ICU pain and chronic opioid use [26,27]. The authors explained this phenomenon with implementation of nonopioid pain management, change of opioids prescribing pattern for noncancer pain and lack of adequate tool for chronic pain syndromes definition [26]. One finding of this study was that chronic opioid use before ICU admission and length of hospital stay "were associated with postdischarge chronic opioid use" [26]. As this study was retrospective based on electronic charts analysis, many possible influencing factors were missing including type and amount of opioid medication, adjuvant medications, physical therapy, sedation pattern and many other factors that can influence course of ICU stay and therefore chronic opioid use [26]. No difference in chronic opioid use was found between medical and surgical patients [26].

Preventive measures

According literature data, pain experienced during ICU stay, is the most common memory in ICU survivors [27,28]. Although overall number of ICU admissions around the world is unknown, just in United States annually 5.7 million patients are admitted to the ICU [29]. Leading health problems that require ICU admission include respiratory system disease, acute myocardial infarction, intracranial bleeding/cerebral infarction, percutaneous procedures with drug–eluting stents and septicemia [29]. Obstacles forPICS preventive strategy practice include ICU patients heterogenicity, fluctuation in patient health state, changes in circadian rhythm, different response to therapy and difference in biological adaptation mechanisms among patients [30].

Moderate and severe pain in the ICU needs to be treated with opioids as part of multimodal analgesia. The analgesia therapy should be based on patient individualized needs including balance between minimal needed dose of opioids for pain relief based on regular pain assessment [22]. Pain management in surgical ICU patient is more complex as his pain condition includes pain caused by incision and drains. Additionally,it is important to prevent and treat procedural pain. Patient health state improvement, and lower pain intensity, should be accompanied with a careful opioid tapering along with opioid free analgesia introduction.

Detailed analysis of patient preadmission state, including preexisting chronic pain and opioids therapy, has significant role in identification of patients who are under risk to develop post ICU discharge chronic pain and opioid dependence. In the future, knowing patients' genetic characteristics, can lead to personilized pain management in the intensive care [31,32].

Chronodisruption (circadian disruption) is a novel syndrome describing sleep-awake pattern disruption in patients during ICU stay. ICU environment is characterized with 24-hours activity monitors noise, intense daylight and night light presence, medical staff activity connected with medication delivery and care [33]. Patient's critical state, psychological distress and pain are internal causes of chronodisruption [34]. Potential benefits of melatonin use can be summarized as reduced incidence of delirium, neuroprotection, antioxidant, antineoplastic and antinflammatory properties [35,36]. Based on circadian rhythmicity, "personalized" melatonin dose is suggested as well as duration of treatment and manner of treatment with more profound knowledge of pharmacokinetics and pharmacodynamics of melatonin [36]. In addition to melatonin, lights adjustments as imitation of day/night pattern and windowed rooms can improve circardian rhythm (chronoenhancement) [33,37].

Ketamine is NMDA receptor agonist, widely used to reduce intensity of postoperative pain and prevent chronic postoperative pain [38]. Other beneficial effects of ketamine are antidepressive, neuroprotective effects and improved cognition [41,42]. However, ketamine "might cause harm by inducing negative experiences"increasing the incidence of hallucinations and nightmares [41]. One more conflicting reason against ketamine application in the ICU, is possible effect on cardiovascular system and central nervous system in critically ill patient.

Alpha 2 agonists, antiepileptics and corticosteroids are medications that might have influence on acute ICU pain characteristics and consequently on CPIP development. Use of regional anesthesia in ICU can be compromised by infection presence, acquired coagulopathies and immunocompromised state. Carefull decision about neuroaxial blocks and regional anesthesia performance in ICU patients is based on risk and benefits of alternative analgesia techniques, benefits from blocks and risks for central nervous system infection [42].

The aim of nonpharmacological methods introduction and combination with medications used for sedation and analgesia is to reduce amount of medications and consequences of their long-term use. Psychological support is important as ICU patients are under stress, with fear of dying, anxiety and can experience hallucinations [43]. Patient and medical staff centered care includes patient and family involvementin decision making and high quality communication between medical staff, patient and family [2,44]. It is suggested that physical rehabilitation should be started as soon as certain level of physiological stability is achieved [45]. Virtual reality and music therapy are explored for use in ICU patients. Music listening based on patient's choice was presented as beneficial for patients with coronary heart disease, especially after myocardial infarction [46]. Positive effects of music therapy can be summarized as anxiety reduction, improvement of blood pressure, heart and respiratory rate, quality of sleep and pain [46].

Conclusion

The main principles of chronic pain and opioid dependence prevention still needs to be established. This needs systematic individualized multimodal treatment and prevention, with multidisciplinary approach. So far, no single medication or technique is available for prevention of chronic pain and opioid dependence in ICU survivors. Based on our experience and literature data, we suggest bundle of measures, analgesia protocols adjustable for crital illness and specific patient, proper assessment and follow up of the pain management, use of the lowest possible dose of opioids that is still effective,

with the aim of the earlist possible decline of the dose and slow transition to non opioids medications, early mobilisation and non pharmacological methods implementation.

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WHICH HEMODYNAMIC PARAMETER SHOULD WE TARGET FOR RESUSCITATION?

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Patient safety during general anaesthesia has evolved significantly in the last decades thanks to the improvement in medical technology, pharmacology and detailed investigation of the perioperative pathophysiological mechanisms. However, mortality and morbidity rates are humble in patient populations graded as ASA I-II for elective surgery anaesthesiologists are frequently involved in the management of fragile patients in state of shock especially in emergency settings [1]. Beyond that, the aging population with significant co-morbidities and complicated surgical techniques is a real challenge for the anaesthetists of the 21st century.

Hemodynamic optimization throughout an individualized concept can significantly ameliorate the perioperative outcome even in high risk patients. As macrohemodynamic indices go hand in hand with the microcirculatory pattern the advanced hemodynamic monitoring has an utmost importance in this concept [2]. Assessing the physiological variables (MAP, CI, SVI, GEDVI, GEF), controlling the balance of oxygen delivery and consumption (Hb, SpO_2, $ScvO_2$) along with the observation of major organ functions (e.g. diuresis) and measurements reflecting of microcirculation (lactate, dCO_2), all can aid us to put the pieces together [3].

Assembling the puzzle is the key cornerstone of the multimodal approach what requires a high level of physiological cognition and proper knowledge of initiating fluid, vazopressor and inotrop therapy at the right time for the optimization of the hemodynamic variables and preventing over resuscitation in case of circulatory failure and shock.

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PERIOPERATIVE RISK ASSESSMENT: IS PREANESTHETIC VISIT ENOUGH?

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More than 310 milion operations are performed worldwide each year. Major surgery is associated with a physiological stress response that may cause significant morbidity and mortality in the perioperative period. Advances in surgical techniques and perioperative care have influenced a remarkable decrease in mortality after complex interventions. The mortality rate after abdominal surgery is generally lower than 1.5% but can be as high as 40% in a subset of geriatric patients undergoing upper gastrointestinal surgery. The attention of clinicians and researchers in the past years has moved from mortality to other outcome measures, such as morbidity and quality of life. Postoperative complications are the leading cause of postoperative morbidity and mortality. It has been shown that the occurrence of postoperative complication has a deeper impact on long-term survival after surgery than the preoperative condition of the patient and intraoperative incidents. Costs arising from a complicated postoperative course are enormous both for the patient and for the healthcare system.

A large observational study showed that a small subset of high-risk patients accounts for 80% of mortality following surgery. It also revealed that 75% of patients who died after surgery didn't have any access to the intensive care unit (ICU). The main goal of ICU admission after the operation is to improve outcome, since unplanned or urgent admissions are associated with higher mortality. However, ICU resources are limited and usually not more than 5-10% of hospital beds are allocated to this level of care. High-risk surgical patients have the greatest benefit from ICU treatment, but "high-risk" is still not well defined.

Preoperative risk assessment is an important part of the patient's preparation for surgery, since it enables all stakeholders to make informed decisions and plan perioperative strategies as well as the level of postoperative care. A number of scoring systems that stratify patient risk are in use, and they are mainly based on patient's preoperative characteristics and a planned type of surgery. American Society of Anesthesiologists Physical Status (ASA) and Duke Activity Index are simple and widely used tools for risk stratification with a huge limitation that they don't take into account the complexity of upcoming operation. Several specialized risk scales for prediction of major adverse cardiac events are recommended by the latest guidelines issued by the European Society of Anesthesiology (ESA) and European Heart Association. Biomarkers (troponin and BNP) are becoming increasingly popular for prediction of postoperative morbidity after non-cardiac surgery in combination with clinical data. The POSSUM scoring system has been validated for morbidity and mortality prediction in different surgical populations. However, the calculation of this score is cumbersome since it uses 12 physiological and 6 operative variables. The National Surgical Quality Improvement Program (NSQIP) Surgical Risk Calculator is a detailed, procedure-specific, online available risk prediction tool developed using multiple regression models on data from milions of patients from NSQIP database. However, it is not yet established whether it can be reliable for an individual risk assessment of patients outside the United States.

Along with patient's preoperative physical status, the complexity of surgery, and intraoperative events also contribute to the overall risk. It has been shown that simple tools, such as the Surgical Apgar Score that takes into account only three parameters (intraoperative blood loss, the lowest heart rate, and the lowest mean arterial pressure) may help in clinical decision about the triage to the ICU straight after operation. The characteristics of structure and process of care can also influence the outcome of surgery. Even the term of the scheduled operation (during weekends and August) may be the risk factor for postoperative complications. Finally, the early postoperative period represents the time when the improvement of perfusion disturbances may still reduce the risk for adverse outcomes. Majority of elective surgical patients need vital signs monitoring, analgesia, fluid management, early mobilization, early enteral feeding, since it has been well documented that these measures improve outcome. None of these should be necessarily provided in the ICU setting. In reality,the hospital's structure, the availability of post-anesthesia care unit, intermediate care units, the equipment and human resources dictate the admission to the ICU in order to ensure patient safety. Unnecessary ICU admissions should be avoided whenever possible in order to avoid harm of hospital infections, over-sedation, delirium, immobilization, and psychological issues related to the ICU stay. Patients who develop complications requiring advanced monitoring and organ support certainly benefit from ICU treatment. These complications mostly occur later during hospital stay, on a surgical ward.

Our experience from a high-volume center for elective abdominal surgery is that around 4.6% of patients are at high-risk for unfavorable outcome with predicted mortality over 5%. Severe complications requiring organ support actually occured in 15% of these patients, and most of them not during a planned ICU stay following surgery. Several variables were independently associated with the occurrence of postoperative complications, but the only one that could be detected during a prean-

esthetic visit was the history of diabetes. All other relevant risk factors originated from the intraoperative and the early postoperative period.

Future studies should elucidate the best approach to perioperative risk stratification that will enable an accurate estimation of the individual risk for different outcomes of surgery. Then, it will be possible to organize the perioperative care to provide the optimum care with rational use of the available resources.

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ANESTHETIC-SURGICAL RISK ASSESSMENT IN CHEST SURGERY

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A unitary, reproducible and universally accepted risk index in chest surgery is yet to be developed. Hence, the perioperative anesthetic-surgical risk is defined by general indicators, such as mortality, morbidity, postoperative complications and quality of life.

The preoperative investigation is individualized, with a certain degree of complexity that depends on the type of surgery and the pathology of the patient. In services that have protocols applying to such cases, the patient usually gets to the surgical and pre-anesthetic consultation having already a complete set of investigations performed by the pulmonology service, so the anesthesiologist only has to supplement and summarize the data and establish the anesthetic and surgical risks, once the surgeon specifies the intent and scope of the surgery, as well as the technique of choice.

ASA Classification

Everyone involved in the surgical intervention, regardless of the surgical site, are used to assessing the anesthetic-surgical risk based on the physical status classification system, suggested by the American Society of Anesthesiologists **(ASA-PS)**. This assessment scale is meant to establish *the fitness of the patient before anesthesia and surgery*. Most importantly, this classification is a means of communication with the other colleagues, with the patients and their family, being used for statistics and, to some extent, forensic purposes. ASA-PS is not very accurate in predicting the postoperative outcome and should be supplemented with other types of assessment. A single example in this respect is sufficient: the outcome for an ASA III patient subject to mediastinoscopy will not consist of the same possible postoperative complications as a patient in the same ASA class subject to pneumonectomy!

The ASA-PS classification is essential in drawing the anesthesiologist's attention on further investigating the patient (for instance, in some services, the protocol states that a patient in the ASA III category must be consulted by an experienced anesthesiologist!) to judge how seriously the function of an organ or system is impaired.

Cardiovascular risk

All patients proposed for lung resection surgery will be subject to a cardiology assessment, preferably before the lung function tests. The minimum requirements are medical history, physical examination, ECG and establishing the risk of cardiac complications. The risk of major cardiac complications after lung resections is assessed at 3%. In 1999 Lee at al. suggested a simple score for assessing the risk of major cardiac complications in non-cardiac surgery, following an extensive study on 1,422 patients, called *Revised Cardiac Risk Index* (RCRI), which would rate 6 variables, each with one point: high-risk surgery, a history of ischemic heart disease, congestive heart failure and cerebrovascular disease, preoperative treatment with insulin and serum creatinine>2.0 mg/dL. The authors included acute myocardial infarction, acute lung edema, ventricular fibrillation or cardiac arrest and complete atrio-ventricular block as major complications.

Major cardiac complications for the RCRI risk classes are, from I to IV, 0.4%, 0.9%, 6% and 11%, respectively. The fact that only 12% of the patients included in the study were subject to chest surgery resulted in the need for subsequent studies to validate this risk scale specifically for lung surgery.

Subsequently, Brunelliet al. proposed a RCRI that predicts cardiovascular morbidity after major lung resections, lobectomy at least, Thoracic Revised Cardiac Risk Index (ThRCRI).

This classification keeps only four variables that proved to be linked to the most significant cardiac complications: cerebrovascular conditions (1.5 points), myocardial ischemia (1.5 points), kidney failure (1 point) and pneumonectomy (1.5 points). The average rate of major cardiovascular complications was 3.3%. Assessing the risk by ThRCRI is still out for debate, but the validity was backed by a study on 1,455 patients with a 2.4% average incidence of major cardiovascular complications, a value that changes with the score (Table 1). The major complications that were considered were acute pulmonary edema (APE), acute myocardial infarction (AMI), ventricular fibrillation (VF) or another type of cardiac arrest, complete atrioventricular block and cardiac-related mortality in the first 30 days after surgery.

Table 1 Recalibrated Revised Cardiac Risk Index (ThRCRI) for chest surgery (according to Brunelli et al.)

ThRCRI score	Class of risk	Major cardiac complications
0	A	1.5%
1-1.5	B	5.8%
2-2.5	C	19%
>2.5	D	23%

Age is a factor that has little influence on the prognosis, but should be considered in case of chest surgery, which is ranked in the category with an intermediate risk of major postoperative cardiac complications, between 1-5%.

Respiratory risk

Patients in the *ASA I-II class* proposed for thoracic-pulmonary surgery rarely require special investigations. The guidelines of the American College of Chest Physicians (ACCP) and the British Thoracic Society (BTS) suggest that a FEV_1 higher than 2L in pneumonectomies and equal to 1.5 l in lobectomies are values indicating that the patient is highly likely to tolerate the surgery. Another way of expressing FEV_1 is by percentage, a preoperative value above 60-80% indicating that the patient can tolerate, in terms of respiratory function, a lung resection, including right pneumonectomy, with low risk of developing complications. *FEV_1 remains a simple indicator that correlates well with potential respiratory complications following lung surgery*, especially in this category of patients. Most patients are ranked in the *ASA III or even IV* category, with hardly compensated or even difficult to control related conditions, long-time smokers, old people with a respiratory function that is already impaired before the surgery. In this group of patients, a preoperative FEV_1 (FEV_1ppo) of 35%-40% or 1.2L and a forced vital capacity (FVC) lower than three times the tidal volume indicates that the risk of developing respiratory problems is rather high in the days following surgery. The formula below is used to make the calculations:

$$FEV_1 ppo\% = FEV_1 preop\ \% \ x$$
$$(1 - \text{no. of resected segments} / \text{total no. of segments})$$

The assessment of the FEV_1 ppo by scintigraphy is slightly more accurate. Patients with FEV_1 ranging between 40% and 70% have increased risk of respiratory complications after lung resection and patients with FEV_1< 40% require a higher level of investigations. The latest ERS/ESTS guidelines published in 2009 recommend a FEV_1 ppo > 30% for lung resections with a high, yet acceptable risk of respiratory complications.

Depending on the equipment existing in the service, inexpensive function tests can also be used to indicate to some extent the risk of complications after lung resection. They include the *six minute walk test (6MWT)*, the s*huttle walk test (SWT)* and the *stair climb test (SCT)* and they help define correlations with the *cardio-pulmonary exercise test (CPET*) or ergospirometry. The oxygen consumption (VO_2-max) can stratify patients at risk for complications after lung resections. A VO_2-max below 10ml/kgcorp/min or 35% of predicted value indicates a high risk of postoperative morbidity and mortality. Values between 10 and 20ml/kgcorp/min (75% of predicted value) indicate an intermediate risk. *Gas exchanges* are explored by arterial pressure of oxygen (*PaO_2*), carbon dioxide (*$PaCO_2$*) and *DLCO*. Traditionally, PaO_2 values below 60 mmHg and $PaCO_2$ values above 45mm Hg were usually linked to postoperative complications. DLCO ppo is deemed to have at least the same predictive value as FEV_1 ppo for morbidity and mortality after lung resections and is calculated the same as FEV_1 ppo, with the minimum value generating significant risks at 30%.

Preoperative assessment of patients with lung resection indication

An indicative algorithm can be built on the above-mentioned investigations, using the evidence-based clinical practice guidelines of ACCP (American College of Chest Physicians) and ESC/ESA (European Society of Cardiology/ European Society of Anesthesiology). Patient stratification by order of conducting tests and interpretation based on their share start from the classical three-legged stool that correlates the mechanics of breathing with the cardiopulmonary reserve and function of the lung parenchyma.

Step 1. Risk stratification is done after a preliminary cardiological assessment.

- *define the cardiac risk class based on a scale recommended in the guidelines, such as ThRCRI.*
- *patients at low cardiac risk, whose disease is controlled by medication, are subject to the respiratory investigation.*
- *patients at high cardiac risk (ThRCRI score* >2) *are referred to cardiology and treated according to the ASA/ESC guidelines, then they undergo respiratory tests. Interventional cardiology or coronary bypass, if needed*
- *all elderly patients (> 75 years of age) go through the full respiratory investigation, regardless of the cardiac risk class.*

Step 2. Respiratory investigation. *All patients proposed for major lung resection will undergo spirometry and DLCO, to calculate FEV_1 ppo% and DLCO ppo%*

- *if FEV_1 ppo% and DLCO ppo% are higher than 60%, or their product is* >1,650, *no additional tests are needed.*
- *if FEV_1 ppo% and DLCO ppo% range between 30% and 60%, regular respiratory function tests are recommended, such as 6MWT, stair climb test or ST. Some scintigraphy ventilation/perfusion tests might be useful, in selected cases, to recalculate the remaining pulmonary functional structures after surgery.*
- *if 6MWT<400m or no 22m of stairs can be climbed, a cardio-pulmonary exercise test (CPET) is recommended, while determining the VO_2-max*
- *a VO_2-max < 10ml/kgcorp/min or < 35% of predicted value recommends a reconsideration of the surgical attitude towards limited lung resections or towards other oncology therapies (mortality > 10%)*
- *at VO_2-max values between 10 and 20ml/kgcorp/min, the risk of complications is intermediate and should be judged while considering the other existing comorbidities.*
- *!!! in patients under neoadjuvant therapy before surgery, the values for spirometry and gas exchanges must be reassessed prior to surgery. Chemotherapy may lead to a 10%-20% decrease in DLCO, increasing the chances of postoperative respiratory complications.*

Patients at high risk of respiratory complications, according to the aforesaid algorithm, are recommended to undergo preoperative respiratory rehabilitation.

Conclusions

The rate of respiratory complications after thoracic-lung surgery is highly dependent on the preoperative performance of the respiratory function and on the surgery scope, as well as other independent risk factors, such as age, BMI (> 30Kg/m^2), active smoking or the presence of other comorbidities (ASA >III class). Their incidence varies by the inclusion criteria, going up to 80% in some studies, 15-20% being major complications that contribute to a postoperative mortality of approximately 4%.

In terms of major cardiac complications, they stay at about 3%, with patients undergoing preoperative assessment and stratification in one of the risk classes of the existing cardiac risk scales, such as ThRCRI.

Cardiorespiratory complications after thoracic-chest surgery are common in the first week after surgery, within a 15%-40% range. Proper postoperative follow-up and care in each and every case, including the adoption of the recent ERAS recommendations, result in both shorter stays in ICU and in the hospital and lower postoperative mortality.

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ERAS PROTOCOLOS IN THORACIC SURGERY

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Enhanced recovery after surgery (ERAS) program is a multimodal evidence-based plan of perioperative care aimed at optimising patient before surgery, minimizing intraoperative stress response, consequently reducing complications, accelerating recovery and reducing lenght of hospital stay and healthcare costs [1]. The beginnings of ERAS program date back to 1990 [2], when this concept was primarly developed for patients undergoing colorectal surgery and it became the basis for ERAS protocols in other surgical specialities.

Enhanced recovery after thoracic surgery (ERATS) program represents relatively new concept. There is a growing body of evidence that implementation of ERATS principles significantly reduce morbidity,enhance patients recovery and reduce hospital costs [3,4]. Due to variations in ERATS there was a need to standardize ERATS practice.

Therefore, in 2018 the first ERAS guideline for lung resection was published. Recommendations that are made by European Society of Thoracic Surgeons (ESTS) and ERAS Society are based on the quality of evidence and the balance between desirable and undesirable effects [5].

The ERATS concept consists of three phases: preoperative, intraoperative and postoperative.

Preoperative phase

Most of the patients undergoing thoracic surgery are high-risk patients. Preoperatively, the key point of ERATS programme is to identify patients at higher risk, to address modifiable risk factors and to optimize the patient before the surgery. Malnutrition is common in cancer patients, and is associated with complications such as impaired wound healing, muscle weakness which in addition leads to delayed recovery [6]. There is no difference between ERAS elements in colorectal surgery and thoracic surgery regarding preoperative fasting and nutrition. There is strong recommendation that patients' at increased risk should be given active nutritional support 5-7 days prior thoracic surgery [5]. Preoperative administration of carbohydrate liquids up to 2h before surgery is advised as it does not increase gastric content, and is associated with faster recovery and decreased insuline resistance [7]. Smoking is the strongest modifiable independent risk factor for postoperative pulmonary complications after lung surgery [8]. Active smoking at the time of pulmonary resection increases the risk of postoperative complications such as pneumonia, myocardial infarction, and stroke, and is associated with a higher likelihood of death within 30 days after surgery. Although there are conflicting data about ideal duration of smoking cessation, patients should be advised to stop smoking irrespective of timing of operation, ideally at least 4 weeks before surgery.

Many of the patients undergoing lung resections already have poor pulmonary function due to severe COPD, smoking, impaired funcional capacity. There is strong correlation between preoperative exercise capacity and long and short-clinical outcomes, postoperative complications and survival following lung cancer surgery. Funcional condition is essential for operabilty of the patients wih lung cancer. Preoperative pulmonary rehabilitation can improve exercise capacity, as well as reduce postoperative morbidity and mortality in patients with lung cancer. It can significantly improve forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) [8]. In addition, there are reports that preoperative pulmonary rehabilitation can increse the number of candidates eligible for pulmonary resection [9]. Preoperative pulmonary rehabilitation is an important element of ERATS programme. However concensus should be made regarding exercise training programmes. Patients are also members of the multidisciplinary ERATS team, and they should be encouraged to actively participate in their care as it can contribute to enhanced recovery.

Intraoperative phase

Two key points of ERATS during intraoperative phase are related to surgical techniqe and anesthetic management.

Posterolateral thoracotomy (PLT) offeres surgeons better surgical view but is associated with inspiratory effort due to severe postoperative pain. In contrast to PLT muscle-sparing thoracotomy using antero-lateral approach results in less postoperative pain up to 1 month [10]. In comparison to PLT VATS is associated with significantly lower incidence of complications, wound infections, atelectasis and reduced mortality [11]. The benefits of VATS procedures have been also prooved in patients with poor predicted postoperative lung function [12]. Therefore, VATS presents one of the main elements of ERATS protocol. A VATS approach is recommended for early stage cancer (strong recommendation, high level of evidence) [5]. However, there is still no recommendation regarding number of ports.

Anesthetic management directed at improving patients' recovery includes: maintenance of normothermia, the use of short-acting agents, protective lung ventilation (PLV), avoidance of fluid overload and effective analgesia. One lung ventilation (OLV) is proinflammmatory state associated with increased risk of atelectrauma, shear stres, reperfusion injury and hypoxemia. Therefore, over last few decades the focus has turned towards preventing lung injury by performing protective lung ventilation

(PLV). It has been proved that although it improves oxygenation conventional OLV with high tidal volumes (10ml/kg) is associated with lung injury [13]. The aim of PLV is to minimize pulmonary trauma and avoid respiratory complications including lung injury. Recommendations for OLV suggest that tidal volume of 4-6ml/kg is protective, while an adequate PEEP applied to the dependant lung recruits alveoli, improves oxygenation and decreases lung injury**.** The value of PEEP should be adjusted according to the respiratory mechanics of the patient (5-10 cm H20), as on the one hand it should prevent lung overdistension, and on the other hand it should recruit alveoli without hemodynamic impairment. In thoracic surgery, PLV is strongly recommended and supported by evidence [5].

Fluid management in thoracic surgery is still controversial topic. There are disadvantages at both sides of regimes - liberal and restrictive. While excessive fluid administration can lead to postoperative ALI, there is concern that restrictive regimen can contribute to organ hypoperfusion and acute kidney injury (AKI). Some data have shown that moderately restrictive fluid regimens (2-3ml/kg/h) can be associated with oliguria but with no increased risk of AKI [5]. Other data suggest that crystalloid administration should be < 2 l intraoperatively, and < 3 l during first 24 hours with total fluid balance less than 20 ml/kg during the first 24h postoperatively [14]. The most recent guideline is very critical regarding fluid management, recommending targeting euvolemia.

Postoperative phase

During postoperative period the main goal of ERATS program is to promote early recovery. Inadequate analgesia following thoracic surgery can significantly compromise respiratory function. Thoracic epidural analgesia (TEA) was the gold standard technique for pain control after thoracic surgery and was a mainstay of previous ERATS protocols. Disadventages and risks of this technique are overcome by paravertebral block (PVB) for wich has been reported to be as effective as TEA [15]. Therefore, PVB can be considered new analgesic technique for major thoracic surgery. Regional anesthetic blockade in combination with systemic nonopioid analgesia present the basis of opioid sparing multimodal analgesia in thoracic surgery. Although negative effects of morphine on respiratory function are described, intravenous patient-controlled analgesia (PCA) with morphine and low dose of ketamine is used for posthoracotomy pain management. The addition of low dose of ketamin to PCA morphine provides better analgesia than PCA morphine alone, reduces morphine consumption and improves respiratory function [16].

Early chest tube removal enhances respiratory function, reduces the risk of infection and length of hospital stay. Although there were debate about the ideal fluid threshold before chest drain removal, there is strong recommendation that chest tubes can be safely removed at 450 ml/day volume threshold [5].

Conclusion

Recent guideline highlight that the strenght of recommendations outweights the strenght of evidence. In the future, further evidence is needed to estimate the impact of each element of ERATS. Nevertheless, the evidence suggests that implementation of ERATS from the moment of refferal to discharge, significantly reduces postoperative complications and length of hospital stay. Building a multidisciplinary team is essential for implementation of ERATS protocol.

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OBSTETRIC HEMORRHAGE

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Introduction

Obstetric hemorrhage remains a leading cause of maternal morbidity and mortality worldwide. Hemorrhage may occur in 3% of all deliveries and be life threatening in 1-2%. While the antepartum hemorrhage rate has remained stable, the post-partum hemorrhage rate increased 30% from 1994 to 2006 and blood transfusion nearly doubled to 2005, with 4.6/1000 women received blood products.[1] Yet most (70% or more) of these maternal deaths have been deemed avoidable.[2]

Thus, many organizations have issued guidelines, including California Maternal Quality Care Collaborative (CMQCC), World Health Organization (WHO), American College of Obstetrics & Gynecology (ACOG), National Partnership for Maternal Safety (NPMS), National Health Service (NHS), and others.

Maternal Hemorrhage

The traditional definition of Obstetric hemorrhage was greater than 500 mL after vaginal and greater then 1000 mL after cesarean delivery. However, ACOG has recently redefined postpartum hemorrhage as greater then 1000 ml blood loss in the first 24 hours or blood loss with signs or symptoms of hypovolemia.[3]

The causes of postpartum hemorrhage are well known. Uterine atony accounts for up to 80% of all hemorrhage, and the incidence has been increasing. Risk factors for uterine atony include oxytocin exposure (endogenous or exogenous) for >24 hours, infection (chorioamnionitis), physical abnormality (overdistended from polyhydramnios or multiple gestation, fibroids), multiparity, medications that relax the uterus (magnesium, calcium channel blockers, terbutaline, potent inhaled anesthetics), uterine inversion. Another common source of bleeding is 'obstetric trauma' related to genital tract lacerations. A tear of the cervix or high vaginal lacerations may be difficult to visualize and perhaps initially recognize; repair may require good visualization and anesthesia; transfer to the operating room may be helpful. Hematomas along the genital tract (labial, vaginal, broad ligament or retroperitoneal) may also lead to significant blood loss yet be more difficult to diagnose. Placenta abnormalities also contribute to postpartum hemorrhage including retained placenta (treated with manual removal or curettage), unknown implantation (increta, accrete). Acute coagulation deficits may occur after massive blood loss, prolonged significant tissue hypoperfusion or placental abruption or ammonitic fluid embolism.

Medical Management of postpartum hemorrhage begins with oxytocin and quickly progresses to the direct acting uterotonics methylergonovine 0.2 mg IM every 2-4 hours, 15-methyl Prostaglandin F_{2alpha} IM or intramyometrial every 15 minutes, maximum 8 doses. Misoprostol 600-1000 mcg may be given buccal, rectal or orally once.

Mechanical Management of postpartum hemorrhage due to uterine atony include uterine massage, intrauterine balloon, uterine packing. A uterine compression suture (e.g. B-Lynch or a box stitch) may help. Vascular reduction of blood flow to the uterus that has active bleeding may be helpful by ligating the uterine artery. Ligation of the hypogastric artery has become much less common. Bleeding from a tear or blood vessel requires surgical ligation. Hysterectomy is considered the definitive treatment for bleeding from the uterus, when other therapies have failed and bleeding continues.

Uterine artery embolization may be helpful in identifying the source of bleeding and embolizing in patients who are hemodynamically stable yet have persistent slow bleeding that did not respond to the above therapies.

The NPMS obstetric hemorrhage safety bundle creates 4 action domains and 13 key elements. The action domains include readiness, recognition, response and reporting. Every labor unit should be ready with hemorrhage cart, supplies, checklist hemorrhage medications, response teams, massive transfusion protocols and unit-based drills. Every patient should be evaluated with recognition of hemorrhage and prevention best practices using assessment tools, measuring blood loss (Quantitated blood loss – by weighing or technology) and active management of 3rd stage of labor (oxytocin administration after delivery shoulder – don't need to wait for placenta). Responses for every stage (severity of blood loss and vital signs) hemorrhage includes standardized emergency management plan, support for patients, families and staff. Reporting systems will establish debrief sessions after events, multidisciplinary reviews of hemorrhages and quality improvement outcomes and metrics.

Stage 1 blood loss as defined by CMQCC includes >500 ml vaginal delivery, z< 1000 ml cesarean, stage 2 blood loss <1500 mL, stage 3 >1500 ml or unstable.[4] Stage 1 bleeding requires actions to call for help, active OB hemorrhage protocol, start second intravenous, give uterotonics and consider diagnoses. Stage two bleeding requires transfusion PRBC based on clinical signs, without waiting for laboratory analysis and starting FFP if >2 units of PRBC given; unstable Vital signs may require laparotomy. Stage 3 bleeding requires movement to operating room if not already there, massive transfusion

protocol, additional intravenous access and possible hysterectomy. Recall, that transfusion based on clinical instability or continued bleeding, do not wait for labs. The equivalent of whole blood may be better, with PRBC: FFP of 1:1 or 1:1 after the first 2 PRBC. If >10 units PRBC, or if fibrinogen <80 mg/dL, cryoprecipitate should be given to raise the level by 80-100 mg/dL. Platelets are given in stage 3 hemorrhage.

However, visual estimated blood loss (relatively subjective) has been shown to have large variations, with large blood losses underestimated up to 50% and small blood losses overestimated. Quantitated blood loss (relatively objective) should be used by weighting sponges and lap pads, graduated markings under buttock drapes or technology to quantitate blood loss (e.g. Triton, by Gauss surgical). A maternal obstetric early warning system should be utilized (NHS-UK), although the reliability of vital signs in blunt trauma with heart rate >120 bpm was 13% sensitivity and 95% specificity. [5]

Fluid therapy preference has shifted away from crystalloid towards colloid. Transfuse blood early in massive hemorrhage, and minimize colloid to 3.5L, or 2 L if blood immediately available. [6]

Communication remains important for good patient care especially during suspected or severe hemorrhage. Review of malpractice closed claims shows communication to be an important contributor to problems including blood bank urgency, obtaining help or equipment, instability or efficacy of treatment. [7] Obstetric hemorrhage account for a disproportionate high amount (30%) of all hemorrhage claims with a higher mortality rate (77% vs 27% non-hemorrhage) with delay in transfusion. [8] While closed claims shows 60% of cases had lapses in communication, 43% had possibility for improvement. [9]

Improved outcomes

Use of the CMQCC obstetric hemorrhage protocols showed improved outcomes and decreased total consumption of FFP, PRBC, platelets and cryoprecipitate despite a 37% increase of stage 2 diagnosis to 9.6/1000 deliveries and a 60% increase of stage 3 to 4.3/1000 deliveries. [10]

Tranexamic acid (TXA)

Tranexamic acid is an anti-fibrinolytic, with 1-gram dose improving survival from trauma hemorrhage. The CRASH-2 analysis showed improved survival in all risk groups with reduced adverse events. [11] A meta-analysis shows TXA improved survival and that delay in administration reduces the benefit - a 10% decrease survival benefit/15-minute delay until 3 hours, then no further benefit seen. [12] The WOMAN trail showed benefit from TXA administration in 20,600 deliveries, and NNT of 250 women. [13] However, a similar Australian cohort questioned the applicability of the WOMAN trial to Western countries with a NNT of 35,587 women. The authors suggested "…TXA should not be used routinely for obstetric hemorrhage in women from high income countries. [14]

Fibrinogen

Fibrinogen will decrease from the normal elevated pregnancy level of 3.7-6.2 g/L[15] during massive hemorrhage. Women with severe PPH had a 2.6-fold higher occurrence for each 1 g/L decrease in fibrinogen, with a negative predictive value of 79% for >4g/L and 100% positive predictive value for <2g/L. [16] Indeed, fibrinogen level was the best correlated of increasing volume of hemorrhage.[17] However, pre-emptive treatment with fibrinogen did not decrease RBC or incidence of severe hemorrhage.[18] Availability of fibrinogen replacement varies between countries and hospitals. Fresh frozen plasma has limited fibrinogen content (approximately 1-3 g/L, with 2 units FFP increasing plasma fibrinogen by 0.4 g/L. Cryoprecipitate, manufactured from pooled plasma, contains 200-250 mg fibrinogen, with pooled units given in massive hemorrhage, 8-10 units and also contains von Willebrand factors, factor VIII and factor XIII. Fibrinogen concentrate may also be used and is commercially pooled with viral reduction; some guidelines may specifically recommend fibrinogen concentrate. Management may be best guided by viscoelastic testing.

Viscoelastic testing

Use of real time information with viscoelastic testing guiding blood product replacement during PPH has been helpful in reducing total blood products used.[19] ROTEM guided transfusion management may reduce the number of blood products transfused and lower costs.[20] A low Fibtem A5 predicted progression to PPH of >2500 mL.[21] Note that ROTEM values in pregnancy may be altered at baseline, with significantly lower INTEM CT, INTEM CFT and EXTEM CFT and higher INTEM (11%), EXTEM (11%) and FIBTEM (47%) in pregnancy.[22]

Factor VII

Although Factor VII administration was considered a potentially useful tool in PPH, routine use cannot be supported (CMQCC v2-2015). In extreme circumstances, recombinant factor VII administration may be used when criteria are met including DIC, active bleeding, >10 uPRBC with appropriate FFP, fibrinogen and platelet, with pH >7.2 and temperature>35oC at a dose of 30-90 mcg/kg and carries increased risk of thromboembolism.

Conclusion

Obstetric hemorrhage remains a major cause of maternal morbidity and mortality. Proactive monitoring, active management of uterine atony and early use of guided blood and coagulation products can improve outcomes.

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PERIOPERATIVE MYOCARDIAL INFARCTION

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Introduction

The reported incidence of postoperative myocardial infarction (PMI) among patients undergoing noncardiac surgery in several large-scale studies is between 0.3% to 36%, depending on the target population, study design, and the PMI definition used.[1-3]

Worldwide, more than 200 million adults undergo major noncardiac surgery each year, and considering demographic change is resulting in an increasing number of surgical patients with elevated cardiovascular risk, and because of that strategies to improve the detection, treatment, and outcome of PMI may have the potential to provide major medical benefts.[4-5]A missed diagnosis inevitably leads to a missed chance for treatment. Therefore, rapid and reliable detection of PMI is a crucial first step in efforts aiming to improve outcomes of this underappreciated perioperative complication.[4-5] A perioperative MI (PMI) has an associated in-hospital mortality of 15-25% and an increased risk of subsequent cardiovascular death or MI.[1,2]

Etiology

The etiology and pathophysiology of myocardial ischemia and infarction after noncardiac surgery is still subject of controversies. In perioperative setting, it may involve thrombosis over a vulnerable plaque or decreased oxygen supply secondary to anemia or hypotension, hypoxemia, hypercarbia, intravascular fluid shifts (bleeding or volume overload), or coronary vasoconstriction, designated type 1 and type 2 by the universal definition of MI.[6]Depending on the predominant mechanism, prognosis and treatment may be different.

Clinical picture

Most PMIs occur in the first 24-48 hours after surgery. Only 6% of patients with PMI experience typical chest pain, clearly indicating major differences from spontaneous myocardial infarction.[6]They are mostly of silent type; ECG changes include ST depression, tachycardia and absence of Q waves and ST elevation. The pain is masked by the analgesia and residual anesthesia provided intraoperatively. PMI is associated with substantial 30-day and 1-year mortality (9% and 22%), with similar mortality in patients with PMI not fulflling the additional criteria for spontaneous myocardial infarction criteria versus those who do. Major differences between PMI and spontaneous myocardial infarction mandate scrutiny in the individualized selection of treatment strategies after PMI.[6]

Emerging evidence suggests that many patients sustain myocardial injury in the perioperative period which will not satisfy the diagnostic criteria for myocardial infarction.[4] Among 21842 patients ≥45 years of age undergoing noncardiac surgery at 23 centers worldwide, nearly 1 in 5 had evidence of myocardial injury as determined by elevated high-sensitivity troponin T (hsTnT) in the first 3 days postoperatively, 93% without any ischemic symptoms to support a diagnosis of myocardial infarction.[7]The results of a Cox proportional model based analysis showed that an elevated postoperative hsTnT (i.e., 20 to 65 ng/l with an absolute change >5 ng/l or hs-TnT>65 ng/l) by itself, without an ischemic feature, was associated with higher 30-day mortality (adjusted HR: 3.20; 95% CI: 2.37-4.32). So, the concept of myocardial injury after non cardiac surgery (MINS) has been proposed. VISION study confirmed the independent prognostic impact of Myocardial Injury after Noncardiac Surgery (MINS).[7]Further, there is a graded increase in 30-day mortality with higher hsTnT levels.[4] This suggests that a new diagnosis of MINS may be useful to patients and clinicians. Proposed definition of MINS is as follows myocardial injury caused by ischemia (that may or may not result in necrosis), has prognostic relevance and occurs during or within 30 days after noncardiac surgery. The definition of MINS is broader than the definition of myocardial infarction in that it includes not only myocardial infarction but also the other prognostically relevant perioperative myocardial injuries due to ischemia.[7,8]

Treatment

Up to now, perioperative patient management has largely focused on MI prevention, and few studies have attempted to determine the impact of MI secondary preventive therapies in patients with isolated troponin elevation.[8] Strategies that reduce myocardial oxygen demand (β-blocker therapy, adequate pain control) and increase myocardial oxygen supply (adequate oxygenation and coronary blood flow, correction of anemia - if hemoglobin was less than 8g/dl], adequate intravascular volume status, correction of hypotension) likely have the biggest impact in preventing and treating acute coronary syndrome in patients undergoing noncardiac surgery. Also, the American College of Cardiology/American Heart Association (ACC/AHA) and European guidelines on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery focus

on prevention and detection of PMI; however, specific recommendations on effective management of PMI are not available due to a paucity of data.[10,11] Although the role of revascularization in the acute coronary syndrome setting is well established, performance of percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery in the early post-operative setting is challenging due to patient comorbidities and relatively higher bleeding risk. PCI performance requires the mandatory use of adjunctive potent antithrombotic and antiplatelet therapies. There is no a single randomised controlled trial of therapeutic interventions for peri-operative myocardial infarction, despite randomised controlled trials for myocardial infarction dating back to the 1980s. Major bleeding especially in the nonaccess site has been consistently associated with poor short and long-term outcomes in multiple PCI dataset. Fibrinolytic drugs for ST-segment elevation myocardial infarction are likely to be contraindicated in the postoperative period because they pose an unacceptable risk of bleeding.[12]

The retrospective case controlled study by Foucrier et al.[13] comprised a total of 66 patients who suffered MINS after major vascular surgery. The authors analyzed the effect of starting a new or of increasing the dose of existing medications(antiplatelet drugs, β-blockers, ACE inhibitors, and statins) that are commonly prescribed to treat stable coronary artery disease according to established guideline recommendations for nonsurgical patients. The main finding of this study was that a long-term increase in adverse cardiovascular events (HR: 2.80; 95% CI, 1.05– 24.2; P = 0.04) was observed in patients with perioperative cTnI elevation when they did not receive evidence-based medical therapy for the treatment of coronary artery disease.[13]

The MANAGE (Management of Myocardial Injury after Noncardiac Surgery; NCT01661101) trial is randomized study including 1754patientsrandomly assigned to receive dabigatranor placebo.[14]Among patients who had MINS, dabigatran 110 mg twice daily lowered the risk of major vascular complications, with no significant increase in major bleeding.[14]

In our institution, we use similar strategies as in non-surgical patients, but adapt the application of antiplatelet drugs to the perioperative situation. For decision making concerning early invasive vs. conservative treatment of patients suffering from perioperative ACS, cTn levels are crucial. There is also no evidence to indicate whether a conservative medical therapeutic approach or an acutely invasive coronary approach is preferable for patients with stable and unstable peri- operative myocardial infarction. Both these approaches need to be prospectively investigated.

Conclusion

A multidisciplinary discussion about bleeding risk vs ischemic risk in patients with perioperative myocardial infarction is always appropriate to determine the best individual strategy.

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LOOK FROM INSIDE – THE NEUROMUSCULAR JUNCTION

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Neuromuscular junction (NMJ) is one of the most studied and best explained of all the synapses in the human body [1]. The neuromuscular junction consists of a presynaptic nerve terminal, the synaptic cleft, and post-synaptic nicotinic receptors (PNHR) on the muscle membrane.

Presynaptic part of NMJ: structure and function

Presynaptic nerve terminal consists of the terminal part of the motor neurone which originates from the ventral horn of the spinal cord. Synaptic vesicles (SV) are located in the nerve terminal, each of which contains 5000–10 000 molecules of the neurotransmitter acetylcholine (ACh) deposited. Neurotransmitter is packed together with the molecules of ATP (adenosine triphosphate) and proteoglycan in the vesicles, added to ions H^+, Mg^{2+} and Ca^{2+}. Molar ratio in the vesicles between ACh and ATP is in the range from 10:1 to 1:1 [2,3]. The arrival of the action potential at the nerve terminal results in opening of the voltage-gated calcium (Ca^{2+}) (P/Q and possibly N-type) channels. Increase in free Ca^{2+} within the nerve terminal initiates a train of events which result in mobilization, docking and release of their quanta of ACh into the synaptic cleft with trough formation of SNARE complex [4]. Three proteins, synaptobrevin, syntaxin, and synaptosome-associated protein SNAP-25, are involved in the attachment of ACh vesicles to the presynaptic cell membrane [5]. Neurotoxins produced by the anaerobic Gram-positive organism *Clostridium botulinum* target different proteins at the presynaptic region of the NMJ (e.g. toxin types A and E target the SNAP-25 protein of the SNARE complex), all cause failure of release of Ach from the terminal [6].

There is evidence that L-type calcium channels may also be present on the nerve terminals which could explain why the action of non-depolarizing NMBAs is prolonged by calcium channel blockers. The P-type calcium channels are blocked by cations such as magnesium, cadmium, and manganese and presence of antibodies to the calcium channels may cause muscle weakness. Lambert–Eaton myasthenic syndrome is a rare autoimmune condition, in which divalent IgG antibodies cross-link the presynaptic voltage-gated Ca^{2+} channels, disrupting the normal parallel architecture of the channels, and reducing the number of active zone complexes [7]. In absence of action potential SV`s are stuck in the filamentous linkage comprising of actin, synapsin and spectrine [8,9].

There are some new evidences that Schwann cells play an important role in nerve homeostasis by providing stability and secreting growth and trophic factors. During re-innervation, for instance, after crush injury, Schwann cells control the number of NMJs by the interaction with the immune molecules, major histocompatibility Class [1a] present in motor neurons [6]. Also, now, there are strong evidences that presynaptic neuronal nicotinic receptors ($\alpha_3\beta_2$) act as a target for neuromuscular blocking agents (NMBAs) [5].

Synaptic cleft

Synaptic cleft is 50nm wide space which is located between nerve terminal and postsynaptic membrane. ACh diffuses through synaptic cleft in milliseconds after release from main nerve terminal. However, almost a half of total released ACh never reaches its goal on a postsynaptic membrane because it quickly decomposes to choline and acetate under the influence of acetylcholinesterase (ACHE), enzyme which is strategically located inside the synaptic cleft. Variants of AChE, lipoprotein receptor-related protein 4 (Lrp4), agrin, and several collagens including collagen Q (ColQ) interact in the cleft not only to enhance neuromuscular transmission but also to contribute to the pre patterning of muscles in respect of Ach receptors formation on the crests of the post-junctional folds. The basal lamina of the post-synaptic membrane is also made up of proteins which contribute to cell adhesion and aid neuromuscular signaling and the most important one molecule is muscle-specific tyrosine kinase (MuSK) [1,3,9].

MuSK association is essential to NMJ formation and triggers AChR clustering even before the nerve contacts the muscle during development. Its actions are regulated by ColQ. Patients with ColQ mutations develop congenital myasthenic syndrome with AChE deficiency [10].

Postsynaptic part

Post-junctional membrane consists of multiple folds with shoulders bearing the high-density clusters of AChR (10 000 receptors per µm.), and clefts containing voltage-gated sodium channels. The density is achieved by two mechanisms: anchoring the receptors through rapsyn and other critical muscle proteins into the post-synaptic membrane and selectively increasing expression of the genes coding for these receptors in the myofibril nuclei positioned near the synaptic site. This process is called 'synapse-specific transcription'.

It is known today that mammalian PNHR consists of 5 protein subunits, joined together so they create a cylinder which is prominent on the both sides of the postsynaptic

membrane. Each protein subunit is coded by a particular gene and each of them has different physical and chemical properties, including different molecular weight. Different PNHR subunits are marked with the Greek alphabet letters: α, β, γ, δ and ε. Alpha subunit is the first isolated protein molecule of the postsynaptic membrane. 9 different types of the α subunits (α1-α9), 4 different types of β subunits, and one subunit of γ, δ and ε each were revealed until today. However, every mature adult PNHR consists of the exact order of protein subunits: double α, and one β, γ, δ and ε subunit each ($2\alpha_1\beta_1\delta\varepsilon$). In the fetal stage, γ subunits are present instead of ε subunits ($2\alpha_1\beta_1\delta\gamma$). Expression regulation of humane γ and ε genes together with these receptor subunits` way exchanging is insufficiently explained today. Today, we know for sure that mRNA levels coded by γ and ε subunits exchange reciprocally immediately after birth. Complete exchange of γ PNHR gradually completes within the first 3 weeks of life, during the dynamic phase of synaptogenesis, respectively). Each receptor spreads transmembrane, on the both sides of postjunctional cellular membrane. A central tunnel, which denotes specific cationic channel, is formed by specific linking of protein subunits. M_2 helice of each subunit borders the inside of the cationic channel. Ionic channel is 4 nm in diameter at its widest spot at the entrance of the channel itself. After that, diameter gradually reduces below 0.7 nm around cellular membrane. Several specific proteins seem to have an important role in linking receptors themselves to the cytoskeleton, with rapsyn and agrin having the most important role [11-14].

Many central nervous system diseases (e.g. stroke, spinal cord injury, and multiple sclerosis) and peripheral nerve diseases (e.g. Guillain–Barre´ syndrome) result in a secondary up-regulation of PNHR because of a decrease in the exposure of the receptors to Ach [15]. Myasthenia gravis is the most common disorder affecting the PNHR. It is associated with an IgG antibody raised against the PNHR. The anti-PNHR antibodies reduce the number of effective receptors to approximately one-third of the normal number [15-17].

Conclusion

In this short narrative review, latest developments in our understanding of neuromuscular physiology have been labeled. Still, there are numerous so called “blind spots” even MNJ is very well described.

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UPDATE ON RESIDUAL NEUROMUSCULAR BLOCKADE

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For many decades, a TOF ratio of 0.7 has been considered to represent adequate neuromuscular recovery. This was mainly based on the observation that two parameters of pulmonary function, that is tidal volume and vital capacity, start to recover at a TOF ratio of 0.7 [1]. Although higher degrees of neuromuscular recovery are needed before they return to baseline, a TOF ratio of 0.7 was for a long time accepted as the minimum neuromuscular recovery. However, our understanding of the pathophysiologic consequences of residual paralysis has continuously improved over the last decades. The pathophysiological consequences are now better understood and it is now generally accepted that even small degrees of residual paralysis (i.e., a train-of-four ratio 0.7-0.9) may be clinically harmful [2]. As a consequence, any TOF ratio of less than 0.9 must be considered as residual paralysis and needs appropriated treatment.

Pathophysiological consequences of residual paralysis

- *Pulmonary muscles*: In the 1970s, researchers investigated the effects of residual paralysis on the respiratory muscle function in anesthetized patients [1]. They found that when the first response of the TOF (i.e. T1) at the adductor pollicis muscle is less than 10% of baseline, the patient has neuromuscular block induced apnea. Moreover, tachypnea and reduced respiratory volume are observed at a T1 response around 25% (corresponding to three responses to TOF stimulation). In addition, the investigators also found, that the tidal volume of spontaneously breathing g patients becomes adequate at a T1 response of at least 50% (corresponding to a TOF ratio of approximately 0.3). However, the impairment of forced vital capacity (FVC) from the effects of neuromuscular blockade still persists at these degrees of neuromuscular recovery. Return of FVC to baseline values only occurs at a TOF ratio of at least 0.8.
- *Pharyngeal function*: Eriksson et al evaluated pharyngeal function during partial neuromuscular blockade using video radiography and computerized pharyngeal manometry. They could demonstrate that the pharyngeal muscles have a particular sensitivity to the effects of neuromuscular blockade leading to an increased risk of pulmonary inhalation [3]. This risk persists even a small degrees of residual paralysis, i.e. a TOF ratio between 0.7 and 0.9.
- *Upper airway*: Inspiratory obstruction of the upper airway can occur in the presence of residual neuromuscular blockade. At a TOF ratio of 0.5, there is marked impairment of inspiratory flow around 50% of baseline and even at a TOF ratio ≥ 0.8, upper airway dysfunction persists as manifest by decreased peak inspiratory flow, impaired ability to swallow, diminished upper airway volume, and impaired function of the genioglossus muscle [4]. Thus impaired upper airway function with the risk of inspiratory upper airway obstruction persists even at minimal residual neuromuscular block.
- *Respiratory control*: The hypoxia-related increase in ventilation is mediated by chemoreceptors in the carotid body. Residual paralysis weakens this increase in ventilation and baseline values are not reached until recovery of the TOF ratio to 0.9 [5].

Incidence of residual paralysis

The extent of neuromuscular recovery at the end of an intervention depends not only of the pharmacological properties and the amount of the neuromuscular blocking agent (NMBA) administered, the duration of the intervention, gender, and co-existing diseases, but also on the anesthetic technique. Indeed, at the same NMBA dose and the same duration of anesthesia, residual paralysis occurs more frequently after volatile anesthesia than after intravenous anesthesia [6,7]. Moreover, the risk of residual paralysis after a single dose of a muscle relaxant is much greater, the shorter shorter the surgery. According to a meta)-analysis published by Naguib et the incidence of residual paralysis after an intermediate-acting NMBA was as high 41% [8].

Prevention of residual paralysis

Neuromuscular monitoring and reversal are key elements in the prevention of residual paralysis [9]. Neuromuscular blocking agents should never be used without appropriate monitoring, and reversal agents should always be used when sufficient neuromuscular recovery cannot be documented by objective monitoring.

- *Neuromuscular monitoring*: Simple nerve stimulators are not equipped with a readout, and allow only stimulation of the target nerve. The limitation of these devices is the determination of complete neuromuscular recovery, as from a TOF ratio > 0.4 no fade can b e detected with these devices. Applying DBVS rather than TOF allows to push the limits of detection from 0.4 to 0.6, but still the benchmark of 0.9 cannot be detected reliably with this devices [10].

Thus, they should not be considered as a diagnostic tool and whenever they are used, the indication for pharmacological reversal should be large. Quantitative nerve stimulators permit the anesthesiologist to objectively measure the muscle response [11]. Acceleromyography is most ofter applied and the TOF Scan is the latest device based on this technology.

- *Pharmacological reversal*: For several decades, the action of NMBA could only be antagonized by drugs which inhibit the acetyl-cholinesterase. Their use, however, has several pitfalls. Indeed, they are associated with muscarinic effects, may increase postoperative nausea and vomiting, and cannot antagonize deeper level of neuromuscular blockade (indeed, all 4 responses should be present before neostigmine-based reversal should be started). The most important limitation of these compounds is their slow and rather unpredictable onset of action, especially with an volatile anesthetic background [12]. The release of sugammadex expands the arsenal of drugs that the anesthesiologist can use to antagonize steroidal neuromuscular blockade. However, appropriate dosing is important when using this compounds, also. Therefor they should also, be used together with a nerve stimulator.

Current practice in Europe

However, the Popular study recently assessed current practice of neuromuscular management across Europe [13]. It gives a distressing snapshot of a hazardous practice [14]!

According to this survey, of 17150 patients exposed to NMBA around 10000 had no neuromuscular monitoring at all, and in approximately 12000 patients extubation was exclusively based on clinical signs. At the end of the day only 2839 patients of the 17150 had a documented TIOF ratio of at least 0.9 at the moment of extubation. Thus this study revealed an alarmingly high incidence of inappropriate neuromuscular management, a situation which is completely unacceptable and which compromise patients outcome.

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POST-ANAESTHESIA PULMONARY COMPLICATIONS AFTER USE OF MUSCLE RELAXANTS: A PROSPECTIVE MULTICENTRE OBSERVATIONAL STUDY (POPULAR)

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Please download the complete POPULAR material at my institution's webpage:
http://www.anaesth.med.tum.de/inhalt/Popular

Results from retrospective studies suggest that use of neuromuscular blocking agents during general anaesthesia may be linked to postoperative pulmonary complications. POPULAR is a prospective European multicentre non-interventional cohort study to evaluate if use of neuromuscular blocking agents is associated with postoperative pulmonary complications.

Data from 22,803 patients in 28 European countries receiving general anaesthesia were prospectively collected over a two-week period between July 2014 and April 2015. In addition to a chart review, each patient underwent postoperative physical examination within three days to detect adverse pulmonary events. Logistic regression analyses provided odds ratios (OR) [95% confidence intervals] and absolute risk reduction (ARR) adjusted for surgical factors and the patients' preoperative physical status.

Use of neuromuscular blocking agents was associated with an increased risk of postoperative pulmonary complications ($OR_{adj.}$ 1·86 [1·53–2·26], $ARR_{adj.}$ -4·4% [-5·5% – -3·2%]). Only 2·3% of high-risk surgical patients and those with adverse respiratory profiles were anaesthetized without neuromuscular blocking agents. The use of neuromuscular monitoring ($OR_{adj.}$ 1·31 [1·15–1·49], $ARR_{adj.}$ -2·6% [-3·9% – -1·4%]) and the administration of reversal agents ($OR_{adj.}$ 1·23 [1·07–1·41], $ARR_{adj.}$ -1·9% [-3·2% – -0·7%]) is not associated with a decreased risk of pulmonary complications. Neither the choice of sugammadex instead of neostigmine for reversal ($OR_{adj.}$ 0·93 [0·73–1·18], $ARR_{adj.}$ -0·3% [-2·4% – 1·5%]) nor extubation at a train-of-four ratio ≥ 0·9 ($OR_{adj.}$ 1·03 [0·82–1·31], $ARR_{adj.}$ -0·4% [-3·5% – 2·2%]) is associated with better pulmonary outcomes.

POPULAR demonstrates that use of neuromuscular blocking drugs per se is associated with an increased risk of postoperative pulmonary complications. Anaesthetists have to balance the potential benefits of neuromuscular blockade against the increased risk for postoperative pulmonary complications.

PREOXYGENATION: THIS UNKNOWN!

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As anesthesiologists taking care of airway management in our patients, we very often need apnea, as it is meaningful of the best possible condition for achieving control of the patients' airways.

On the other hand, apnea (and especially pharmacologically-induced apnea) represents a challenging moment for any anesthesiologist, a sustained worrying bracket between drugs administration and airway device correct placement.

Desaturation is a logarithmic process, so that moving from 100% to 90% takes much longer than moving from 70% to 30%, and anesthetic state does not influence the basal oxygen consumption of about 250ml/min of an average healthy individual.

Any mean to prevent desaturation is thus crucial in airway management, and it needs to be established on solid physiological bases.

Looking at the different lung compartments, functional residual capacity (FRC) is the most important one in perspective of oxygen storage. Breathing room air (oxygen 21%) , for an FRC volume ~2100 ml, we will be able to store 273ml of oxygen. Given the standard consumption, this will result in one minute of safe apnea time, after which desaturation will start.

Differently, if we saturate FRC in pure oxygen, the same volume FRC will contain 1638 ml of oxygen, that is around 6 minutes of safe apnea time in a healthy individual.

So, the first issue of any preoxygenation technique is administering 100% oxygen, with different techniques (tidal volume for 3 minutes, forced vital capacity for 1 minute and so on) but taking account of perfect interface contact and constant FiO_2 delivery. Any reduction in inspired oxygen will be immediately translated in dramatic reduction of safe apnea time, so it is also important to monitor pre-oxygenation effectiveness with End Tidal oxygen monitoring, targeting at 0.8-0.9 EtO_2.

Other respiratory parameters influencing preoxygenation are FRC integrity (reduced in obesity, pregnancy, childhood, lung pathology), time constants (depending on lung pathology) and alveolar ventilation.

On the other hand, oxygen needs to be transported to tissues, so we also have cardiovascular determinants of preoxygenation, including shunt, blood volume, cardiac output and oxygen consumption rate (VO_2). Intuitively, any condition affecting one or more of those factors will worsen or abolish pre-oxygenation effectiveness.

Preoxygenation has been claimed to determine a delay on esophageal intubation detection, due to slower saturation; nevertheless, we could consider this a false myth, as only reliable proof of correct intubation are direct visualization and detection of repeated and morphologically regular carbon dioxide traces on capnography.

Preoxygenation has also been claimed to increase oxidative stress and free radicals damage, which might be admissible for long time exposures, and has no proof of damage for short exposures such as preoxygenation. Not counting the real clinical benefit outweighting the potential risk.

Finally, preoxygenation has been claim to produce atelectasis; this is true, but physiology recalls us that we are talking about readsorption atelectasis, so the amount of lung parenchima "lost" by a well performed preoxygenation will be immediately recovered with short period of adequate lung recruitment.

As a conclusion, the clinical benefit of preoxygenation overwhelms any real or potential side effect, so preoxygenation should be performed in any patient and any setting providing adequate delivery method.

Obese patients and generally FRC-reduced patient will benefit only of a positive pressure preoxygenation, using CPAP and/or PSV with the purpose of recruiting FRC before saturating it in pure oxygen. Critically ill patient might need also this approach, or even adjuncts such as high-flow nasal cannulas as from the recent OPTI-NIV trial; in any case, these patients often benefit of adequate cardio-hemodynamic preparation, providing fluids/blodd pre-filling before airway instrumentation, or use of cardio-vaso-active drugs.

Position of the patient is also important, the head-elevated or beach-chair position being the best ones for preoxygenation, and they are mandatory to be performed in obese and FRC-reduced patients.

Preoxygenation should then be performed in all patients, for the sake of safety, always reminding the positive cost/benefit ratio, independently of possibility of difficult airway management.

An adequate oxygenation status will extend its benefits (or, oppositely, side effects) beyond the airway instrumentation phase, and needs to be continued peri-procedurally with adequate ventilation strategies, adequate preoxygenation before extubation and adequate oxygen administration and monitoring on the postoperative phases, taking care to reduce FiO2 to the lowest admittable accordingly to recent evidences on outcome and oxygen administration.

We cannot live in too much oxygen, we would probably *burn too fast* as Lavoisiers' candles; nevertheless, we can't survive without, so we need to find the optimal compromise with clinical care and physiology knowledge.

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NON-INVASIVE VENTILATION IN ACUTE AND CHRONIC RESPIRATORY FAILURE

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Noninvasive ventilation (NIV) or noninvasive positive pressure ventilation (NPPV) has become a very important part of the treatment of acute and chronic respiratory failure in and out of the intensive care unit (ICU), home settings and in emergency departments. Regarding the acute exacerbation of chronic obstructive pulmonary diseases (AECOPD) NIV is the respectable alternative to invasive mechanical ventilation (IMV) and according to the guidelines [1,2] it is the first therapy of choice for severe acute respiratory acidosis in this patients. Acute respiratory acidosis is defined as pH <7.35 and a PCO2 >6.5 kPa, which are the thresholds for using NIV, whether pH <7.25 There is no doubt about the effectiveness of using NIV in acute hypercapnic respiratory failure (AHRF) caused by AECOPD, but not in all hypercapnic respiratory failures caused by other diseases. Acute respiratory acidosis HRF is defined as pH <7.35 and a PCO2 >6.5 kPa persisting after initial standard medical and oxygen therapy and this values have been used as a threshold for considering the use of non-invasive ventilation. Addition of NPPV in AECOPD reduces mortality, need for ETI and length of hospital stay. More severe degrees of acidosis, such as pH<7.25, have been used as a threshold for considering the IMV.

Also, NIV is the first-choice ventilator pattern in patients with cardiogenic pulmonary oedema, in immunosuppressed patients with severe hypoxemic RF (preventing ventilator associated pneumonia) and in patients with chronic hypercapnic RF in after extubation period.

Acute hypoxemic, nonhypercapnic respiratory failure in patients whitout underlying chronic pulmonary diseases, as acute respiratory distress syndrome (ARDS) or pneumonia are the so called ''grey zone'' for implementing NIV in therapeutic protocols. Using the NIV in patients with ARDS was associated with improvement in oxygenation, but not with the reduced need for IMV or better outcomes. In Lung safe study [3] with 2,813 patients with ARDS, NIV was associated with higher ICU mortality in patients with a PaO2/FiO2 lower than 150 mm Hg. There are several reasons for lacking improvement regarding the gas exchange in this patients. First, applying the protective low tidal volume (TV) ventilation using the NIV in patients with ARDS is very difficult, because TV in not intubated patients is a result from airway pressure set by the ventilator and patient's respiratory drive generated respiratory muscle. Official ERS/ATS guidelines [1] for using NIV for acute RF do not recommend the use of NIV in this patients, especially if NIV is not provided by an experienced clinical team for preventing the late intubation in case of lack of improvement. In patients with severe ARDS (SARS), like in patients with pandemic influenza A H1N1 infections, NIV is also not clearly recommended due to the results of several RCTs with a high rate of NIV failure.

Between the indications for NIV which are still controversial is asthma exacerbation. The reasons could be explained with inhomogeneous obstruction of the airways and problems with respond to external PEEP (positive end-expiratory pressure). Patients with neuromuscular disorders has benefit from NIV, especially the patients with Duchenne muscular dystrophy myasthenia gravis or Guillain-Barré syndrome. In this patients NIV success depends on the simultaneous application of techniques for airway clearance and on the degree of bulbar paralysis [4].

Another very important place for using NIV is facilitation of weaning from mechanical ventilation. Cochrane systematic review [5] concluded that weaning with use of NIV, especially in patients with COPD or chronic hypercapnic respiratory failure was followed by reduces mortality risk, VAP incidence, risk of weaning failure and length of stay in the ICU. In patients with nonhypercapnic intubated patients the results are controversial [1].

In conclusion, NIV is one of the best therapeutic solutions in many cases with acute or chronic respiratory failure, but ,avoiding the ''fashion in medicine'', it has to be associated with the good back up e.g. without the team inexperience, poor interface tolerance, inefficient secretion clearance and patient–ventilator dyssynchronies.

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TECHNOLOGY DRIVEN CHANGES: LABOR ANALGESIA 2019 AND BEYOND

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Introduction

Technology changes have accelerated, yet the basics of giving birth have remained unchanged. How do we incorporate new technologies to improve patient safety, analgesia and the patient experience? We will examine some current trends and opportunities for improvement and change.

Obstetric Management

To tailor our anesthetic management we conduct the symphony of labor analgesia, which incorporates basic physiology, patient preference, dynamic course of labor, obstetrical practices and anesthetic drugs and techniques. The ARRIVE trial showed not just safety but a decrease in the cesarean rate with elective induction of healthy nulliparous women at 39 weeks compared to expectant management. [1] An increase number of elective inductions will increase occupancy on labor units for a longer period of time. Outpatient use of cervical ripening agents and techniques may offset this expected increase occupancy on labor units. Alternative delivery locations are also expected to increase and the push for lowering the cesarean rate to <22% for NTSV, and a >30% VBAC success rate is a goal of Healthy People 2030. Technology may allow women to track their labor and stay at home longer.

Patients are demanding and ACOG has suggested to use fewer medical interventions during labor. Non-pharmacologic pain management, continuous one-to-one emotional support, frequent position changes and a period of rest may be offered during the second stage, especially for nulliparous women with an epidural. [2]

Non-Pharmacologic techniques to help manage pain include continuous support (labor coach), aromatherapy, use of a water tub, and Virtual Reality distraction therapy. With an emphasis on the total patient experience, the evolution beyond patient satisfaction, priorities may change. Some have proposed eliminating an objective pain scale in favor of a 'coping scale'. Merely changing the 'conversation' from pain to coping implies some degree of pain is acceptable. While Virtual Reality is talked about in the media, the absolute value of pain scale reduction is limited. In a study of hospitalized non-obstetric patients, viewing a 3-dimental virtual reality decreased pain score 1.2 (10 point visual analog scale) while use of a 2-dimentional screen decreased pain scores 0.6. [3] Success has been higher using virtual reality as a distraction tool for pediatric patients receiving blood draws or intravenous.

Technology utilization

In 2017 about 25% of people in the United States had a wearable technology. Almost 4 billion Health apps were downloaded by people, although only 2% had significant market share (>500,000 downloads).Patient engagement will increase via use of personal devices, especially phone-based apps. Hospitals and practices are starting to use online educational tools and patient reminders. At least one hospital program is having great success using a phone app for Enhanced Recovery after Cesarean – by educating patients what to expect starting at 36 weeks, reminding NPO and carbohydrate load 2 hours prior to cesarean, and even tracking movement and pain medications in hospital and after discharge. We should embrace online education and patient tracking/interactions. This can yield current ongoing data to change patient-physician interactions. A universal digital platform provides opportunities to decrease health disparities by providing tools and education in the language and style of learning preferred by the learner. Digital health priorities may produce positive results with chronic disease management as well as wellness.

Continual monitoring

Monitoring fetal heart rate continuously after admission to a hospital labor ward is common, although no improvement in outcome has been shown. Maternal monitoring post labor epidural at best is intermittent, albeit more frequent in the short period following insertion and start of epidural labor analgesia. Yet, the technology now exists to have frequent continual monitoring post-labor epidural. These wireless devices can send information regarding blood pressure, pulse, oxygen saturation. We will be able to detect trends towards hypotension and high neuraxial block sooner, and with expected better outcomes. This data may feed into the electronic medical record and be part of a Maternal Obstetric Warning system, as suggested by many organizations including the NHS in UK and CMQCC.org among others. Systems currently exist for non-invasive measurement of cardiac output, systemic vascular resistance and stroke volume. This information may be helpful in performing goal directed fluid therapy/resuscitation. Artificial intelligence systems will help with earlier identification of problems using real time data to detect hemorrhage, hypertension and sepsis. [4] Point of Care Ultrasound has become easier with better quality images and portability. These devices may be helpful for placement of difficult neuraxial anesthetics. As well, I routinely use the basic FATE parasternal short axis view of the left ventricle to assess fluid volume and cardiac contractility in patients during hemorrhage or other episodes

of clinical deterioration or change. Individual monitoring devices for metabolism and glucose currently are on the market. We will be able to obtain metabolic, cardiovascular, behavior and compliance. Wearable devices will track patient movement and medications.

Simulation

Technology has improved for high fidelity simulation. All labor units should have practice drills and simulations for emergencies. Some suggest that virtual reality can enhance the simulation experience and improve training.

Quantitated blood loss

Estimated blood loss has a lower accuracy rate then desired, with underestimation of EBL by up to 50%. Quantitated blood loss has been mandated by CMQCC and other organizations. An alternative to weighing all the laps and sponges is a technology that uses internet-based platform to calculate the hemoglobin on the laps and in the cannister, improving accuracy and removing disagreements over the EBL.

Anesthetic management

While standardization of medical care improves outcomes, we also strive to individualize anesthetic analgesia to changing preferences during labor. Every woman's labor is different, with individual sensitivity to medications, labor patterns, oxytocin administration, position of the fetal head and obstetric preferences for second stage of labor pushing. We can incorporate information regarding a patient's desire for degree of pain relief with simple screening questions regarding their expected sensitivity to pain. We can use genetic and pharmacogenetic information about variations in metabolism, and how that will affect medication dosing and requirements. Knowledge of individuals'' CYP2D6 polymorphism will help guide individualization of medication choice and dosage. If the culture around labor analgesia shifts from pain relief to coping – the degree of analgesia we need to deliver will differ.

Time efficiency

Physicians spend up to 25% of their time entering data into the electronic medical record. As Artificial Intelligence and voice translation improves, expect being able to dictate your notes and easing the burden of electronic medical records.

Pain

While the trend may be shifting away from complete pain relief, we must keep in mind the linkage between severe pain day one after delivery has been associated with increased risk for chronic pain and post-partum depression.[5] An artificial intelligence system has been developed to read facial expressions to detect pain levels. Perhaps in the near future we can utilize facial expression of pain to guide the degree of labor analgesia.

Opioid epidemic

More people have become chronic users of opioids, with a corresponding increase in opioid overdose deaths in the United States. The death rate from opioid overdose in the United States has vastly increased due to traditional non-prescriptionopioid 'street drugs' being diluted with cheap fentanyl (illegally imported from Mexico) or fentanyl derivatives (imported from China).

Perhaps we will shift towards the opioid-free delivery and opioid free cesarean. Opioids prescribed during pregnancy occur from 9.5-42% in the united states[6]; the veterans system reports a 10% opioid prescription rate during pregnancy[7]. With 20-25% of women having vaginal delivery receiving opioids in the 24 hours prior to discharge,[8] 12% filling opioid prescriptions after discharge and 1.6% filling a second opioid prescription[9], opioids as routine therapy will need to be altered.

The mainstay of labor epidural analgesia has been dilute local anesthetic combined with opioid. Perhaps we will use opiate-less epidural infusions or ligand-biased opioids. Acute tolerance to opioid develops very quickly. At Cedars-Sinai Medical Center in Los Angeles our most common labor epidural infusion is ropivacaine 0.12-0.15% without narcotic (N=10,000+). If motor block builds up over time, the infusion is turned off for 30-60 minutes and restarted.

The Society of Obstetric Anesthesia and Perinatology is releasing an Enhanced Recovery after Cesarean document around May 2019; consideration is being made for a similar document for vaginal delivery.

Ligand biased opioids

Ligand specific opioids are in development which target the G-protein subunit of the mu-opioid receptor. Oliceridine is one such molecularly designed opioid that produces analgesia by activating the G-protein while not stimulating the Beta-arrestin protein that increases adverse effects and downregulates the mu-opioid receptor.[10] The beta-arrestin protein starts to downregulate the mu receptor and affect acute short-term tolerance in less than an hour.

Conclusion

Technology, patient expectations and improved outcomes will drive changes in labor analgesia in 2019 and beyond. Artificial intelligence will guide monitoring, we will have continual data, patient centric adjustments of medications. The future remains bright and interesting.

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DURAL PUNCTURE EPIDURAL (DPE) – A NOVEL TECHNIQUE FOR LABOR ANALGESIA

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Introduction

Dural puncture epidural (DPE) represents a technical modification of the combined spinal-epidural anesthesia (CSE), considering intentional perforation of the dura using a Whitacre spinal needle. Unlike CSE technique, direct administration of medications into the subarachnoid space is not performed in this method. A hole made with spinal needle enables translocation of epidural drugs from the epidural to the subarachnoid space. Following insertion of the epidural catheter and administration of medications into the epidural space, it is expected that some amount of local anesthetic solution diffuse into subarachnoid space. The extent of drugs reaching the subarachnoid space is different regarding the size of the dural puncture, the distance between the puncture location and epidural drug administration and the pressure gradient between the two compartments. Some other factors may influence diffusion of the local anesthetic solution, such as its volume and concentration and pressure in epidural space, provided by epidural bolus.

DPE technique was originally described by Suzuki et al.[1] There was no report earlier, evaluating the effect of dural puncture on the spread of epidural anesthesia with a spinal needle without injection of local anesthetic into the subarachnoid space. Study was based on the facts that after inadvertent dural puncture with epidural needle, inflow of contrast medium is possible from the epidural to the subarachnoid space and it was confirmed radiologically. The mechanism seems to be due to the translocation of epidural medications through a dural puncture. In this study, dural puncture with a 26-G Whitacre spinal needle resulted in faster onset and improved sacral spread after 18 mL of 2% mepivacaine for knee arthroscopy. No alterations in cephalad level of anesthesia were observed.

These results have been promising regarding labor analgesia, because of need for excellent sacral spread of local anesthetic solution in advanced labor. Thomas et al.[2] attempted to repeat findings of Suzuki et al. in a group of parturients of mixed parity, using DPE technique for labor analgesia, but without success. This prospective, double-blind, randomized study was designed to examine whether the combined spinal-epidural technique without subarachnoid drug administration may improve epidural catheter function when compared with the traditional epidural technique.

Authors found no significant differences when dural puncture with a 27-G Whitacre needle preceded an epidural dose of 10 mL of lidocaine 2% followed by infusion of bupivacaine 0.1% + fentanyl 2 μg/mL (PCEA - Patient controlled epidural analgesia).

Quality of labor epidural analgesia (inadequate, unilateral, sacral sparing, or number of top-up doses required) or catheter manipulation or replacement rates were similar in both groups (epidural and DPE).

To date, need for additional dural puncture without application of spinal analgesia is still debatable in obstetric anesthesia, regarding type of spinal needle, onset on analgesia, quality of analgesia and side effects (e.g. hemodynamic instability, foetal bradycardia, pruritus).

Type of spinal needle

Three years later, Cappiello et al.[3] hypothesized that size of the spinal needle is important factor which can improve quality of DPE labor analgesia in comparison to classical epidural analgesia (EA). After performing dural puncture with 25G pencil point needle, authors observed improvement in sacral spread, onset and bilateral pain relief produced by epidural bupivacaine in nullipara patients. These findings were consistent with in vitro studies, which investigated permeability of intact and perforated dura in monkeys.[4] An *in vitro* study of cadaver dura found that lidocaine flux through dura punctured with a 27-G Whitacre spinal needle was not significantly greater than through intact dural tissue, but dural puncture with a 24-G Sprotte spinal needle was associated with increased flux. Capiello et al. stated that type and concentration of local anesthetic solution play significant role in quality of analgesia and onset time. They administered loading epidural dose of 12 mL of bupivacaine 0.25% over 5 min through the catheter.

On the contrary, recent study of Yadav et al.[5] showed superiority of DPE labor analgesia over EA using 27G Whitacre spinal needle provided with CSE kit. Onset of adequate analgesia was significantly faster in DE group (11.00 ± 3.86 min Vs. 13.33 ± 2.39 min; $p < 0.05$).

According to all mentioned above, the kinetics of local anesthetic passage through a dural hole, as well as the necessary hole proximity and drug dose, concentration and volume, required to make significant clinical difference requires further investigation.

Onset of analgesia, quality of analgesia

There are differing views regarding superiority of DPE technique over conventional epidural technique for labor analgesia. Cappiello et al.[3] were the first who published advantages of DPE.

In this investigation, an improvement in the onset of labor analgesia was observed, as well as the higher inci-

dence of an S1 sensory block (the majority bilateral). Authors presumed that these qualities, particularly the relatively rapid (within an average of 25 min) onset of sacral analgesia, with no changes in the cephalad level, would be potentially beneficial effects of the DPE technique, particularly in the second stage of labor. Otherwise, after initiation of analgesia, local anesthetic requirements (number of boluses per hour for the first 3 h) did not differ between groups. Flux through a 25 G dural puncture may therefore be limited to a certain amount of time after the puncture or dependent on the volume or epidural pressure generated with epidural medication boluses. The low incidence of PDPH after a 25 G Whitacre needle dural puncture would suggest that CSF flux is a time-limited phenomenon.

Thomas et al.[2] and Gupta et al.[6] in their studies showed that DPE technique did not provide superior labor analgesia when compared with a traditional epidural technique, but Cappiello et al.[3] suggested that DPE technique might benefit parturient by improving sacral spread.

Study of Yadav et al.[5] showed that number of parturients achieving adequate analgesia in 5 min and 10 min was significantly higher in group DPE than in group EA ($p < 0.05$). Quality of analgesia was excellent in all parturients from DPE group, while in EA group analgesia was excellent in 86.7% parturients. Overall, mean NPRS (numeric pain rating score) for assessing the quality of analgesia, was significantly higher (3.0) in group DPE than in group EA (2.87 ± 0.35, $p < 0.05$). No difference in mean time to request for first topup dose was noted.

In recent study Chau et al.[7] compared CSE, DPE and EA techniques. Analgesia onset was most rapid with CSE with no difference between DPE and EA techniques. The DPE technique has improved block quality over the EA technique with fewer maternal and fetal side effects than the CSE technique for parturients requesting early labor analgesia. Findings of Chau et al. have been criticized by some obstetric anesthesia experts, because of defining the onset of analgesia as time until verbal numeric pain score ≤1. [8] Explanation was that onset of anesthesia was difficult to assess in early labor. Furthermore, they commented on inappropriate randomization among groups. Women in the EA group may have had more painful and longer labors, suggested by higher cesarean delivery rate (27%). That is 5.5-fold higher than in the CSE group (5%), and nearly 3-fold higher than in the DPE group (10%).

Side effects

It was previously speculated that CSE analgesia induced uterine tachysystole (excessively frequent uterine contractions) by the rapid onset of analgesia attributable to the spinal component of technique.[9] Consequently, the plasma concentration of epinephrine, a hormone with tocolytic effects, is rapidly decreased, and this may result in an increase in uterine tone. Uterine tachysystole may worsen uterine vascular resistance and subsequently reduces fetal oxygenation, leading to nonreassuring fetal heart rate (FHR) tracings. A DPE compared to CSE technique may minimize exposure to intrathecal opioids, which are frequently used as sole or adjuvant drugs in the initiation of CSE analgesia and may be associated with fetal heart rate abnormalities in a dose-related manner.[3] DPE is not associated with high incidence of pruritus and hypotension in comparison to CSE labor analgesia.

Comparison of standard epidural or CSE versus DPE technique is summarized in table 1.

Table 1.	Standard		Novel
	EA	CSE	DPE
Onset of analgesia	Slowest	Fastest	Modest
Spread of analgesia	Modest	Better	Better
Catheter reposition	Highest	Medium	Lowest
Block quality	Modest	Better	Better
Physician top-up	Modest	Earlier	Fewer
Maternal side effects	Fewer	Higher	Fewer
Uterine hypertonus	Less	Greatest	Less

Conclusions

Possible advantages of dural puncture epidural (DPE) are faster onset of labour analgesia giving a better quality, reliable, and consistent block compared with the epidural technique. Greater sacral spread and block symmetry have been observed in obstetric patients receiving the DPE technique, compared to EA technique. Onset of labor analgesia should follow this order: CSE > DPE > EPL techniques. In comparison with CSE, DPE technique has less maternal and foetal side effects, but further investigation is warranted.

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ANESTHESIA FOR CESAREAN DELIVERY: „NO NEED TO ARGUE“?

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Cesarean delivery (CD) is the most common operating room procedure in women (1.22 million hospital stays in 2011). American Society of Anesthesiologists (ASA) and the Society for Obstetric Anesthesia and Perinatology (SOAP) recommended selecting neuraxial techniques in preference to general anesthesia for most cesarean deliveries[1]. In developed countries, the majority of cesarean deliveries are performed with neuraxial anesthesia (spinal, epidural and combined spinal-epidural). Generally, anesthesia for cesarean delivery is getting safer since anesthetic-related maternal mortality decreased by nearly 60% when data from 1979-1990 were compared with the data from 1991-2002. On the whole, regional anesthesia is safer than general anesthesia, but the resulting risk ratio between the two techniques is changing in different periods: from 2.3 (1979-1985) to 16.7 (1985-1990) to 1.7 (1997-2002)[2].

Besides safety, regional anesthesia has some other advantages over general anesthesia. Neuraxial administration of hydrophilic opioids (morphine) is the basics of quality postoperative analgesia for CD, and as a part of multimodal analgesia with „around the clock“ NSAIDs and/or paracetamol is the gold standard for postcesarean delivery pain[3]. Neuraxial anesthesia in CD enables skin to skin contact (SSC) at birth or the placing of the naked newly born baby prone on the mother’s bare chest at birth or soon afterward. SSC is a significant part of the transition from intrauterine to extrauterine life; it improves breastfeeding, SSC infants have higher stability of the cardio-respiratory system (SCRIP) scores[4]; SSC has a neurobehavioral benefit and positive parenting impact that could be evident even after a decade. SSC, also known as Kangaroo mother care can reduce morbidity and mortality in low birthweight infants.

Based on all of the above, it can be assumed that regional anesthesia can contribute to patient satisfaction. At Clinical Center Niš in the last few years, there has been an increase in the number of CD with neuraxial anesthesia (26, 18 % in 2016, 49% in 2017, and 67, 61% in 2018). This led to the fact that in this period there was a significant number of women in whom one or more previous CD was performed with general anesthesia and the last one with neuraxial anesthesia. According to the unpublished, ongoing survey, when asked what kind of anesthesia they would choose in the case of next CD, 89, 5% of 200 women answered that they would choose regional anesthesia, and 7, 3% would choose general anesthesia.

Although safety general anesthesia has been improved in past two decades[5], due to postoperative analgesia, the possibility of „skin to skin” contact and probably improved mother satisfaction neuraxial blocks are still the anesthesia of choice for Cesarean delivery.

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ECO-SUSTAINABLE ANESTHESIA: WHERE WE ARE AND WHAT COULD WE DO

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When thinking of the *greenhouse effect* most of people would immediately address their thought to environmental pollution, to industrial revolution, to vehicular traffic and Freon gases and dangerous sprays.

But how many people would ever think of Anesthesia as a contributing element to such a phenomenon? Less than expected, for sure, most of anesthesiologists being the first to ignore the ecological impact of their daily activity.

Global warming is the gradual increase of the earth's surface temperature due to cumulative impact of *greenhouse* gases in the environment (the so-called *Greenhouse Effect*). Greenhouse gases are compounds that have a significant atmospheric lifetime, and possess infrared absorption bands that overlap with the outgoing radiation from the earth's lower atmosphere. Gases that absorb strongly in the atmospheric window, (spectral region between approximately 714 and 1250 cm^{-1} in the earth's infrared emission spectrum) where absorption by the naturally occurring greenhouse gases is relatively minor, are particularly effective at affecting the earth's radiative balance. CO2 represents 80% of greenhouse gas in Industrialized Countries, where 25 billions tons of CO2 are annually released in atmosphere. Chloro-Fluoro-Carbures (CFC) are the only antropic/non-natural greenhouse gases, with a significant greenhouse effect, and the large family of CFC also includes anesthetic vapors.

Interestingly, the Montreal Protocol (1987) banned CFC use for civil and other purposes, and the subsequent Kyoto Protocol (1997) determined a gas emissions limitation under the protocol for CO_2, nitrous oxide, methane and sulphahexa-fluoride, HFCs, and perfluorocarbons (PFCs, only contain carbon and fluorine) with significant reduction targets for 2012, 2020 and 2050.

On the other hand, hospitals, which should represent the mission of healing, turn into a source of sickness, contributing to greenhouse effect in different terms:

- Direct energy absorption (lighting, heating and conditioning, food preparation, waist elimination, and so on)
- Indirect contribution to sour rain, greenhouse gases, smog and air pollution, O_3 depletion and introduction of air cancerogen agents in the atmosphere.

The contribution of Anesthesia is not insignificant: in our daily practice, we can interfere with planetary well-being on different levels: we use and release anesthetic vapors in the atmosphere, we produce a large medication waste, we consume energy, we produce contaminants and waste with either disposable and reusable devices.

For example, choosing our anesthetic inhalational agent, we don't have perception that we variably contribute to global warming and ozone layer depletion. Ozone layer is in the lower stratosphere, being composed of Ozone molecules (O_3) and approximately 10 km thick; it works as a barrier absorbing 97-99% of the UV radiation. Many gases and chemical products do interphere with ozone layer depletion; unexpectedly, between them, also anesthetic vapors. Isoflurane produces chlorine-mediated catalytic destruction of stratospheric ozone, while atmospheric oxidation of desflurane and sevoflurane does result in the formation of CF_3 radicals, which add O_2 to give CF_3O_2 radicals followed by reaction with nitric oxide to give CF_3O radicals. The chlorine-containing isoflurane, enflurane, and halothane, with the latter also containing a bromine substituent in addition to chlorine, are all ozone-depleting substances. This is of some concern mostly with halothane, as it is only in significant use in some developing countries.

On the other hand, total intravenous anesthesia is not *tout court* a viable alternative, as propofol, for example, is known to be a powerful environmental polluting agent, tipically largely consumed and equally largely wasted. Some studies showed that simply offering different volume vials might reduce the waste and indirectly reduce environmental pollution, as propofol should be incinerated at 1000 degrees to abolish its chemical environmental impact.

Drug waste is known also for other medications, including atropine or adrenaline loaded in syringe for case of emergency and normally largely unused; some viable alternatives come from the recent introduction on the market of pre-filled syringes with larger storage interval and larger multiple use potential.

It is nowadays clear that reducing the impact of Anesthesia on climatic change is possible through adoption of different (easy) behaviors: we can't do unless of anesthetic medications and devices, so we need to optimize the cost/benefit ratio and to introduce accessory behaviors to minimize their environmental impact. A series of (apparently unrelated) behaviors might include:

- prescribing antibiotics according to local guidelines;
- reducing variation in practice and optimizing treatments or procedures;
- encouraging consumption of less alcohol, meat, and promoting exercise;
- working with an organisation's quality improvement team to accelerate the adoption of lean working practices;
- avoiding the use of intravenous drugs when possible, (carbon footprint);
- reducing, reusing, recycling, and disposing of waste correctly;

- collaborating with others towards the common purchasing of bulky or high-volume items to reduce transport emissions;
- encouraging patients to take responsibility for their own health;
- discussing resuscitation decisions with the patient at an early stage, to ensure that resources are not used to provide unwanted treatment;
- use of low flow anesthesia and promotion of anesthetic vapor re-use;
- improving teamwork and life-cycle assessment based decisional processes.

As anesthesiologists, we are also called to understand the *cradle-to-grave* process behind any medication, device or tool that we use, that is evaluating the entire life-cycle including costs and resources from preparation to wasting, addressing our choices also in this perspective. Some devices, due to materials needed for preparation and packaging and for processes and resources needed for wasting need to be correctly evaluated in terms of clinical benefit and life-cycle, so that we might find out that reusable laryngeal masks might be more beneficial of disposable ones (given same performance) in terms of environmental impact, and same conclusion was reached also for reusable laryngoscopes compared with disposable ones. Oppositely, pre-packed central venous lines kit seem to be better performing, environmentally speaking, if compared with hospital-arranged operative kits. Furtherly, medical textiles choice is not clearly addressed by research, whereas the battle between disposable and reusable airway endoscopes seems to end up in a draw.

It is clear that there is large space for research and for improvement of our understandings and behaviors, the most important piece of the puzzle being sensibilization of anesthesiologist's population to the problem of environmental impact of our daily practice, including the culture of recycling, and pushing in the direction that we need to take care not only of our patients, but of the whole planet hosting them (and us).

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GUIDELINES ON PERIOPERATIVE USE OF ULTRASOUND-GUIDANCE (PERSEUS) FROM THE EUROPEAN SOCIETY OF ANAESTHESIOLOGY

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The use of point-of-care ultrasound (POCUS) is now considered common practice and standard of care for diagnosis and treatment in many areas of medicine. The application of POCUS in anesthesiology is nowadays frequently used in vascular access placement and in regional anesthesia not only when the landmark technique is failing. Previous guidelines and recommendations from other scientific societies have been presented in the past years with different conclusions on the use of ultrasound-guidance (USG). Some of them considered USG as primary choice when patients present clear difficulties as lack of landmarks (e.g. obese and children) or when the risk of developing life-threatening complications is high (e.g. thrombocytopenic patients) while other guidelines recommend USG only if available. The aim of these new guidelines is to focus on the mainly common procedures performed in the operating rooms: vascular access placement and nerve/neuraxial blocks. The guideline has been developed according the GRADE/RAND methodology and it will provide recommendations also on how to train and provide certificates of proficiency on how to perform ultrasound-guided vascular procedures and nerve blocks. The guideline should be used to develop national recommendations or local standard operating procedures on the use of ultrasound-guidance.

DIVERSITY IN EDUCATION: THE HEART OF THE SURGICAL OUTCOME DIFFERENCES AND PERIOPERATIVE SAFETY

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Efficacy of any medical and surgical program are influenced by various factors and often hidden within the numbers and "snowed under" obvious statistical data. Assessment of surgical outcome is difficult and implementing of high standards in surgical practice is very hard to measure thru its final outcome. Complications of surgery and deterioration of general medical condition may be much delayed, and follow-up of patients is limited and potentially biased. [1]

Perioperative clinicians and researchers: surgeons, obstetricians, anaesthesiologists, intensivists and the number of epidemiologists and public health experts are traying to develop strategy to transform research into practice, to address disparities in access and outcomes in perioperative, surgical care. Collaboration, together with strategically guided population-based research and clinical practice, may allow the perioperative healthcare team of the future to implement strategies to achieve health equity, an important dimension of quality, in surgical fields. [2]

There is a global need to detect structural measure that can show characteristics of efficient surgical and medical health care service. Number of procedures is the most often used variable illustrating surgical volume. Often, quality is analyzed in correlation of high procedure volume and improved long-term survival. Hospital resources and organization as well as manpower planning strategy certainly have significant impact. Level of training, the organization of hospital personnel, the availability of up-to-date technology and financial resources are structural components that should be focused on. [3]

A number of scoring systems and identification of risk factors are often included: American Society of Anesthesiologists Physical Status classification, urgency of surgery, high-risk surgical procedures (gastrointestinal, thoracic, vascular), surgical severity, cancer dissemination and age. [4]

Burning issues of the global manpower problem in anaesthesioliogy, surgery and intensive medicine professionals are recently documented. Significant part of the solution may be systematic approach to education. Massive disparities in the number of anesthesia and other healthcare providers, with particularly low workforce density in low- and middle-income countries are detected. The Lancet Commission on Global Surgery (LCoGS) estimated that there will need to be a doubling of the specialist physician surgical workforce (SAO providers: surgeons, anesthesiologists and obstetricians) in order to achieve UHC by 2030. [5] The WFSA Global Anesthesia Workforce Survey found that 43 countries worldwide had a physician anaesthesia provider (PAP) density of less than 1 per 100,000 population compared to around 20 per 100,000 in many high-income countries (HICs). 77 countries had a PAP density of less than 5 per 100,000 population. When non-physician anaesthesia providers (NPAPs) were included in the analysis, 70 countries still had a density of less than 5 per 100,000. The survey estimated that over 136,000 additional PAPs would need to be trained at 2016 population levels to achieve a modest workforce density of 5 per 100,000 worldwide. [6]

In 2015, the World Health Assembly accepted Resolution 68.15 which calls on member states to strengthen anesthesia and surgical care and encourages the development of appropriate core competencies that are part of relevant health curricula, training and education. [7] Main concern are at the inadequate training of the surgical workforce and suggests member states to promote emergency and essential surgery and anaesthesia capacity as components integral to achieving universal health coverage (UHC). The resolution goes on to ask the World Health Organisation (WHO) to support member states "to devise policies and strategies that enhance the skills of the appropriate health workforce for emergency and essential surgical care and anaesthesia, especially at primary health care and first-referral hospital levels".

The WFSA has an official liaison role with the WHO. Recently, the leadership of the WFSA initiated larger mission to increase access to safe anesthesia services worldwide. Substantial efforts have been invested in basic drafted document that will provide a framework, as well as a tool that anesthesiologists around the world can use to expand the number of training programs while ensuring high-quality education and safe care.

To increase the awareness of burning patient's safety issues of manpower problem and compromised level of training, together with anaesthesia provision by insufficiently trained hospital personal in some parts of the world, WFSA Council member and the past president of the Nigerian society of anaesthesiologists, professor Bisola Onajin-Obembe said: "Surgery is as strong as the weakest link, anaesthesia manpower. It is not a competition. If surgeons realize the importance of anaesthesia and perioperative care and the need for physician anaesthetists, they will promote the scaling up of anaesthesia practice instead of looking to replace physicians with whoever they think will serve their purpose".

Education must be at the heart of our global response. Increased numbers of safe anesthesia providers and intensive medicine professionals will only be pos-

sible if we have good quality educational programs tailored to meet the growing needs. The final result would be better patient care. [8]

As a part of the global efforts, 'A Global Anesthesia Training Framework' is initiated earlier and accepted by the WFSA leadership in April 2018. There are numerous pathways for anesthesia provider training and there has been considerable discussion regarding the best categorization of training programs for the purpose of this framework. Preliminary proposed categorization is in alphabetical order: A, B and C. Category A corresponds to a minimum level of training, category B corresponds to an intermediate level of training and category C corresponds to a higher level of training consistent with existing specialist anesthesiologist training programs. The categories are defined by competencies rather than specific provider type. Intention was to generate discussion and serve as a structure for ongoing work and consultation. [9]

Several other global educational effort are still in a draft and preliminary application status:

'The Anaesthesia Patient Safety Curriculum', is a project proposed by the WFSA Safety and Quality of Practice Committee and WFSA Education Committee. Objectives of the program would be: to apply theories to promote patient safety, enhance quality care, and improve anesthesia practice; to communicate effectively with patients, families, healthcare professionals and public; and to demonstrate leadership skills to meet the challenges of increasingly complex health care and educational environments impacting anesthesiologists.

'Strategy for WFSA fellowship Monitoring, Evaluation and Learning (MEL)'. WFSA Education Committee and Subcommittee for Monitoring and Evaluation are developing model of monitoring and evaluation of our own educational efforts thru Fellowships developed in partnership with National societies, universities and teaching hospitals globally. Didactically we are proposing 5 levels of a fellowship's potential impact to increase capacity for specialized anesthesia care in the fellow's home country. Anticipated provision of high-quality teaching will facilitate the learning of new knowledge, skills and attitudes (KSA). Higher levels can potentially be obtained once the fellow returns to his home country and often will require mentorship and guidance from the fellowship program. There may be many obstacles for transferring the newly acquired KSAs to the home environment. A comprehensive support structure and evaluation process should be in place to better identify these barriers as well as methods for overcoming them.

Finally, we are still looking for the measure based on socio-economic, demographic, geographical and clinical factors associated with access to quality surgical care. In last several years, international research groups have been focused on patient safety and published results that promote careful impact assessment in surgery.

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EXTRACORPOREAL ORGAN SUPPORT AS A TOOL IN CLINICAL STRATEGY FOR CARDIORESPIRATORY FAILURE

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Concept of extracorporeal organ support for treatment of cardiorespiratory failure

Cardiorespiratory failure is a top challenge for any intensivist, hence the clinical strategy for its treatment is of particular importance. If it is accepted that extracorporeal organ support (ECOS) for cardiopulmonary failure should be a temporary support tool, then the indications will be significantly expanded, and the timing for its initiation significantly reduced. The development and evaluation of novel therapies for support of failing organ systems are closely related to the Extracorporeal Life Support Organization (ELSO) mission, which aim is to maintain a registry of, at least, use of extracorporeal membrane oxygenation (ECMO) in active ELSO centers.

Venovenous extracorporeal membrane oxygenation (V-V ECMO) and extracorporeal carbon dioxide removal ($ECCO_2R$) for respiratory failure, venoarterial (V-A) ECMO, ventricular assist devices (VAD) and total artificial heart for cardiac failure, are useful and life-saving extracorporeal therapeutic options for both pulmonary and cardiac support in patients at high risk of mortality. They have their own historical background with their light and moderate periods with modern returns to the therapeutic scene. There is still a lack of randomized studies that will confirm their effects on the outcome, and controversial exists because of varying interpretation of the available evidence, but it is certainly that VV-ECMO has benefit for acute respiratory distress syndrome.

V-V ECMO for hypoxemia

V-V ECMO is usually used in severe acute respiratory failure. This technique oxygenates blood outside the body, obviating the need for gas exchange in the lungs, and, if necessary, provides cardiovascular support. In the treatment of severe acute respiratory distress syndrome (ARDS), ECMO was used as rescue therapy as final of the previous ones, prone position, recruitment maneuvers, inhaled nitric oxide and high frequency oscillatory ventilation [1]. However, the impact of these therapies on mortality remained unproven till recent clinical trial published in New England Journal of Medicine which showed that compared with conventional mechanical ventilation, use of V-V ECMO in adults with ARDS was associated with reduced 60-day mortality [2]. Hence, it would be reasonable to accept that V-V ECMO can be used for correction of hypoxemia refractory to lung-protective ventilation and prone position in patients with ARDS. Nowadays, ECMO is increasingly used as a useful tool for bridging to lung transplantation in patients with terminal chronic obstructive pulmonary disease or cystic fibrosis. It should be noted that the tendency is that these patients have to stay awake and spontaneously breathing without being intubated. The concept of resting the lungs to enabling protective lung ventilation involves the use of an $ECCO_2R$ technique which only removes CO_2, and although it does not oxygenate the blood, it still maintains oxygenation. It is interesting that the concept of resting the lungs is accepted even before the concepts of atelectotrauma and baby lung [3]. Furthermore, patients with acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease (COPD) are at risk of failing noninvasive ventilation. $ECCO_2R$ added to noninvasive ventilation improves outcome and decrease the need for intubation [4].

Although ECMO in this matter is inaccurately referred to as "protective" ventilation, it could be considered as "least-damaging lung ventilation" [5]. In addition, it should be considered that patients with severe acute respiratory failure should be examined for a potential mobile V-V ECMO until their transport to a larger specialized center [6].

Venoatrial ECMO as part of ECOS

Despite the technical progress in coronary revascularization, cardiogenic shock as a complication of acute myocardial infarction with ST elevation (STEMI), remains an unresolved medical challenge. To minimize circulatory effects of catecholamine, transition to mechanical circulatory assist (MCS) devices seems justified. The goals of MCS are to fill the insufficient heart and to help maintain blood flow to vital organs and to improve cardiac function while waiting solving the cause of cardiogenic shock. Devices for mechanical support (MCS) are used for partial or complete replacement of left ventricular function (LVAD), right ventricular (RVAD) or both ventricles (BiVAD) and might be combined with ECMO. VAD for few days or weeks is used for urgent support in acute etiology when waiting for resolving the cause of cardiogenic shock, while VAD for few months or years is surgical implanted. According to the ESC guidelines for the diagnosis and treatment of acute and chronic heart failure from 2016, at the patient with refractory shock due to myocardial infarct or myocarditis, after cardiac surgery and in the case of refractory cardiac arrest, ECOS and V-A ECMO may be used to support patients with left or biventricular failure until cardiac and other organ function have recovered [7]. MCS devices and ECMO, can be used as a 'bridge to decision' in patients with acute and

rapidly deteriorating heart failure or cardiogenic shock to stabilize haemodynamics, recover end-organ function and allow for a full clinical evaluation for the possibility of either heart transplant or a more durable MCS devicce[8]. V-A ECMO is temporary circulatory support for failing lungs and failing heart in cardiogenic shock[9]. Unless the decision for the best treatment, V-A ECMO allows stabilization of the patient by perfusing vital organs with oxygenated blood. The concept of the percutaneous ECMO system is a modified heart-lung machine that mainly consists of a centrifugal pump, a heat exchanger and a membrane oxygenator. ECMO can provide hemodynamic support and reduce the preload of left ventricle, also to increase left ventricular afterload and thus increasing oxygen demand and providing myocardial protection. Nowadays, promising results are published for the application of ECMO in massive pulmonary embolism, characterized by severe shock, inadequate perfusion, high lactate levels and cardiac arrest. ECMO can be rapidly applied and has a rapid effect and fewer side effects compared to surgery[10].

ECMO and transport to the referred centers

Morbidity and mortality remain high for patients requiring acute mechanical circulatory support or ECMO. Question arises whether extracorporeal membrane oxygenation centers have to become mandatory and whether this might be beneficial for the outcome? Early initiation of treatment at a referring hospital before inter-hospital transfer may present an opportunity to improve outcomes. When applying ECMO treatment we must take into account that it is a complex, high-risk and costly procedure. There are several techniques, and the number of patients which are considered to ECMO is still small, not only in our country but also in the world. Not all centers can allow the use of ECMO, but it is especially important that ECMO should be a tool that is part of an appropriate algorithm and that the centers should recognize ECMO indications and allow transport to centers that apply advanced technology[11]. The initial evaluation of a patient who is a candidate for ECMO is a task of an intensives who must recognize a patient who has some form of refractory but potentially reversible respiratory or cardiac failure. This patient should be transported to a specialized center whether it be cardiac surgery, lung transplantation or other organ transplantation, or if it requires specialist treatment for severe respiratory insufficiency. Certainly, transport safety is of crucial importance.

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POST-INTENSIVE CARE SYNDROME – ANAESTHESIOLOGISTS "NIGHTMARE"

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Introduction

PICS is now being recognized as a public health burden due to the associated neuropsychological and functional disability, however its exact prevalence remains unknown. It has been reported to occur on average in 25% of ICU survivors, but few studies have shown its incidence to be significantly high, occurring in more than 3/4th of ICU survivors [1]. The major risk factors associated with it are duration of delirium in ICU, acute brain dysfunction (stroke, alcoholism), hypoxia (ARDS, cardiac arrest), hypotension (severe sepsis, trauma), glucose dysregulation, respiratory failure requiring prolonged mechanical ventilation, severe sepsis, use of renal replacement therapy, and acute respiratory distress syndrome (ARDS), prior cognitive impairment (older age, preexisting cognitive deficits, premorbid health conditions) [1-10].

What is Post-Intensive Care Syndrome?

Intensive care can affect a person's body, thoughts, feelings, mind and interactions with friends or family. This is referred to as post-intensive care syndrome, or PICS. It can be as obvious as weakened muscles, or less obvious like problems with thinking and judgment, depression or anxiety. The risk that your loved one may experience PICS increases if they:

- Were in the ICU longer than three to five days.
- Have an infection or sepsis that needs daily care.
- Multiple affected organs like their lungs, kidney, skin, heart, brain or others.
- Need a mechanical ventilator to help them breathe.
- Weakness from degenerated nerves and muscle.
- Poor nutrition.
- Trouble with attention, memory or reasoning.
- Post-traumatic stress disorder symptoms with frightening memories or hallucinations [1-19].

What are the risk factors?

The risk factors for developing PICS have yet to be fully defined. At this time, illness requiring admission to an Intensive Care Unit (ICU) and development of delirium during the ICU stay are the two risk factors most closely associated with risk for developing PICS. Other risk factors thought to contribute to the development of PICS include: mechanical ventilation during the ICU stay, older age, ICU stay >48 hours, a diagnosis of sepsis, and use of sedative medications. As our overall knowledge of PICS expands, so will our understanding of what places our patients at risk for this syndrome [2-6].

How is PICS diagnosed?

There is no one specific test used to diagnose PICS. This syndrome is diagnosed based on the patient's history of critical illness and the development of new or worsening impairments of cognitive, mental, and/or physical functioning following the critical illness. Because this syndrome typically develops following discharge from the ICU, it is usually recognized by non-ICU healthcare providers and/or the patient's primary care provider [3-8].

What are the signs and symptoms of PICS?

As the definition of PICS highlights, this syndrome can affect one or several aspects of a person's life. The mental, physical, and cognitive affects are highlighted below.

- Body: Muscles weakness, difficulty with balance
- Thoughts/Feelings: Anxiety, depression, sleep disturbance, nightmares
- Mind: Problems with thinking, problems with memory, difficulty concentrating, difficulty completing daily tasks [8-11].

How is PICS prevented?

This includes but is not limited to ICU interventions such as:

- Ensuring quality sleep.
- Preventing the development of delirium.
- Limiting the amount of medications used to sedate patients.
- Limiting the need for and length of mechanical ventilation.
- Getting patients up, out of bed, and mobile as early as possible during their ICU stay.
- Encouraging daily journaling while in the ICU by patients, caregivers, and/or family [12-5].

What can be done to treat PICS?

Treatment of PICS depends on the area of function affected by the condition. Discussion with the patient and family during hospitalization can help identify potential problems early. ICU follow up may also play a vital role in identifying Appropriate post-ICU experts may be needed to provide support.

Post-intensive care syndrome (PICS) describes the disability that remains in the surviving the critical illness. This comprises of impairment in cognition, psychological health, and physical function of the intensive care unit

(ICU) survivor.[1,2] Consequent to this, the psychological health of family members of the survivor may also be affected in an adverse manner, termed as PICS-Family (PICS-F).[1,2] It has been observed that up to 30% of family or the caregivers experience stress, anxiety, depression, and complicated grief[2-16].

Prevention and management

All patients being admitted into the ICU facility should undergo a psychological evaluation that includes: (a) preadmission history, (b) ability to adapt to stress in past, (c) medication history, (d) current mental and clinical status, and (e) environmental and family factors. The treatment of the ICU syndrome includes: (a) the elimination or correction of causative factors, (b) the appropriate administration of sedatives (anxiolytic and antipsychotic agents), (c) reduction or elimination of sources of environmental stress, and (d) frequent patient and family communication[1-19].

Conclusions

The ABCDE bundle has been used with good preventive rates for PICS. This comprises of:

- Awakening (using light or minimal sedation);
- Breathing (spontaneous breathing trials);
- Coordination of care and communication among various disciplines;
- Delirium monitoring, assessment, and management;
- Early ambulation in the ICU.

Additional interventions to prevent PICS include: (1) Avoiding hypoglycemia and hypoxemia. (2) ICU diaries: Maintenance of ICU diary prospectively by the family members, health care providers, or both during the patient's ICU stay.

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THE ROLE OF PLASMAPHERESIS IN THE INTENSIVE CARE UNIT

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Since the ancient time, it has been speculated that there are harmful substances which accumulate in the blood of sick patients and that the removal of these substances would make patients feel better. It is well known that there are four major constituents of blood: red blood cells, white blood cells, platelets, and plasma. With modern techniques, blood can be sequestered into each of these four components. Hence, if a particular blood component is causing harm, it can be selectively removed and substituted with the same blood component from healthy donors. Term "apheresis" is originated from the Greek word aphaeresis, meaning "to take away" and it has been used to explain the process of removal of blood components by extracorporeal blood purification methods. Plasmapheresis is an apheresis procedure that separates and removes the plasma component from a patient. The term plasma exchange (PE) involves separation and removal of plasma and its replacement with various fluids. By therapeutic plasma exchange (TPE) large molecular weight substances can be eliminated. Examples of these substances include pathogenic autoantibodies, immune complexes, cryoglobulins, myeloma light chains, endotoxins, and cholesterol-containing lipoproteins. Accordingly, the purpose of TPE is to remove these substances and hence reduce further damage and reversal of the pathological process.

TPE has been used to treat a variety of conditions that are associated with an aberrant immune response. It was first used in 1952 in the setting of multiple myeloma to treat hyperviscosity [1] and since then has emerged as an important treatment modality [2]. Plasmapheresis has been used to treat diverse pathologies, especially in the fields of neurology, hematology, nephrology and rheumatology, although the grade of evidence for these treatments varies. The American Society for Apheresis (ASFA) periodically revises the indications for plasmapheresis and classifies them according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.

The guidelines from the ASFA published in 2013 recommended its use as a first-line treatment in a number of diseases [3]. In the severe forms of these diseases, patients may be referred to the intensive care unit (ICU) for the management of life-threatening complications such as coma, seizures, acute respiratory failure, intraalveolar hemorrhage, or severe acute kidney injury. According to the ASFA guidelines, the indications for TPE are classified into four categories. Category I includes diseases in which TPE is considered as the first-line therapy [(for example, myasthenia gravis, Guillain–Barre syndrome, thrombotic thrombocytopenic purpura (TTP)]; Category II, in which TPE is considered as stand-alone therapy or in conjunction with other modes of treatment (i.e. mushroom poisoning, catastrophic antiphospholipid syndrome, multiple sclerosis, and systemic lupus erythematosus); Category III, wherein the optimum role of TPE is not established yet the treating physician may make his/her own judgment to run the procedure; and Category IV, diseases in which the published evidence suggests TPE to be either ineffective or harmful, for example, inclusion body myositis, lupus nephritis, etc.

TPE techniques

Devices used to perform TPE can be divided into two broad categories, those that separate the plasma from the cellular components based on size and those that separate components based on density. Devices separating based on size use filters, whereas those separating by density use centrifugation. In the former, whole blood flows over a membrane that separates the plasma from the cellular elements, which are then returned to the patient. Centrifugation apheresis is commonly performed by transfusiologist. A major advantage is that there is no limit on the size of the molecules being removed. Filtration plasmapheresis is commonly performed by nephrologists and intensivist. Its major advantage is that a large filter can be easily added to the existing continuous venovenous hemodialysis circuit without much interruption to patient care. However, a disadvantage is that the size of the molecules removed is limited by the size of the pore of the filter. Vascular access and blood flow through the extracorporeal circuit are fundamental for the success of the procedure. Vascular access can vary depending on the plasmapheresis technique, the condition being treated, and/or the duration of the treatment. In plasmapheresis by intermittent centrifugation and short-term procedures, peripheral venous accesses that provide blood flow of 50–90ml per minute can be used. In acute processes, the most commonly used accesses are temporary central venous catheters (jugular, subclavian or femoral) that provide blood flow of at least 70ml per minute, making it possible to complete the procedure in 2–3 hours.

Substitution fluids

The removal of a substance in the plasma and limited to the intravascular space. Because of the dilution of the plasma by the replacement fluid, the particular substance cannot be completely removed from the circula-

tion. For each 1-1.5 plasma volume exchanged, approximately 60%-70% of substances present in the plasma at the start of that plasma volume will be removed. As additional plasma volumes are exchanged, the absolute quantity removed becomes lower, although removal of a fixed 60%-70% still occurs. For this reason, the usual practice is to exchange only 1-1.5 plasma volumes during a TPE. A formula for determining the needed volume of single TPE was suggested by Kaplan AA. [4]:

Volume TPE = [0.065 x body weight (kg)] x (1 − Hct)
where kg: kilograms and Hct: hematocrit.

An easier way to assess the needed TPE volume is 30–50 ml/kg body weight.

As previously stated, TPE is a procedure in which a large volume of plasma is removed from a patient [5]. The volume removed is such that if it were not replaced, significant hypovolemia resulting in the vasomotor collapse would happen. As a result, the removed plasma needs replacement with some form of replacement fluid. The use of crystalloids as replacement fluid is inefficient, as they are not competent to preserve the intravascular oncotic pressure. Therefore, replacement involves the use of 5% human albumin, fresh frozen plasma (FFP) or both. Because TPE means massive removal of plasma, anything circulating in the plasma will also be removed. The procedure is nonselective, eliminating both normal and pathologic plasma components. For example, throughout one plasma volume exchange using albumin as the replacement fluid, coagulation factor activity decreases and coagulation tests may become abnormal. Significant declines in factor V (FV), FVII, FVIII, FIX, FX, and von Willebrand factor (VWF) activity occurs. Activities of FVIII, FIX, and VWF return to normal within 4 hours after TPE, whereas the remaining coagulation factors reach pre-TPE activity levels by 24 hours. The exemption to this is fibrinogen, which reaches 66% of pre-apheresis levels by 72 hours. Accordingly, the major disadvantage of albumin replacement is the depletion of coagulation factors. Therefore FFP can be applied after TPE. In some diseases, the replacement fluid should consist of FFP only— for example, hemolytic-uremic syndrome (HUS), TTP, and so on. Other indications for FFP use are the reduction of plasma fibrinogen level below 1.25 g/l, increase of prothrombin time more than 2 s above normal values and increased risk of bleeding (pulmonary hemorrhage, 48 h after biopsy/surgery) [6]. FFP should be used with caution, as its application is associated with hypotension, citrate-associated paraesthesia, urticaria, anaphylaxis, and blood-borne infections. Drugs elimination during TPE is widespread. Predisposing factors include greater bonding of the drug to proteins (>75%), lower volume of distribution (<0.3L/kg), and a shorter time between the administration of the dose and the start of plasmapheresis. Whenever possible, drugs should be administered after plasmapheresis.

TPE in Disseminated Intravascular Coagulopathy (DIC)

DIC is characterized by intravascular activation of coagulation causing consumption and exhaustion of coagulation proteins and platelets with extensive fibrin deposition in small and middle-sized vessels in all organs [7-9]. One of the suggested mechanisms for DIC is that systemic inflammation such happens in sepsis activates leukocytes and endothelium. These cells then synthesize, express, and release tissue factor. Tissue factor forms a complex with factor VII, leading to the activation of coagulation and resulting in disseminated microvascular thrombosis with fibrin-rich microthrombi [10]. Clinically, these patients present with shock and in a prothrombotic and antifibrinolytic state with a sequential bleeding diathesis. Many case series and observational studies suggest that TPE might have a beneficial effect in DIC [11-14]. TPE is believed to normalize the blood coagulation to homeostasis milieu by removing tissue factor, and plasminogen activator inhibitors type I and by replacing antithrombin III, protein C, and coagulation factors. Still, the ASFA does not have a specific recommendation for TPE in DIC. However, the ASFA gives a category III recommendation for TPE in sepsis with multiorgan failure [6]. Large trials have documented that sepsis can induce thrombotic microangiopathy, and, in particular, sepsis-induced DIC which is present in 30% to 50% of patients with severe sepsis [15,16]. DIC is one of the major contributing mechanisms to multiorgan failure in critically ill patients. Thus, there is a biologic plausibility that the beneficial treatment effect of TPE in sepsis with multiorgan failure could be from modifying DIC. Recently, investigators observed that pediatric patients with thrombocytopenia associated multiorgan failure (TAMOF) have thrombotic microangiopathy and that TPE may have a beneficial effect [17]. These investigators reported that pediatric patients with new-onset thrombocytopenia defined as platelet count less than 100,000/mm3 and at least three failing organs have a pathophysiologic process similar to that of TTP such as low ADAMTS-13 activities, the presence of ultra-large VWF, and high VWF activities. A subset of TAMOF patients also had prolonged prothrombin time suggesting fibrin pathway activation, as in DIC. On autopsies, pediatric TAMOF patients have VWF-rich and platelet-rich microthrombi similar to patients with TTP and also fibrin-rich microthrombi similar to patients with DIC. In a small single-center trial, they stated that TPE had a significant beneficial treatment effect in reducing organ failure score and mortality. Of note, all of these patients had concomitant sepsis. Thus, the ASFA category III recommendation for TPE in sepsis with multiorgan failure [18]as discussed earlier, encompasses sepsis-induced TAMOF. Because the underlying pathology could be in part from deficient coagulation factors due to consumption, the recommended TPE replacement fluid is plasma.

TPE in Sepsis

Sepsis is a usually devastating medical condition and the most common cause of death among critically ill patients [19,20]. A dysregulated host response to infection may provoke endotoxin storm, cytokine storm, subsequent endothelial dysfunction, and life-threatening multi-organ dysfunction. Patients with sepsis initially experience an early phase resulting from massive and deregulated activation of innate and adaptive immunity, which is followed by a second late phase caused by immunosuppression and lymphocyte exhaustion [21]. Therefore, the

primary goal of blood purification is to attenuate the overwhelming systemic inflammation and subsequent immunosuppression. Removal of endotoxins, cytokines, and toxic mediators may play a crucial role in reducing endothelial and multiorgan dysfunction. Thus, the theoretical concept of TPE in sepsis combines two major aspects in one intervention: 1) removal of harmful circulating molecules (as part of the injurious cytokine storm) that directly contribute to the manifestation of the disease; and 2) replacement of protective plasma proteins that compensate for the loss of factors needed for coagulation (e.g., activated protein C, antithrombin, tissue factor pathway inhibitor) and fibrinolysis (e.g., von Willebrand factor-cleaving proteases). Consequently, by neutralizing inflammation and vascular leakage (e.g., angiopoietin-1, vascular endothelial growth factor (VEGF)), it may restore hemostasis ultimately [22]. So far, the available data on TPE in sepsis are sparse compared with other blood purification techniques [23]; mostly case reports [24] and uncontrolled retrospective studies [25,26] have been published. A recent meta-analysis found only two single-center randomized controlled trials (RCTs) in adults in which reduced mortality was reported [27]. The largest RCT showed that the treatment with TPE was associated with a significant reduction in all-cause mortality in adults [28]. The ASFA declared in their 2016 guidelines "the optimum role of apheresis therapy is not established; decision making should be individualized", and gave a weak recommendation [29]. Given the pathogenesis of sepsis, with increased understanding of the damage resulting from both severe inflammation and anti-inflammation, strategies to modulate the immune response may confer real benefits for these patients, for whom morbidity and mortality remain high. However, whether this strategy is most effectively delivered by plasma exchange or by pharmacologic manipulation of the immune response remains to be seen.

TPE in Pancreatitis

Pancreatitis from this perspective of severely elevated triglyceride (TG) levels is often observed in the clinical setting. The mechanism of HTIP (hypertriglyceridemia-induced pancreatitis) is assumed to involve increased lipolysis of triglyceride-rich lipid particles by pancreatic lipase, with resultant production of free fatty acids (FFAs). These FFAs cause free radical damage to the pancreatic acinar cells, hence initiating a self-perpetuating cycle of pancreatic inflammation and destruction [30]. Progressively higher TG levels have been associated with disease severity and multiorgan failure [31]. Though various modalities exist for the management of such patients, plasmapheresis is one such lesser-known therapeutic option. According to a committee of the ASFA in 2013, TPE is recommended to treat patients with HTIP as Category III indication [3]. TPE can cause a rapid decline in the TG levels, with a documented decrease by as much as 70% after a single session [32]. Although there are no established guidelines for timing of initiation of TPE, there is some evidence from small studies and case reports that early initiation of plasmapheresis within 48 hours of presentation results in improved morbidity and mortality. Current data regarding the replacement fluid in TPE is sparse; historically, both albumin and fresh frozen plasma have been used. FFP has a theoretical advantage over albumin since it provides the patient with lipoprotein lipase and apolipoprotein, both necessary for the hydrolysis of TGs [33].

Conclusion

Plasma exchange is a therapeutic procedure adopted to treat a broad variety of diseases by plasma removal. Whereas the mechanism of action has been considered to be the removal of pathologic immunoglobulins, there is data suggesting an immunomodulatory effect. The procedure is safe, with the majority of reactions and complications being mild, easily treated, and of limited duration.

TPE as a therapy has increased use, particularly by those who take care of critically ill patients. Using an evidence-based strategy is the best way to standardize care and to provide a platform for innovation to move forward. Thus, we can expect more extensive use of apheresis in medical practice in the future.

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CONTINUOUS RENAL REPLACEMENT THERAPY IN SEPSIS

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Acute kidney injury (AKI) is frequently associated with sepsis. Its incidence varies from 11% to 42%[1,2] and may be as high as 67% in a septic surgical population.[3] Sepsis is the most common cause of AKI in critical care patients, accounting for 50% of cases in the ICU.[4] AKI incidence rate and severity correlate with the severity of the underlying sepsis.[5] Septic AKI is a hallmark of severe sepsis and septic shock and is associated with worse outcomes including prolonged hospital length of stay, fewer ventilator-free days and increased mortality when compared to patients with non-septic AKI.[2,3] It appears that septic AKI is different than non-septic AKI with respect to the underlying contributing factors, and severity of injury and outcomes. Septic patients develop more severe AKI than in non-septic patients.[2,6]

Several factors have been implicated in the pathogenesis of septic AKI. Hemodynamic changes in the macro circulation (vasodilatation and increased cardiac output), and systemic and renal microcirculation contribute to renal hyperemia coupled with inefficient cellular oxygen extraction. The renal medulla is particularly sensitive to these hemodynamic perturbations and resultant hypoxemia, since it is already functioning at a lower PaO2 level, especially in the nephrons of the cortico-medullary junction. Sepsis is also associated with systemic inflammation and endothelial dysfunction, which also have been shown to contribute to renal injury and enhance microcirculation perturbations.[7,8] The stress response is altered in sepsis;the earliest phase characterized by a short-lived hypo-responsiveness, which is followed by a dramatic phase of hyper-responsiveness. In the hyper-reponsive phase, both pro- and anti-inflammatory cytokines are released in the systemic circulation, The later phase of sepsis is characterized by hypofunctionality of the immune system, which may last from several days to weeks, and increases susceptibility to new or recurrent infections

Sepsis and AKI: Timing and Risk Factors

AKI in the setting of sepsis can be considered in three different domains: sepsis preceding AKI, concurrent presentation of sepsis and AKI and sepsis following AKI.

It is generally well accepted that sepsis greatly increases the risk of AKI, but there is growing evidence that AKI itself increases the risk of sepsis. In a post-hoc analysis of the prospective multicenter PICARD study (AKI patients), 40% of the patients developed sepsis after they developed AKI (median of 5 days), compared to 28% in which sepsis preceded AKI. Mortality was similar between groups, but when they were compared to a group of AKI patients without sepsis, both groups had higher mortality, risk of requiring dialysis and longer hospital length of stay. Significant predictors of sepsis in AKI patients identified in this study were fluid accumulation, oliguria, severity of illness score, non-surgical procedures and dialysis.[10] Different mechanisms may explain increased risk of sepsis in AKI patients.

The risk of developing AKI after sepsis is higher in patients with older age, male sex, increased severity of illness, lower urinary output, higher central venous filling pressures, vasopressor requirements and pre-existing treatment with ACEI/ARB. Serum creatinine at presentation and pH of <7.3 have also been identified as predictive of AKI in septic patients.[1] No specific type of pathogen was associated with increased septic AKI risk compared to others. Several clinical characteristics differ between patients with septic AKI and those with non-septic AKI. Septic AKI patients tend to be older, have more co-morbid disease, are more likely to be admitted to the medical intensive care unit (ICU), have higher severity of underlying illness scores, greater abnormalities in vitals signs, markers of inflammation and blood chemistry.[2]

Considering all of these arguments, it must be emphasized that not only is sepsis a risk factor for AKI, but AKI itself appears to be a risk factor for sepsis. In some situations the sepsis clearly precedes the kidney injury, but other cases might not be so clear leading one to wonder: "Is the kidney a victim or the cause of the sepsis?" AKI may therefore be a cause and a consequence of sepsis.

Recognition and menagement

Septic AKI is defined by AKI in the presence of sepsis without another significant contributing factor explaining AKI. Recent diagnostic and staging criteria for AKI included an absolute increase of serum creatinine of 0.3mg/dl over 48 hours, a relative change in serum creatinine 1.5-1.9 times baseline over 7 days, or a urine output of less than 0.5 ml/kg/h for six hours.[2]

Early identification of AKI in septic patients is crucial, because supportive and therapeutic maneuvers in septic patients are often nephrotoxic (e.g. use of vancomycin and aminoglycosides; or the use of vasopressor therapy with inadequate fluid resuscitation).Factors independently associated with AKI reversibility are early administration of anti-microbial therapy, lower Acute Physiology and Chronic Health Evaluation II score, lower age, and a smaller number of failed organs (excluding renal) on the day of shock, as well as community-acquired infection.[9]

Extracorporeal Blood Purification, RRT

The utility of extracorporeal blood purification therapies for septic patients can be evaluated (and debated) for two different purposes: renal support and immunomodulation therapy. Traditional RRT indications for organ support purposes such as uremia, metabolic disturbances, and fluid overload apply in septic AKI just as in non-septic AKI. Timing of RRT initiation remains heterogeneous in clinical practice. The only published randomized controlled trial available to date did not find significant differences in renal outcomes or patient survival between early and late initiation of hemofiltration. Two trials are now ongoing and will hopefully answer the optimal timing for RRT question: STARRT-AKI trial [10] and recently published the IDEAL-ICU study. [11] The latter is addressing this question specifically in septic AKI patients.

RRT modality choice may have important implications for survivors of septic AKI, because CRRT appears to be associated with better renal recovery than intermittent modalities.

Optimal RRT dosing has been evaluated in two major critical care trials (without specifically focusing on AKI) and the current recommended adequate effluent rate (delivered RRT dose) for CRRT is 25-30 ml/kg/h. [13,14] High volume hemofiltration (HVHF) is defined as effluent rate above 35 ml/kg/h. HVHF has been hypothesized to clear sepsis-associated inflammatory mediators and therefore perhaps helps reduce inflammation-induced organ damage and improve septic shock survival. Since CRRT at standard "renal-dose" does not appear to improve outcomes in septic shock without renal failure [13], studies using higher effluent rates (70-85 ml/kg/h) have been conducted to evaluate this approach. These trials and a recent meta-analysis have all failed to demonstrate any impact on patient survival, hemodynamic status or organ improvement.

Additionally, a prospective observational international study of 1753 patients, showed that patients with septic AKI showed a trend towards higher chances of recovery and dialysis independence compared to non-septic AKI patients even though they had higher risk of death and longer hospital length of stay. [12]

The renal prognosis of septic AKI has not been well described in the literature. Renal recovery is highly unlikely when sepsis is not controlled since the mechanisms of insult persist. Once sepsis is resolved, the likelihood of renal recovery depends on a number of factors such as the patients underlying characteristics (age, underlying CKD, diabetes and other co-morbidities), the severity of underlying insult (prolonged hypotension, sepsis severity and multiple organ involvement) and iatrogenic insults associated with process of care (fluid overload, hypotension associated with RRT, nephrotoxic antibiotics or contrast exposure). In clinical practice, the kidney is often one of the last organs to recover in patients with multiple organ failure due to sepsis and they may require weeks to months of dialysis.

Conclusion and recommendations

AKI associated with sepsis may present in different forms and is independently associated with increased mortality and morbidity. AKI may precede or follow sepsis. Differentiating septic AKI from other forms of AKI is important, as underlying pathophysiologic mechanisms and outcomes differ between these two groups. Identification of high-risk patients and those with early AKI is crucial in influencing patient outcome. Serum creatinine and urine output are imperfect markers of early AKI in septic patients, and other novel tools need to be implemented to identify these patients.

While there are no specific treatments for septic AKI, early antibiotic administration, avoidance of hypotension (through fluid administration or vasopressors), nephrotoxic agents and fluid overload (through judicious use of fluid therapy, diuretics and RRT) can minimize AKI risk. CRRT has been associated with improved renal recovery, and should perhaps be started earlier in AKI evolution, but this need to be validated in future studies. Future trials should be designed to identify high-risk patients with early injury and focus on targeted therapy.

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SYSTEMIC INFLAMMATION AND SEPSIS AFTER MULTIPLE TRAUMA

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Introduction

Mortality after severe trauma has bimodal distribution. Thanks to the therapeutic concept of damage control resuscitation, the percentage of severely traumatized patients dying in the first 24 hours due to bleeding is reduced. However, many of these patients die a few days after the development of immunological dysfunction that can lead to organ dysfunction syndrome (MODS), which is often associated with sepsis.

Inflammatory response after trauma

Severe trauma very quickly, after 30 minutes, leads to excessive proinflammatory response (SIRS). Unlike the sepsis where microbes activate the immune system through pathogen-associated molecular patterns (PAMPs), after trauma and tissue destruction, HMBG1, mitochondria and nuclear DNA, represent endogenous alarms, called DAMPs, generate the inflammatory response. DAMPs through formyl peptide receptor-1 and Toll-like receptor (TLR) 9 activate neutrophils, monocytes, macrophages, T helper-1 lymphocytes (Th-1) and complement. Activation of complement and inflammatory cells leads to the release of pro-inflammatory mediators: interleukin-1 (IL-1), interleukin-2 (IL-2), tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) , interleukin-12 (IL-12), interferon-gamma (IFN-γ). At the same time there is compensatory activation of anti-inflammatory response (CARS), T helper-2 lymphocytes (Th-2), which involves increased serum levels of interleukin-4 (IL-4), interleukine-10 (IL-10), transforming growth factor β TGF-β), with a strong immunosuppressive effect. The proposed new paradigm considers rapid and simultaneous induction of innate genes (both pro- and anti-inflammatory) and suppression of adaptive immunity genes. The level of liberated cytokine in systemic circulation after trauma is directly proportional to the severity of injuries. This uncontrolled proinflammatory response, as well as ischemia and reperfusion after injury, can lead to increased endothelial permeability, migration of neutrophils across damaged endothelium, and their sequestration in organs that were not initially traumatized. The release of proteases, reactive oxygen species from neutrophils, leads to damage to healthy tissue, which can lead to the development of early MODS. An unregulated anti-inflammatory response following severe trauma lead to immunoparese and reduced ability of the organism to fight against pathogenic microorganisms. The neuroendocrine response of the organism to the trauma also contributes to this. Glucocorticoids and catecholamines, which are amplified after trauma, lead to suppression of cytokine production and act strongly against defense of the organism from pathogenic microorganisms. This process can lead to increased risk of sepsis. Early diagnosis of infection in this group of patients and adequate therapy can greatly correct the outcome and reduce mortality. Sepsis in injured patients can be the cause of Late MODS. Injury (“first hit”) primes the immune system for exaggerated and potentially lethal reactivation of the inflammatory response caused by surgical stress or bacterial infections (“second hit”). “Second hit” results in destructive inflammation leading to multiple organ failure (MOF).

Prediction of sepsis and trauma patients

High admission Injury Severity Score, lower admission Glasgow Coma Score, preexisting diseases, older age, male sex, more injuries, number of red blood cells transfused, surgical interventions after trauma are significant independent predictors of sepsis. The diagnosis of post-traumatic sepsis is a major challenge. It is very difficult to discriminate "clean" SIRS from septic SIRS. Although more than 180 biomarkers have been investigated for sepsis, none has shown satisfactory sensitivity and specificity for early diagnosis of sepsis. Biomarkers can be more useful to rule out sepsis than to ruleit in. After the trauma there is a increase of procalcitonin (PCT) that is proportional to the severity of the injury and hypovolemia (hemorrhagic shock). The peak values of PCT are recorded 24-48 h after trauma, followed by a rapid fall in non-complicated patients. Continuous high levels of PCT or secondary increases of PCT can indicate the development of sepsis. C-reactive protein (CRP) and IL-6, which are also widely used in routine clinical practice, have not been shown to be good early predictors of sepsis in trauma. CRP peaks within 3 days of trauma, but returning to basal values is very slow. Il-10 has increased values in patients with sepsis and this represents a risk factor of mortality. White cell counts also lack specificity for bacterial infection. Detection of presepsin plasma concentrations over time could play a potentially helpful role in early diagnosis of sepsis. Persistent SIRS and inadequate 24-hour lactate clearance are also predictive of nosocomial infection after trauma. Microbial cultures also do not provide definitive diagnostic information, since they can be negative in as much as 50% of patients with sepsis.

Prophylactic antibiotics in trauma

In patients with penetrating chest injuries, penetrating abdominal injuries, penetrating head injuries, open bone fractures and lacerated soft tissue injuries, antibiotic prophylaxis is advised by an adequate antibiotic, as it reduces the risk of infection and post-traumatic sepsis. Clinical studies do not confirm the benefit of antibiotic prophylaxis in patients with blunt injuries. However, prolonged prophylactic use of antibiotics (> 48h) is not advised because it is associated with greater incidence of antibitic clinical complications: development of antibiotic resistance, more often late infections, most common pneumonia caused by multidrug-resistant bacteria, diarrhea caused by Clostridium difficile infection, allergic reactions, toxic reactions with hepatic, kidney, heart and hematopoiesis impairment, as well as interactions with other drugs. Immunomodulatory therapy in sepsis after trauma has not yet shown a clear benefit and is in the phase of clinical trials.

Conclusion

Seriously injured patients have a predisposition to develop sepsis in the later course of treatment. Early diagnosis of sepsis is crucial for a good outcome, but it can be a challenge. Trauma and sepsis patients can demonstrate positive SIRS criteria. Sepsis 3.0 criteria are also not reliable in the differentiation of sepsis from sterile inflammation following trauma. In order to diagnose sepsis, it is necessary to identify the potential source of infection, monitor the trend of sepsis biomarkers and examine closely vital parameters.

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EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION (eCPR)

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Sudden cardiac arrest is a life-threatening event requiring a multidisciplinary approach. Many strategies have been proposed to achieve the return of spontaneous circulation (ROSC) and to optimize post-resuscitation care. These include medical, organizational and technical aspects: including hypothermia, oxygen control, specialized post-resuscitation care centres and extracorporeal membrane oxygenation (ECMO).

ECMO was introduced as an additional step in the chain of survival for selected refractory cardiac arrest patients. Several studies evaluated the feasibility and the potential advantages of extracorporeal cardiopulmonary resuscitation (eCPR) in patients with cardiac arrest refractory to the conventional treatment.

In the period between 1997 and 2003 at the University Hospital of Caen 40 patients with refractory in-hospital cardiac arrest (IHCA) were treated with ECMO. The treatment was discontinued in 22 patients due to brain death or multi-organ failure; 18 patients survived to the first 24 hours of treatment but only 8 were still alive without consequences at 18-month follow-up. Chen et al. obtained better results in a 3-yearprospective observational study, reporting a survival rate significantly higher in the ECMO matched group than in the conventional CPR group at discharge, after 30 days and after 1 year from the cardiac arrest. Kagawa et al. and Avalli et al. also described a higher weaning rate from ECMO and more favourable outcomes with ECMO in the IHCA than in the out-of-hospital cardiac (OHCA) patients.

ECMO seems to represents a strategic option before ROSC because it promptly restores circulation and plays a pivotal role in the post-resuscitation period, leaving the heart at rest, ensuring myocardial perfusion and promoting the return of spontaneous rhythm. Furthermore, early patient's stabilization provides a bridge to support critically ill condition and enables diagnosis and intervention for emergency patients, such as the possibility of performing advanced radiologic investigations and definitive surgical or percutaneous treatments even before a ROSC is obtained. Finally, when cerebral death occurs after anoxicinjury due to the cardiac arrest, the extracorporeal circulation could provide peripheral perfusion to make patients organ donor.

Safe and effective ECMO requires a specialized medical expertise and a trained staff and the emergency/intensivist physician currently performs it. Advances in percutaneous vascular cannula insertion, centrifugal pump technologies, and miniaturization of extracorporeal devices have simplified ECMO for deployment in a variety of settings, including the emergency department.

Although progressively more encouraging results were described over time from the use of ECMO in refractory cardiac arrest, the criteria for its positioning are still debated (Table 1).

Refractory cardiac arrest is defined by the lack of ROSC within a period of 30 min of CPR. In this regard, the time to treatment is the pivotal issue, since it reflects the progression and reversibility of tissue damage. Thus, the first point that must be considered in selecting a patient for ECMO is the "no-flow time", defined as the duration of cardiac arrest without cardiac output before CPR. It is clear that no-flow time can be known precisely only in witnessed cardiac arrest and the best candidates to ECMO in this setting are those receiving prompt CPR by bystanders, since the no-flow time can be considered negligible in these patients.

Indications about the best duration of no-flow time to consider patients eligible to ECMO are still lacking or

Table 1. Possible decision criteria for eCPR

Pro criteria	*Contra criteria*
▪ Observed refractory cardiac arrest; ▪ Age < 75 years old; ▪ Presumed cardiac aetiology; ▪ Presence of a reversible cause of cardiac arrest (4H's and HITS); ▪ No-flow time ≤ 5 min; ▪ Low-flow time ≤ 60 min; ▪ Vital signs occurring during CPR, despite no-flow time > 5 min or initial non-shockable rhythm; ▪ $ETCO_2$>10 mmHg (with TV 8-10 ml/kg); ▪ High quality resuscitation measures.	▪ Unwitnessed cardiac arrest; ▪ No- flow time ≥ 10 min; ▪ Clinical signs of severe irreversible brain damage or expected poor neurological prognosis; ▪ Inadequate resuscitation measures; ▪ Comorbidities with reduced life expectancy; ▪ Patient's refusal (advance directive); *Relative contraindications:* ▪ Contraindications to full anticoagulation; ▪ Anatomic constraints preventing adequate cannulation or perfusion.

inhomogeneous in the literature. The French guidelines proposed an algorithm in which no-flow time is matched with the rhythm of presentation: a no-flow time below 5 min is defined as a cut-off for ECMO application when patients are found asystolic, but a time longer than 5 minutes is acceptable to proceed in the algorithm if the presenting rhythm is different from a systole.

The second important factor to assess is the "low-flow time", i.e. the duration of cardiac arrest with low cardiac output during CPR. There is no definitive consensus on the optimal low-flow time limit. It is clear the shorter the low-flow time, the better the outcome, but its duration differs between authors and also depends on CPR quality. Several studies showed a more favourable outcome in patients undergoing ECMO after IHCA compared with those after OHCA, probably due to longer delays between collapse and the start of resuscitation techniques in the second ones. Despite a cut-off of 30 min to start ECMO has been previously suggested, some evidence that ECMO allowed a longer CPR duration than expected in conventional CPR has been described.

The quality of CPR is also a critical issue for neurological outcome. Massetti et al. showed that effectiveness rather than the duration of CPR has to be considered in the ECMO decision process. Various studies demonstrate that out- but also intra-hospital CPR are variably effectiveness even if performed by well-trained medical personnel, reporting about chest compressions too shallow or withheld for half of the time of resuscitation. Moreover, higher chest compression variability emerges in pre-hospital setting as compared to the emergency department. The introduction of automated chest compression devices –such as the LUCAS® (Physio-Control, Inc., Redmond, WA, USA) or the AutoPulse® (ZOLL Resuscitation Products, Chelmsford, MA, USA) systems - may help to overcome the difficulties correlated to CPR execution. These systems were demonstrated to increase diastolic and mean blood pressure during compressions. Moreover a higher tendency toward improved survival and neurological outcome at discharge was found in patients treated with mechanical CPR compared to patients underwent manual CPR.

Several conditions have been identified to be of such high risk and/or low benefit that extracorporeal support can be considered contraindicated. Patients in these conditions require individual consideration to balance the risks with the potential benefit of initiating support. ECPR is usually not offered if the no-flow duration is unknown (unwitnessed collapse) or prolonged to the extent that brain recovery is doubtful (> 5-10 minutes). Advanced age is often considered a relative contraindication to ECMO, but this decision should perhaps consider the age-related physiological state of the patient rather the actual chronological age. Severe comorbidities precluding ICU admission should be considered as contraindications to ECMO positioning: terminal illness, advanced malignancy with limited life expectancy, pre-existing irreversible brain damage, conditions incompatible with life. Patients with end-stage heart or lung failure are not candidates for ECMO unless supported as a bridge to transplant or to destination therapy, such as a ventricular assist device.

An increased risk of significant or fatal complications from bleeding exists in patients with pre-existing intracranial bleeding or bleeding at other sites that cannot be managed. This condition could be considered a relative contraindication, although in uncontrolled haemorrhage shock heparin-free ECMO may represent a bridge to source control. Finally, vascular anomalies or previous surgical interventions may preclude placement of cannulas of sufficient size or in the desired location to achieve the adequate support. Placement of small or incorrectly located cannulas results in inadequate flow and thus increases risks without the potential for full benefits.

Cannulation is one of the most challenging aspect of performing ECMO in emergency situations. It can be performed percutaneously or surgically and the selection for a given patient depends on the experience of the cannulating operator, the body habitus of the patient and additional anatomical or functional (need for central cannulation for high flow) factors. Percutaneous cannulation has become the preferred technique for most ECMO applications: bleeding complications are lower, vessel ligation is avoided (thus allowing distal perfusion) and even the risk of infection is lower. Moreover, ultrasound imaging can be employed to estimate vessel size and identify variations in vascular anatomy, which result in a high success rate. Trans oesophageal echocardiography (TEE) is usually used to guide ongoing cardiopulmonary resuscitation, confirm guidewire placement in the appropriate vessels and position cannulas. If fluoroscopy is available in the intensive care unit (ICU), this imaging technique can ensure the correct venous and arterial positions of the guidewires prior to cannula insertion.

The favourable cannulation sites in VA-ECMO are the femoral vessels. In some cases, oxygenated blood can be distributed by the circuit to the upper body via retrograde flow to the aortic arch. However, when some native cardiac function is present, the upper body is perfused with blood that has traversed the pulmonary circulation and circuit flow is limited to the lower body. Emphasis should be put on the quality of CPR to maintain best possible blood circulation during the deployment of ECMO. It might be reasonable to continue with chest compressions without any interruptions for the interval of cannulation. If providing full ECMO support, which can be assessed by invasive blood pressure measurement, then chest compressions may be stopped. In case at relatively lower blood flow rates chest compression are still needed.

Following cannulation, ECMO support is initiated with the extracorporeal circuit. The modern circuits include centrifugal pumps with low haemolytic potential, membrane oxygenators with high gas exchange capacities and resistance to plasma leakage, and internal heat exchangers. In order to facilitate rapid deployment in emergency situations, the circuits can be primed with crystalloid and maintained in standby mode. Management of the circuit after initiation of support includes the maintenance of low-level anticoagulation, the adjustment of bloodflow to satisfy oxygen delivery requirements and the adjustment of oxygenator sweep gas flow to maintain normocapnia.

Heparin is the optimal anticoagulant for ECMO and it is administered intravenously at 50-100 IU/kg once the vessels have been controlled with guidewires (usual bolus of heparin is 5000 IU, except in cases requiring heparin-free conditions such as haemorrhagic shock). The

management of the circuit includes the maintenance of anticoagulation with a continuous infusion of heparin to achieve an activated clotting time (ACT) of 160–220 or an activated partial thromboplastin time (aPTT) of 45–55 sec.

Due to the need for anticoagulation, ECMO involves a risk of bleeding from both cannulation sites and distant sites, such as intracerebral, oropharyngeal, gastrointestinal, or retroperitoneal haemorrhage sites. The risk of leeding or coagulopathy in patients on ECMO can be decreased when using a heparin-bonded circuit without systemic heparin or by targeting lower levels of anticoagulation. However, the risk of circuit clotting is increased by reduced or absent systemic anticoagulation. Additional complications are: circuit-related haemolysis, pump or oxygenator malfunction or failure, thromboembolism (venous or arterial), left ventricular distension and pulmonary oedema, cannula site infection and cannula-related bloodstream infection.

The decision to discontinue ECMO support should be based on the patient's clinical evolution and the best available evidence for predictors of good outcome. It is essential to have institutional guidelines or at least general agreement on the indications and contraindications for ECMO prior to launching a program. Severe neurological impairment up to brain death, irreversible multiorgan failure or intractable sepsis should warrant ECMO discontinuation.

It is known that a favorable outcome can be expected in a share of patients ranging between 20% and 30%, according to data reported in the literature. For all other patients, therapeutic desistence should be properly assessed in front of the onset of encephalic death and the possibility of organ donation.

In fact, the eCPR could be associated with possible negative evolution presenting a recovery of cardiac function not matched with a good neurological outcome. In this regard, there is a great scientific debate on the need for a new definition of brain death and the development of "ad hoc" organ donation protocols. A recent review by Sandroni et al. shows a rate of cerebral death in ECMO patients of about 28% (definitely higher of 8% than patients treated with conventional CPR) and that 40% of patients are potential donor. These numbers require the development of a specific program for the management of ECMO patients with not only a clinical but also an ethical approach. Given the medical and ethical complexity of eCPR, consideration might be given to the creation of an automatic trigger for ethics involvement early in the ECMO process. Empirical data on the impact of an early ethics involvement is lacking, however the ethical themes and issues to front by ECMO group are clear (Table 2).

A safe and effective eCPR program should be prospectively planned and delivered by a highly rehearsed team. The team further requires a shared approach underpinned by clear clinical practice guidelines on indications, selection criteria, process and management of complications. Within the hospital, a multi-disciplinary approach to the establishment of an eCPR program is very important. Intensive care specialists provide ongoing critical care; interventional cardiology may offer percutaneous coronary intervention in ST-elevation myocardial infarction; interventional radiology may offer services like catheter-directed thrombolysis for pulmonary embolism; and cardiothoracic surgery may offer valuable input to manage surgical complications, cannula management or bridge to ventricular assist devices. This multi-disciplinary approach, along with standardization of equipment across the eCPR providers and recipient centres, allows for smooth transitioning of care. Finally, it is mandatory a training program on all tasks performed by team members, alignment to their scope of professional practice and safety-netting with operational guidance that supports the technique.

In conclusion, sudden cardiac arrest is a complex event with high mortality rate. An optimal conventional treatment should represent the basis for every cardiac arrest patient. Emergent eCPR plays an increasing role in the Emergency Department for selected patients not responding to the conventional approach in the face of life-threatening conditions in which the alternativeis a poor outcome or certain death. ECMO provides a bridge to recovery, definitive therapy, intervention or surgery and requires an appropriately organized and trained staff, equipment resources and logistical planning. Close cooperation between pre-hospital emergency medical services, the ICU, the in-house ECMO program and inpatient specialty services is essential for successful patient outcomes.

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Table 2. Ethics Consultations from an ECMO program. *[Table from Henry et al. Resuscitation, 2018]*

Themes and issues

- Who decides when to stop the circuit?
- Under what circumstances would this occur?
- Does being on ECMO automatically make a patient a DNR?
- Is it justifiable to ask for consent with criteria for how ECMO will be stopped?
- Feeling that not enough time has past for a reasonable trial of therapy?
- Disagreement related to stopping when patient no longer a candidate for destination;
- Limits of prognostication for novel therapies.

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IN THE MAN'S WORLD, AFTER SO MANY YEARS OF PRACTICE WOULD I CHOOSE EMERGENCY MEDICINE AGAIN?

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Introduction

Specialization of Emergency Medicine was first introduced at the University of Belgrade in 1992.And it seems that while building dreams they forgot to set clear goals. 25 years later there is still no final idea about the system and organization of emergency medicine. So we have built the foundation on a dry land and are still waiting for some good solid walls. Emergency medicine in Serbia still has plenty organizational, educational and status problems in Serbia. The position of women in this tangle of problems has not been the subject of discussion yet. Apart from the widely accepted attitude that women are equal, there has been no discussion on this topic neither in professional meetings nor in public administration.

Results

An anonymous survey has been done. All respondents are the members of the Serbian Society of Emergency Physicians and the total numbers of replies are 108. The survey includes 30 questions which are divided into 5 categories: personal data, specialization and training in EM, position of EM in the country, women in EM, free time activities. They are multiple choice questions with the possibility to add your own comment. The total number of replays were108, about 75 % are spec of emergency medicine, residentand doctors who are waiting for spec of EM last ¼ are pediatrician, surgeons, cardiologist. Marital status shows the same percentage of both women and men are divorced, and that is 2%, but there are 13 times more unmarried women than men;35% of respondents have no children and all of them are women. Nearly 20% did not have an opportunity to choose a specialization. They are used to work in EM but would gladly change specialization, and all of them are older than 45 and 70% of them are women. So there were 25,5% are the people who would work in EM in any conditions. There were no differences between the answers given by male and female participants to the following questions: what is the quality of EM specialization? What is the attitude of the patients towards the EM stuff (physicians)? What is the attitude of the colleagues of other specialties towards EM physicians? But all of them think that EM physicians and EM stuff should be treated with more understanding and respect. In general, they all think that EM stuff should have better status. Almost 85% of men say that women are equal while 25% of women think that they are really equal 15% of men say that women are physically weak and unable to work in EM But 75% of women think that they do the same job but don't advance in career, also that they are unselfish and even work harder than mean If we were looking for the differences between male and female doctors, they could be classified into four major groups: physical, psychic, psychological, sociological.

Conclusion

The position of women in society is not easy. Besides their professional life, they are expected to be good partners and gentle mothers. But, don't we have the same requirements for men? It seems that the position of women depends largely on the social and cultural rules of a society. But it also enormously depends on the support of the family.

WHAT IS NEW IN 2019 GUIDELINES ON TRAUMATIC BLEEDING?

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Uncontrolled bleeding is still a major cause of potentially preventable death in trauma. Coagulopathy is present in up to one third of trauma patients at admission and is associated with a five time increased risk of mortality. The early acute traumatic coagulopathy (ACT) is multifactorial and results form the combination of shock, tissue related thrombin- thrombomodulin complex generation, activation of anticoagulant and fibrinolysis pathways, treatment administered and environment-, individual- and trauma specific-related factors [1]. Recommendations on how to manage bleeding trauma patients and ACT have been recentlypublished [2]. These guidelines represent the fifth edition of a document first published in 2007 and updated in 2010, 2013 and 2016 by a pan-European, multidisciplinary Task Force for Advanced Bleeding Care in Trauma, which also includes representatives of the professional societies involved in the care of trauma patients: European Society of Anaesthesiology (ESA), European Society of Intensive Care Medicine (ESICM), European Shock Society (ESS), European Society of Trauma and Emergency Surgery (ESTES), European Society for Emergency Medicine (EuSEM) and the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA). In the 2019 edition the existing recommendations were reconsidered and revised and new recommendations were formulated to reflect current clinical concerns and areas in which new research data have been generated. The overall structure of the text was re-organised to reflect better the temporal sequence of the decision-making process along the patient pathway.

The key messages of the guidelines, also present in the 2016 edition, include:

- Early and quick transportation of trauma patients to a specialised trauma facility;
- Use of immediate bleeding control procedures in patients with an obvious bleeding source and in those presenting with haemorrhagic shock in extremis and a suspected source of bleeding;
- Use of permissive hypotension until major bleeding has been stopped in the initial phase following trauma without brain injury;
- Application of measures to reduce heat loss and warming the hypothermic patient to achieve and maintain normothermia;
- Use of restricted volume replacement therapy to achieve target blood pressure until bleeding can be controlled;
- Administration of vasopressors in addition to fluids in the presence of life threatening hypotension;
- Employment of damage control surgery in severely injured patients presenting with deep haemorrhagic shock, ongoing bleeding and coagulopathy;
- Repeated measurement of haemoglobin (Hb) as an indicator of bleeding and serum lactate and/or base deficit measurements to estimate and monitor the extent of bleeding and shock;
- Initiation of monitoring and measures to support coagulation immediately upon hospital admission;
- Continuation of resuscitation measures using a goal-directed strategy guided by standard laboratory coagulation values and/or viscoleastic tests;
- Red blood cells(RBC) administration to a target Hb of 7 to 9 g/dl and platelet transfusion to maintain a platelet count above 50×10^9/L;
- Local implementation of evidence-based guidelines for management of the bleeding trauma patients;
- Having in place local clinical quality and safety management systems which include parameters to assess keymeasures of bleeding control and outcome.

The changes and/or new recommendations of the fifth edition of the guidelines include:

- For the local bleeding managementin the pre-surgical setting, besides the use of tourniquets, the use of*localcompression and pelvic binders* is recommended to stop life-threatening bleeding from open extremity and suspected pelvic fracture, respectively;
- For the initial assessment of the injured patient,besides the physician clinically evaluation of the extent of traumatic haemorrhage, *the use of the shock index* is suggested to assess the degree of hypovolaemic shock;
- In patients with pelvic ring disruption *the use of aortic balloon occlusion should be considered only under extreme circumstances* in order to gain time until appropriate bleeding control measures can be applied (surgical bleeding control and/or pre- peritoneal packing and/or angiographic embolization);
- Immediate further investigation, *including focused assessment with sonography in trauma (FAST) and contrast-enhanced whole body computed tomography*, is recommended for the detection and identification of type of bleeding and potential source of bleeding;
- *Screening for patients treated with anticoagulants* is recommended;
- In patients treated or suspected of being treated with oral direct anti-factor Xa or thrombin inhibitors agents, *measurement of plasma levels by tests calibrated for specific agents is suggested;*
- Besides early and repeated monitoring of haemostasis using either a combined traditional laboratory determination and/or point of care tests, *platelet function monitoring with point-of-care devices is suggested as an adjunct in patients with suspected platelet dysfunction*;

- For the fluid therapy, *balanced electrolytes solutions and avoidance of saline solutions are both recommended*;
- Tranexamic acid should be administered in trauma patient who is bleeding or at risk of significant haemorrhage as soon as possible, en route to the hospital and *within 3 hours after injury, even before obtaining results from a viscoelastic assessment* [3]*;*
- For the initial coagulation resuscitation in patients with expected massive haemorrhage, there are still two possible strategies to be used: use of plasma, in a plasma–RBC ratio of at least 1:2, or fibrinogen concentrate and RBC as needed; however the ratio-based concept [4] has been challenged as haemostatic resuscitation with standard doses has limited effect on coagulopathy being neither hemostatic nor resuscitative in trauma haemorrhage [5,6]; moreover, not all studies showed a mortality benefit of fixed high plasma-RBC ratios; use of high plasma-RBC ratiosalso take time to achieve hemostasis, lead to dilution and areassociated with complications (e.g. transfusion-related acute lung injury, pathogen transmission, multiple organ dysfunctions)[7];
- If a plasma-based coagulation resuscitation strategy is followed, the use of fresh-frozen plasma (FFP) should be guided by standard laboratory coagulation screening parameters and/or viscoelastic evidence of coagulation factor deficiencies; however, *FFF should not be used for the treatment of hypofibrinogenemia*;
- If a coagulation factor concentrate-based strategy is used, *factor concentrate treatment should be based on standard laboratory coagulation parameters and/ or viscoelastic evidence of a functional coagulation factor deficiency;*
- Fibrinogen concentrate (3-4 g) or cryoprecipitate (15–20 single donor units)supplementation is recommended only *if major bleedings accompanied by hypofibrinogenemia* diagnosed by viscoelastic signs of a functional fibrinogen deficit or a *plasma Claus fibrinogen level of less than 1.5 g/l;*
- If fibrinogen levels are normal in the bleeding patient, prothrombin complex concentrate (PCC) or plasma may be administered based on evidence of delayed coagulation initiation using viscoelastic monitoring, *as well as factor XIII (FXIII) supplementation if there is a functional FXIII deficiency;*
- The use of recombinant factor VIIa may be considered only if major bleeding coagulopathy persist despite all attempts to control bleeding and *never as a first line treatment;*
- In patients with ongoing bleeding*, reversal of antithrombotic agents* is recommended;
- In the bleeding trauma patient on vitamin K-dependent oral anticoagulants emergency reversal includes early use of *both PCC and iv. vitamin K1*;
- In the bleeding trauma patient on direct oral anticoagulants, *PCC may be considered only for reversal of factor X inhibitors*; *dabigatran, a direct thrombin inhibitor, may be reversed by the specific antidote (idarucizumab);* however, tranexamic acid may be administered in life-threatening bleeding due to both types of inhibitors;
- Patients who has been treated with antiplatelet agents and present with continuing bleeding may receive platelet concentrates if platelet dysfunction is documented; *platelet transfusion is also suggested in patients with intracranial haemorrhage (ICH) if they undergo neurosurgery but not in those with ICH who will not undergo surgery* [8]; these patients may benefit from the administration of desmopressin;
- For thromboprophylaxis, early mechanical thromboprophylaxis with intermittent pneumatic compression (IPC) is recommended while the patient is immobile and has a bleeding risk; *combined pharmacological and IPC thromboprophylaxis is recommended within 24 hours after bleeding has been controlled and until the patient is mobile*; neither *the use of graduated compression stockings* nor the routine use of inferior vena cava filters is recommended for thromboprophylaxis.

In conclusion, a multidisciplinary approach and adherence to evidence-based guidance are key to improvingbleeding trauma patient outcomes [9]. These guidelines have the potential to ensure a uniform standard of care across Europe.

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THROMBOELASTOMETRY IN PERIOPERATIVE PERIOD

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Introduction

Perioperative bleeding after major cardiac and non-cardiac surgery, transplantation and traumatic injury is one of the most important causes of death among the adult population [1]. Due to the aging population, comorbidities and complexity of the surgery perioperative bleeding is still the major cause for perioperative complications and it worsens the results of surgical treatment.

Already on admission to the hospital, as many as 25% of the victims have a blood clotting disorder, and in 40% of the victims uncontrollable bleeding is the leading cause of death [2]. Perioperative, post-traumatic bleeding and bleeding in intensive care unit are multifactorial. Sometimes it is difficult to distinguish surgical bleeding from bleeding caused by coagulopathy. It is important to diagnose coagulopathy and provide appropriate treatment but also not to delay surgical reexploration.

Coagulopathies have been treated with fresh frozen plasma (FPP) followed by platelet transfusion for many years as the protocols for massive bleeding have been introduced into clinical practice. The protocols for massive bleeding were based on research, experiences of the clinicians and standard coagulation tests (ST): activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT) and fibrinogen concentration.

The introduction of new laboratory tests based on viscoelastic properties of blood and blood clot and the introduction of new active substances provides an individual approach to the treatment of coagulation disorders of the patients in perioperative time, after injury and in ICU [3].

New laboratory tests thromboelastography (TEG) / thromboelastometry (ROTEM) and aggregometry introduced into clinical practice, are part of point-of-care (POC) diagnostics and help clinicians to detect coagulopathies early, reduce blood loss, transfusion requirements an improve perioperative treatment [4]. In addition to FFP and platelet transfusion new pharmacologic agents such as prothrombin complex, fibrinogen, antifibrinolytics and even recombinant factor VIIa could be administered according to the results of viscoelastic tests.

News in laboratory tests - Point of Care Testing

Standard tests of blood coagulation are plasma-based and evaluate plasmatic activation without the cellular components of whole blood and they do not reflect the physiology of cell based thrombin generation [5]. No information about clot stability or hyper/hypo fibrinolysis is provided by ST which are performed at 37°C and thus ignoring if patient is hypothermic. As coagulation system is a very dynamic process, 40-90 min is too long a period when the information about the coagulation is provided by ST and this delay could lead to inappropriate treatment [6].

To overcome unreliability of ST viscoelastic tests are gaining the popularity as POC tests. Thromboelastography (TEG) was developed during world war II, rotational thromboelastomy (ROTEM) is an enhancement of thromboelastography and was developed during 1995-1997 [7]. These two systems differ in technical implementation and the nomenclature of the results obtained but both tests result in graphic presentation of the formation and disintegration of the blood clot and reference values.

The advantages of viscoelastic hemostasis tests are:

1. test is performed with whole blood and not just plasma;
2. they inform about formation, stabilization and lysis of the blood clot, and
3. test is performed in the operation room or intensive care unit and the result is obtained in median turnaround time 23 min.

The most comprehensive information about coagulation is obtained if viscoelastic tests are interpreted in combination with aggregometric tests. Aggregometric tests reveal disorders of primary hemostasis such as acquired platelet dysfunctions and allow the quantification of the effect of antiplatelet medication.

A graphic presentation of the formation of blood clots obtained in the case of a normal coagulation state is shown in Figure 1 [8]. The graph shows all three stages of blood clot formation: initiation (initiation), strengthening (amplification) and enlargement (propagation).

In the ROTEM system the whole blood sample is put in the cuvette and a cylindrical pin is immersed connected to a detector system. The pin is rotated by a spring alternating to the right and the left. As long as the blood is liquid, the movement is unrestrictive. In TEG system the pin remains still and the cup is moving during the test. As fibrin strings form between the cup and the pin the movement of the pin is restricted inversely with rising the clot firmness. This is detected optically and on the computer the curve as well as the numerical parameters are written.

The parameters of ROTEM analysis

CT (clotting time): time from start of the measurements until initiation of clotting — initiation of clotting, thrombin formation, start of clot polymerisation.

CFT (clot formation time): time from initiation of clotting until a clot firmness of 20mm is detected — fibrin

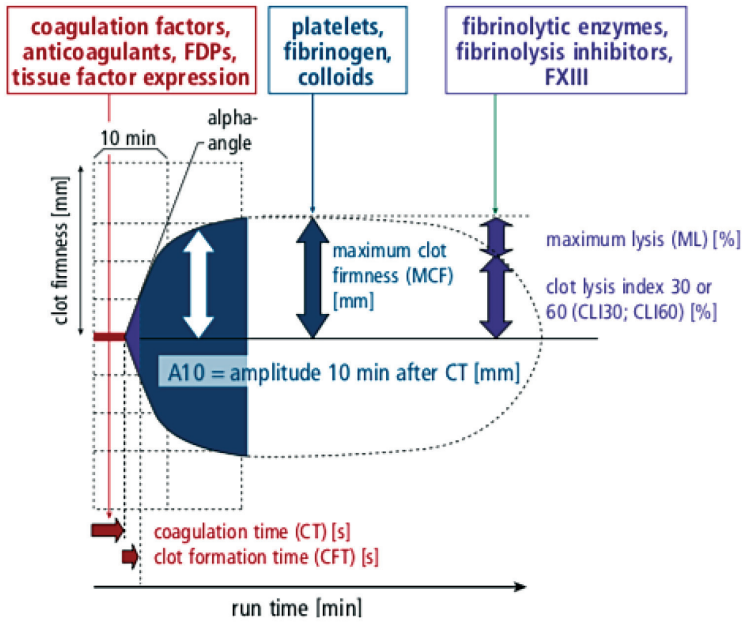

Figure 1. Thromboelastrometry (ROTEM); CT (coagulation time), CFT (clot formation time), MCF (maximum clot firmness), CLI (clot lysis index).

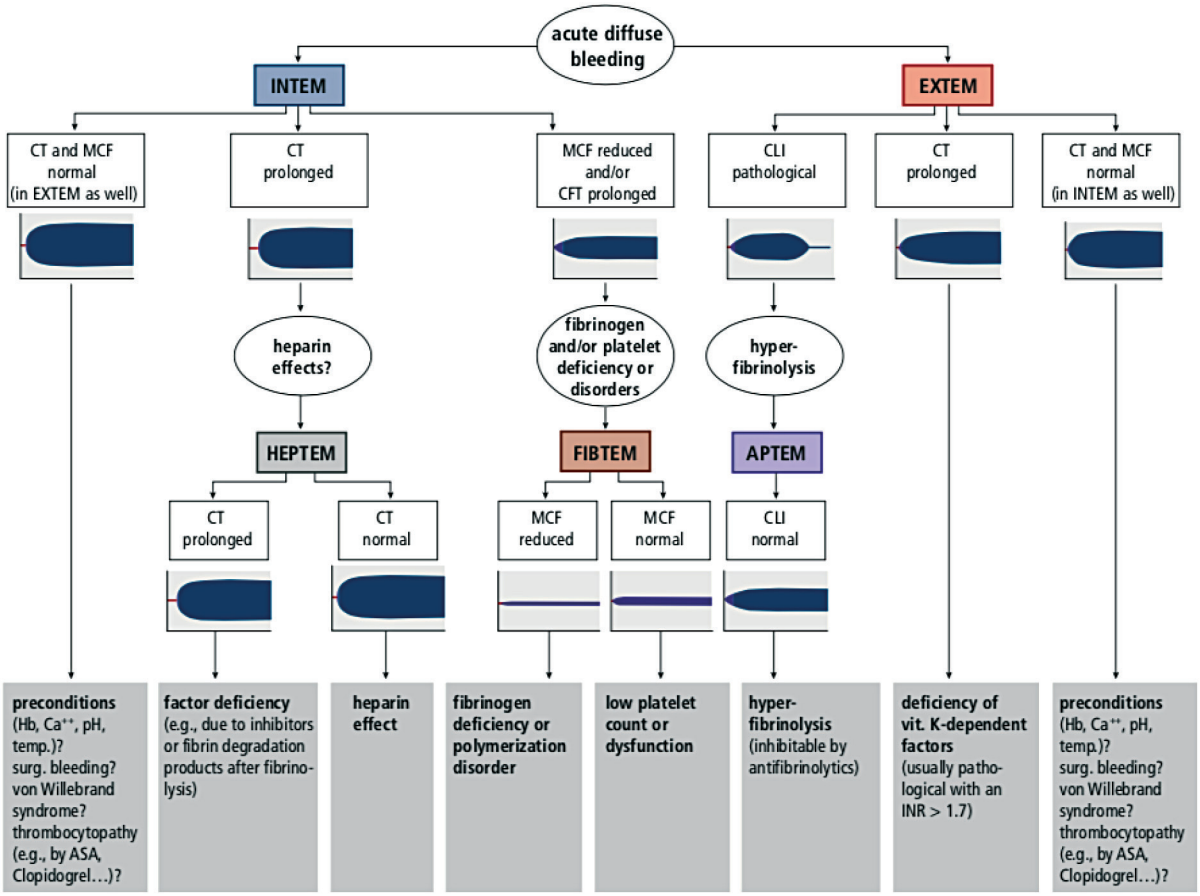

Figure 2. ROTEM diagnostic algorithm of the "Essener-Runde" task force.

polymerisation, stabilisation of the clot with platelet and FXIII.

MCF (maximum clot firmness): firmness of the clot — increasing stabilisation of the clot by the polymerised fibrin, platelets as well as FXIII.

ML (maximum lysis): reduction of clot firmness after MCF in relation to MCF — Stability of the clot (if < 15%) or fibrinolysis (if > 15%).

Rotem tests

EXTEM: coagulation is initiated by a small amount of tissue thromboplastin (tissue factor).

INTEM: coagulation is initiated via the contact phase, it is sensitive for factor deficiencies of the intrinsic system and for the presence of heparin in the sample.

FIBTEM: coagulation is activated as in EXTEM. By the addition of cytochalasin D the platelets are blocked. The resulting clot is only depending on fibrin formation and fibrin polymerisation.

APTEM: coagulation is activated as in EXTEM. By the addition of aprotinin, fibrinolytic processes are inhibited in vitro. The comparison of EXTEM and APTEM allows for rapid detection of hyperfibirinolysis.

HEPTEM: coagulation is activated as in INTEM. The addition of heparinase in the reagent degrades heparin present in the sample and therefor detects coagulopathies due to the excess heparin.

Bleeding in perioperative period

Bleeding in perioperative period is multifactorial and could be due to the surgical trauma or coagulopathies or both. The patient could be at increased risk of bleeding because of congenital or acquired coagulation disorder which should be detected already in preoperative period. Other haemostasis disorders can have several other causes. They could be related to the chronic disease of the haemostasis related organs: liver, kidney, bone marrow or could be related to the hemodilution and consumption of coagulation factors during the surgery or early postoperative period or related to use of heparin and protamin after cardiac surgery. To avoid perioperative bleeding and to improve results of surgical treatment the POC testing were introduced into clinical practice. On the basis of clinical trials the diagnostic algorithm was developed to help clinicians with interpretation of ROTEM results in perioperative settings [8]. The ROTEM diagnostic algorithm of the "Essener-Runde" task force is presented in Figure 2.

ROTEM testing is also proven to be useful for evaluating coagulation disorders in patients receiving direct thrombin inhibitors (dabigatran, argatroban, bivalirudin, hirudin).

In trauma patients ROTEM was proven to detect coagulation disorder which is associated to the injury severity score (ISS) and the mortality. Patients with a mild injury have normal ROTEM tests, patients with ISS between 10 and 25 usually have ROTEM tests with characteristics of hypercoagulability and with patients with ISS between 20-35 plus the most severely injured patients ROTEM test show hypocoagulabities and hyperfibrinolysis [9].

On the basis of ROTEM the goal directed therapy of coagulopathies could be introduced [10].

Conclusion

New laboratory tests and new active substances enable us to better cure coagulopathy in perioperative period. To improve outcome of surgical treatment it is crucial to distinguish coagulopathy from surgical bleeding and start treatment. ROTEM is POC testing which leads to GDT and development of useful algorithm for the clinicians.

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HAEMOSTATIC MONITORING: OLDER VS. NEWER APPROACHES

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Introduction

Clinical management of acute moderate to severe bleeding is one of the major challenges for an anesthetic team. Though substitution of erythrocytes by transfusion of red blood cells (RBC) is a routine task, adequate maintenance of haemostasis may be considerably more demanding. In fact, the underlying cause of bleeding and subsequent treatment may be completely different depending on the clinical scenario. The cause of perioperative bleeding is often multifactorial, and its dynamic nature (i.e., major deterioration in a matter of minutes) calls for rapid diagnosis and immediate interventions. Perioperative coagulopathy involves both procoagulant and anticoagulant proteins as well as cellular components (i.e. platelets and endothelium). Relatively long turnaround time for conventional hematological testing (>30–60 min) is adequate for managing chronic disorders, but it is crucial to have a faster time (<15–20 min) in perioperative, critically ill patients.

The evaluation of coagulopathy is conventionally performed using prothrombin time [(PT) or international normalized ratio; (INR)], activated partial thromboplastin time (aPTT), fibrinogen level (Clauss method), and Platelet count. These represent the so-called **"Standard Laboratory Tests (SLTs)".** Some of the limitations of traditional laboratory testing can be overcome by the use of **viscoelastic coagulation testing (VE)**, or **viscoelastic haemostatic assays (VHA)** in whole blood**. Thromboelastometry®** (ROTEM, TEM Innovations, Munich, Germany) and **Thrombelastography®** (TEG; Haemonetics, Niles, Illinois, USA) are the currently available viscoelastic test devices. SLTs reflect neither the cellular component of haemostasis nor evaluate plasma anticoagulants. SLTs' relevance is limited to the initiation phase of coagulation and measures only the time until generation of the first 2-5% of thrombin. In contrast, VE devices are designed to assess whole-blood clotting kinetics and whole-blood clot strength and better reflect the interaction between pro- and anti-coagulants, pro- and anti-fibrinolytic factors, and platelets.

VE monitoring devices can guide clinicians in more specific haemostatic therapies and fulfill the requirements for a so-called **"Point-of-Care"(POC) test**. POC testing suggests the capability to perform a fast response test at the bedside, easily interpretable and capable to assist decision making for timely interventions. As a consequence, VE monitor-guided haemostatic management may be effective in reducing the number of patients receiving blood products and follow a step by step approach which may lead to more cost saving when compared to SLT-based management strategies and have a better outcome in terms of unnecessary transfusions avoided.

A piece of History

Despite what one might expect, viscoelastic approach to haemostasis is a relatively old issue. After Prothrombin Time (PT) initiation by A. Quick in 1935, it was H. Hartert in Heidelberg, Germany at the end of World War II, who first described thromboelastography (TEG) but the method was left abandoned and rediscovered and developed at the 50s' – 60s'. In the meantime, Langdell, Wagner & Brinkhous, had already presented Activated Partial Thromboplastin Time (APTT) in 1953. By the 80s', TEG was mainly used in acute haemorrhage monitoring and management, mainly in USA and in 1993, TEG®Haemonetics Corporation, IL, USA patented the method of Thromboelastography (and the relevant assays INTEG, EXTEG, FIBTEG etc.). In 1995-7, TEM®, Munich, Germany, under the inspired leading of A. Calatzis, developed the method further and Rotational Thromboelastometry (ROTEM®, with assays as INTEM, EXTEM, FIBTEM, etc.), was initiated in 2003. The major input of K. Goerlinger, Essen, Germany should not be neglected mainly in developing fast response algorithms based in POC viscoelastic testing for different clinical situations.

Standard Laboratory Tests (SLTs)

The cascade model (although now replaced by the cellular model of haemostasis) is quite useful and educational to understand the basis and the differences between standard lab tests (SLTs) and viscoelastic haemostatic assays (VHA) such as Thromboelastography (TEG®) or Rotational Thromboelastometry (ROTEM®)

Activated Partial Thromboplastin Time (aPTT) is the time for plasma to clot in a matrix after activation of the "intrinsic" or contact pathway and the common coagulation pathway. It is actually the necessary time for the haemostatic system to provide the first fibrin monomers after activation of the intrinsic pathway. Citrated plasma is being used along with added activators (like ellagic acid, silicondioxid or kaolin) and cofactors (phospholipids and Ca^{2+}). After an initial preincubation with the activators on a negative charged surface (from which it is often called "contact system") plasma factor XII (FXII) is activated followed by FXI activation. The recalcification of the system leads to activation of FIX, FX, FII (prothrombin to thrombin) and finally FI (fibrinogen) to fibrin. The time spent for this sequence in seconds represents APTT. It is the pathway mainly affected by the presence of heparin or heparin like drugs.

Prothrombin Time (PT) represents the initiation of the "extrinsic" pathway of coagulation and is the time

for plasma to clot after the addition of tissue factor (FIII) in supraphysiologic concentrations. As in APTT measurement, citrated plasma is used and mixed with heparin (to inactivate the intrinsic pathway), cofactors (phospholipids and Ca^{2+}) and recombinant human tissue factor as activator.

Prothrombin ratio (PR) is the ratio of patient's PT / control plasma while **International Normalized Ratio (INR)** was introduced in an attempt to standardize the PT. In its original manifestation, the PT was very variable because different thromboplastins, necessary for the measurement, were non-standardized and derived from many varied sources. PTs performed on the identical specimen by different laboratories were inconsistent. The concept behind the INR is that differences between the thromboplastins are accounted for by a calculation:

INR= [patient's PT / normal MNPT)]^{ISI} - international sensitivity index

The INR has no units (it is a ratio) and is determined to one decimal scale. The first step of the INR calculation is to "normalize" the PT by comparing it to the mean normal prothrombin time (MNPT), the geometric mean of the prothrombin times of the healthy adult population. In the second step, this ratio is raised to a power designated as the **ISI (international sensitivity index).** The ISI is a function of the thromboplastin reagent. Two groups of data are used to derive the ISI (i) normal healthy individuals and (ii) patients stabilized on *warfarin*. Paired PT data are obtained from multiple samples using both the working thromboplastin reagent and the international thromboplastin standard. It becomes evident that INR has been developed to provide guidance for the treatment of patients receiving warfarin anticoagulants and not as mean of the global haemostatic function of the patient.

Thrombin Time (TT) assesses in time the final common pathway and is useful for heparin detection (indirect action) and anticoagulants detection with direct anti-FIIa (thrombin) effect (like dabigatran).

Activated clotting/coagulation time (ACT) is the whole blood ability to form a visible fibrin monomer in a glass tube and used in the OR or at the bedside for patients receiving intravenous heparin anticoagulation (e.g. under extracorporeal circulation or continuous haemofiltration). ACT could be considered as POC testing method assessing heparin action, protamin overdose, platelet lack/dysfunction, or factors deficiency. Nevertheless, ACT provides no specific information about the nature of the haemostatic problem like viscoelastic assays.

Fibrinogen (FIB) plasma levels measurement according to Clauss method, is the commonest way for fibrinogen quantitative measurement, nevertheless it is based on the thrombin Clotting Time (CT): Diluted plasma is clotted with a high concentration of thrombin at 37 °C and the CT is measured. The result is compared with a calibration curve of a reference plasma sample of known FIB concentration to give a result in g/L. Most laboratories use an automated method.

Platelet count (PLT) is a purely quantitative measure and cannot detect pre-existing, drug-induced or perioperative acquired PLT dysfunction.

In general, SLTs use samples of citrate plasma and not whole blood, with activators +/- cofactors and other additives, Ca^{++} (FIV), PLTs (as "activated" surfaces), FV, FVIII, Fibrinogen (FI) (as substrate) with an end point of time measurement until the first fibrin monomers formation (at the very beginning of thrombin generation). Since clot formation is completed with fibrin polymerization and stabilization, there are two "blind" spots in this type of measurement. Problems or deficiency of FXIII or FvW (von Willebrand) are not covered. On the other hand, hyperfibrinolysis, one of the most common issues during acute bleeding of any pathology, is not detected, which may be detrimental if neglected.

PT, aPTT and INR are only indicative of the haemostatic disorder with no proof of haemostatic capacity and limited only at the initial first 2-5% thrombin formation in plasma, without the presence of platelets or other blood cells. Clotting times (PT, aPTT and TT) determine only the speed of thrombin generation but not the mechanical stability of the clot. They are excellent for congenital disorders detection (FVIII-, FIX- haemophilia) and very important for the urgent diagnosis of cases of acquired haemophilia. Useful in heparin detection, but may be falsely long (PT and aPTT) in cases of hypofibrinogenaemia and afibrinogenaemia. They are not designed for intraoperative bleeding disorders and are mostly performed at a standardised temperature of 37 °C, while acute bleeding coagulopathies are very often in the context of hypothermia (like in trauma). Plasma fibrinogen measurement by Clauss method is not standardized and is industry dependant, absolutely quantitative and not qualitative and the same stands for platelets even if they are counted in a blood smear examination under a microscope. The cellular haemostatic component is not evident and there is no information on clot formation over time and no hyperfibrinolysis detection.

Finally, they are time consuming and have long turnaround times (40 - 90 min) which delay results, while most probably when results are available, patient's condition is much more different from that in the moment of blood sampling.

For all these reasons the recent 2016 Guidelines First Update for the management of severe perioperative bleeding (S. A. Kozek-Langenecker et al.) recommends the use of standardised questionnaires on bleeding and drug history as preferable to the routine use of conventional coagulation screening tests such as aPTT, INR and platelet count in elective surgery and also recommends the application of intervention algorithms incorporating pre-defined triggers and targets based on viscoelastic haemostatic assay (VHA) coagulation monitoring to guide individualised haemostatic intervention in the case of perioperative bleeding.

Viscoelastic Haemostatic Assay (VHA) Monitoring

VHA monitoring like **Thromboelastography (TEG®)** or **Rotational thromboelastometry (ROTEM®)** is a fast bedside (point-of-care) diagnostic approach of haemostatic derangements through whole blood viscoelastic properties assessment. VE devices provide results much more quickly than SLTs (in minutes), reflect the cellular component of haemostasis and evaluate plasma anticoagulants. They interpret the cell-based model of coagulation, with the tissue factor (FIII) initiation of coagulation and platelet binding to collagen, followed by the

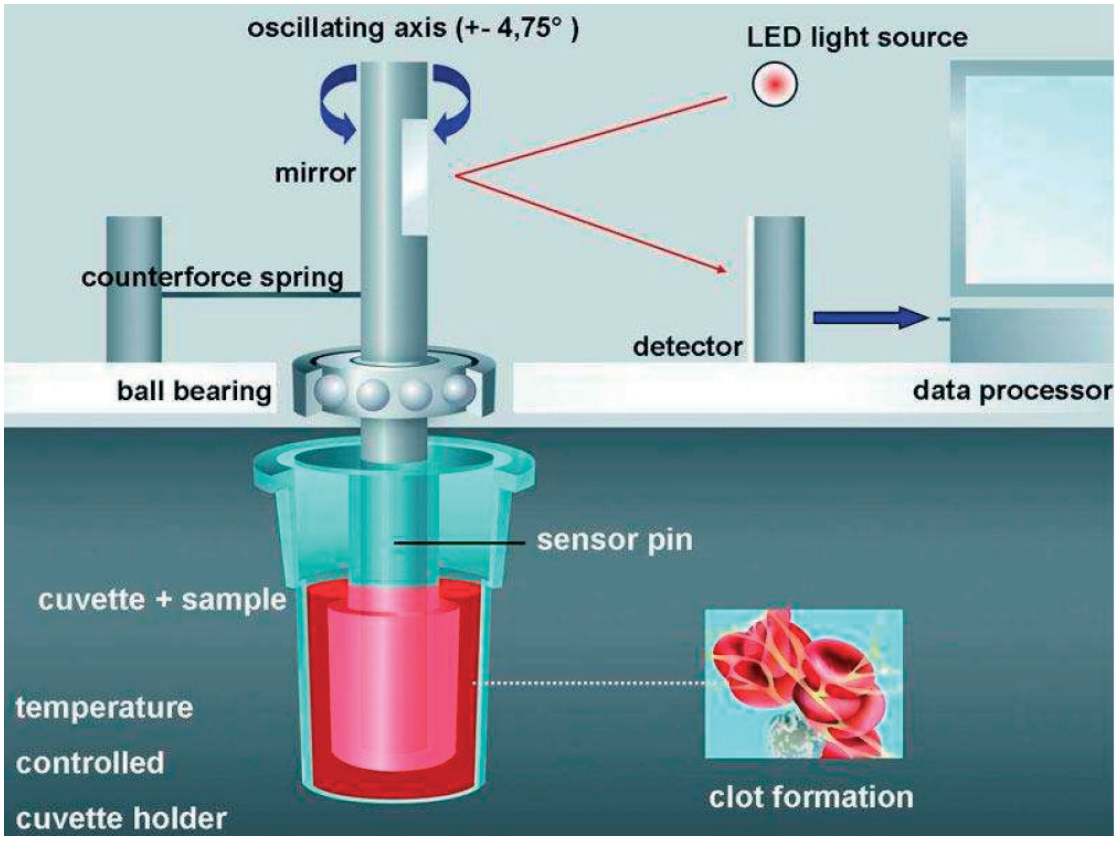

Fig. 1. The principle of rotational Thromboelastometry (ROTEM®). (See text for explanation)

propagation phase with platelet recruitment to growing thrombus and amplification of the coagulation cascade and finally, clot stabilization with platelet to platelet interaction and polymerized fibrin deposition. Moreover, normal (or abnormal) (hyper-) fibrinolysis can be detected in minutes and lead to antifibrinolytic treatment. Goal directed treatment of acute haemostatic disorders can be achieved and unnecessary transfusions may be prevented.

Thromboelastometry (ROTEM®) and thrombelastography (TEG®) are the currently available viscoelastic test devices. Clot formation is assessed in whole blood by measuring the tensile (viscoelastic) force development between the cup/cuvette (where the whole blood is put along with specific reagents) and the immersed pin. In TEG the cup rotates facilitating clot formation, while in ROTEM the cuvette remains stable and the suspended sensor pin rotates forwards and backwards, on a oscillating axis by +/- 4,75°. Clot formation in the cuvette impedes free pin oscillation. This "viscoelastic signal", created by a beam of light from a LED source falling on the oscillating pin is detected and processed to a graphical representation (i.e. thromboelastogram) of a real time clot formation (Fig 1). Thromboelastogram is highly dependent on endogenous thrombin generation, fibrin polymerization, and fibrin interactions with platelet glycoprotein IIb/IIIa receptors. In cases of systemic fibrinolysis, early clot degradation by plasmin can be observed (Fig. 2). Both ROTEM and TEG offer similar types of tests, and yield closely related clotting measurements, but these two systems are not interchangeable because of different types of reagents and blood samples (recalcified citrated blood or fresh whole blood, accordingly). Heparinase cups are specifically requested for TEG, but the reagents for EXTEM, FIBTEM, and APTEM for ROTEM contain hexadimethrine (polybrene), which neutralizes heparin. In terms of the reference ranges, it is recommended that local values are set according to the specific patient population that is, adults or children, ethnicity, and disease types.

After starting a ROTEM analysis, a typical trace is displayed providing information about clot formation (Fig. 3). The **clotting time (CT)** reflects initial fibrin formation following thrombin generation and is defined by reaching an amplitude of 2 mm. Clot formation is further described by the time to increase amplitude from 2 mm to 20 mm (**CFT; clot formation time**) and **alpha (α) angle** (tangent of the slope). The amplitude of clot strength can be assessed 5, 10, 15, and 20 minutes after CT (**A5, A10, A15,** and **A20**, respectively) until the maximum amplitude is reached (**MCF; maximum clot firmness**). A5 and A10 can be used to predict MCF reliably for early decision making. The MCF assesses the combined effect of platelet activation and aggregation, fibrin polymerization and cross-linking by FXIII.

As all stages of clot formation are influenced by the activity of procoagulants and anticoagulants from clot formation to its dissolution, thromboelastometry (and thrombelastography) represents the gold standard in detecting hyperfibrinolysis. This is defined by detecting more than 15% breakdown in clot strength compared with MCF within one hour after the clotting time (ML; maximum lysis).

The most notable advance in haemostatic management using viscoelastic testing is a fibrin-specific clot assessment. The system uses a combination of assays to characterize the

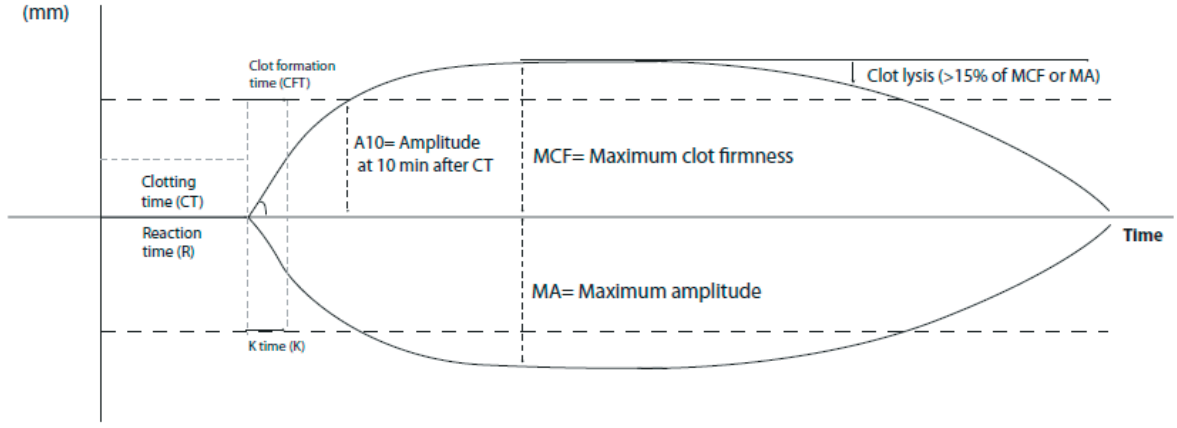

Fig. 2. Changes in whole blood viscoelasticity are detected optically in ROTEM, and electromechanically in TEG and clot formation parameters are generated on ROTEM (upper panel) and TEG (lower panel). Plasmatic coagulation is reflected on CT and R time, and initial clot development is shown on CFT and K time (also on a angle). Maximal viscoelasticity is defined by MA or MCF for TEG and ROTEM, respectively. Systemic fibrinolysis is suspected when clot breakdown (>15% of MA or MCF) is observed within 1 h. CT, clotting time; CFT, clot formation time; MA, maximum amplitude; MCF, maximum clot firmness.

coagulation profile for obtaining more detailed information about haemostasis and suggests the cause of the observed coagulopathy. It allows for rapid differential diagnosis between different haemostasis defects and anticoagulant drug effects. In general, the most frequently used assays are EXTEM, INTEM, FIBTEM, and APTEM. Initial screening is performed using INTEM and EXTEM assays. The addition of a contact activator (ellagic acid) provides information on the so-called "intrinsic" pathway that is comparable to aPTT measurement (INTEM assay). Extrinsic activation can be initiated by adding recombinant tissue factor, an analogue to PT measurement (EXTEM assay). Fibrin polymerization can be assessed by running an EXTEM test with the addition of a platelet inhibitor Cytochalasin D (FIBTEM assay). The FIBTEM assay on the ROTEM allows a rapid assessment (<5–10 min) of fibrin polymerization in whole blood, and it correlates with plasma fibrinogen levels. In combination with EXTEM, FIBTEM can delineate hypofibrinogenemia from isolated thrombocytopenia, both of which decrease the overall clot strength.

Heparin effects can be identified by adding heparinase to an INTEM test (HEPTEM assay) and comparing

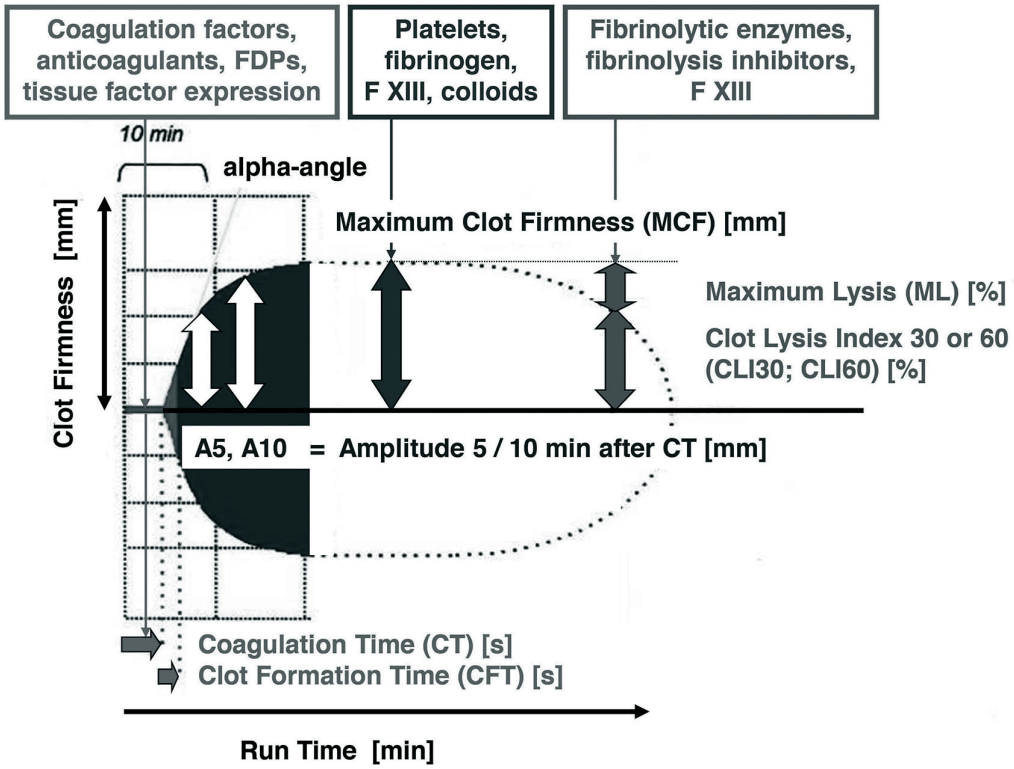

Fig. 3. A typical thromboelastogram created by ROTEM® using citrated whole blood. Each phase of the clot formation and lysis can be use to interpret specific alterations or deficiencies of coagulation factors, anticoagulant drugs, tissue factor expression, platelets and fibrinogen participation and finally the action of the fibrinolytic system. (See text for more explanation)

the results to the INTEM test. Hyperfibrinolysis is suspected when the decrease of the amplitude over 1h is more than 15% of the maximum amplitude on TEG or ROTEM. To confirm hyperfibrinolysis, an EXTEM test can be performed with the addition of aprotinin which inhibits plasmin-induced fibrinolysis in vitro (APTEM assay). When these assays are normal, surgical bleeding rather than coagulopathy should be suspected. Alternatively, EXTEM and FIBTEM can be used mainly in clinical settings. For example, if CT in EXTEM is prolonged, prothrombin complex is given; if MCF of EXTEM is less than 40mm and/or MCF of FIBTEM is less than 8mm, fibrinogen concentrate is given to the patient.

Taken together, viscoelastic coagulation testing, particularly ROTEM, primarily focuses on the correction of hypofibrinogenemia, and, if any, fibrinolysis, which is followed by the correction of thrombocytopenia (or platelet dysfunction) and/or procoagulant factor deficiency. Several clinical studies have demonstrated the hemostatic effectiveness of this approach, and reduced the need for plasma transfusion.

There is a distinct influence of haematocrit on ROTEM® measurements. A low hematocrit (<25%) leads to an increase in the plasma fraction of the whole blood specimen, which in turn, may result in increased FIBTEM MCF. However, the correlation between FIBTEM MCF and plasma fibrinogen levels is higher if haematocrit is decreased, and thus, the FIBTEM assay offers an adequate method to determine fibrinogen deficiency. Bleeding patients are frequently treated with colloids, particularly with hydroxyethyl starch (HES), and this treatment has been demonstrated to have an impact on fibrinogen measurements. In the presence of HES, erroneously high levels of plasma fibrinogen have been measured using photometric assays. In this case, the ROTEM® FIBTEM test appears to be the most reliable method to detect fibrin polymerisation defects.

Experimental and Clinical Studies

Martini et al., in an experimental study investigated the independent and combined effects of hypothermia and hemorrhage with resuscitation on coagulation in swine and evaluated clinically relevant tests of coagulation. Hypothermia and hemorrhagic shock contribute to coagulopathy after trauma. The authors concluded that hypothermia inhibited clotting times and clotting rate, whereas hemorrhage impaired clot strength. Combining hypothermia with hemorrhage impaired all these clotting parameters. PT, aPTT were not sensitive whereas ACT was not specific in detecting these coagulation defects. Only TEG differentiated mechanism related to clotting abnormalities, and thus may allow focused treatment of clotting alterations associated with hypothermia and hemorrhagic shock.

The weakness of SLTs to estimate active coagulopathy in the course of severe perioperative bleeding has been described by Kim et al. in a study of healthy volunteers, where the authors investigated the performance and feasibility of ROTEM profile by comparing prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT) results with ROTEM parameters. They tested EXTEM and INTEM activated determinations, mainly focusing on 5 basic parameters: Clotting time (CT), clot formation time (CFT), a angle, clot formation rate (CFR), and maximum clot firmness (MCF). They compared then PT and APTT results with ROTEM parameters and observed no significant correlations between any of the ROTEM EXTEM or INTEM parameters and PT results. Only 1 parameter, the INTEM CT value, was significantly correlated with APTT results ($r^2 = 0.165$, $P < .05$).

Haas et. al reviewed thoroughly and exhaustively the evidence for the continued use of standard laboratory tests (SLTs) of coagulation and their usefulness to assess coagulopathy and to guide bleeding management in the perioperative and massive bleeding setting. Medline was searched for investigations using results of SLTs as a means to determine coagulopathy or to guide bleeding management, and the outcomes (i.e. blood loss, transfusion requirements, mortality) were reported. A total of 11 guidelines for management of massive bleeding or perioperative bleeding and 64 studies investigating the usefulness of SLTs in this setting were identified and were included for final data synthesis. Referenced evidence for the usefulness of SLTs was found in only three prospective trials, investigating a total of 108 patients (whereby microvascular bleeding was a rare finding). Furthermore, no data from randomized controlled trials support the use of SLTs. In contrast, numerous investigations have challenged the reliability of SLTs to assess coagulopathy or guide bleeding management. They concluded that there is actually no sound evidence from well-designed studies that confirm the usefulness of SLTs for diagnosis of coagulopathy or to guide haemostatic therapy.

In a Health Technology Assessment study, Whiting et al. examined viscoelastic point-of-care testing performing a systematic review and a cost-effectiveness analysis (PROSPERO Study). The study was funded by the Health Technology Assessment program on behalf of NICE (National Institute of Excellence), UK and aimed to assess the clinical effectiveness and cost-effectiveness of VE devices to assist with the diagnosis, management and monitoring of haemostasis disorders during and after cardiac surgery, trauma-induced coagulopathy and post-partum haemorrhage (PPH). Sixteen databases were searched to December 2013. The health-economic analysis considered the costs and quality-adjusted life-years of ROTEM and TEG compared with SLTs in cardiac surgery and trauma patients. A decision tree was used to take into account short-term complications and longer-term side effects from transfusion. The model assumed a 1-year time horizon. Thirty-one studies (39 publications) were included in the clinical effectiveness review. Eleven RCTs assessed VE devices in 1089 patients undergoing cardiac surgery; six assessed thrombelastography (TEG) and five assessed ROTEM. There was a significant reduction in RBC transfusion [RR 0.88, 95% confidence interval (CI) 0.80 to 0.96; six studies], platelet transfusion (RR 0.72, 95% CI 0.58 to 0.89; six studies) and fresh frozen plasma to transfusion (RR 0.47, 95% CI 0.35 to 0.65; five studies) in VE testing groups compared with control. There were no significant differences between groups in terms of other blood products transfused. Continuous data on blood product use supported these findings. Clinical outcomes did not differ significantly between groups. There were no apparent differences between ROTEM or TEG.

There were no data on the clinical effectiveness of VE devices in trauma patients or women with PPH. VE testing was cost-saving and more effective than SLTs. For the cardiac surgery model, the cost-saving was £43 for ROTEM, £79 for TEG and £132 for Sonoclot (a relevant device less used). For the trauma population, the cost-savings owing to VE testing were more substantial, amounting to per-patient savings of £688 for ROTEM compared with SLTs, £721 for TEG. This finding was entirely dependent on material costs, which are slightly higher for ROTEM. VE testing remained cost-saving following various scenario analyses. The authors concluded that VE testing is cost-saving and more effective than SLTs, in both patients undergoing cardiac surgery and trauma patients.

Nevertheless, subsequent studies revealed the usefulness of VE testing in PPH of several etiologies. A more relevant population with deranged and "rebalanced" haemostasis is patients with cirrhosis. Despite PT, aPTT and INR indicating coagulopathy, global coagulation tests (thrombin generation and TEG/ROTEM) suggest that haemostasis is balanced in stable chronic liver disease. In this context ESA Bleeding Guidelines (2013, 2016) discourage FFP perioperative transfusion in patients with cirrhosis. VE testing is a valuable tool in the intraoperative management of these patients, mainly during liver transplantation. Allogeneic blood products transfusion during liver transplantation (LT) can be associated with increased morbidity and mortality. TEG®/ROTEM® information, allows creation of goal-directed, individualized treatment algorithms that may improve patient outcome. In liver transplantation such algorithms have become standard with impressive benefits: reduced transfusion needs, less complications, shorter length of ICU and hospital stay, better survival and reduced treatment costs. Kirchner et al. evaluated retrospectively the safety events observed with this approach in their clinic. 266 LT patients were identified by chart review. A ROTEM-based algorithm with clotting factors concentrates (CFC), namely fibrinogen concentrate and/or PCC, guided the haemostatic therapy. Doppler ultrasound was used to evaluate thrombosis in the hepatic artery, portal vein, and hepatic veins. Stroke, myocardial ischemia, pulmonary embolism, and transfusion variables were recorded. 156 patients receiving CFC were included in the CFC group and 110 not receiving CFC were included in the non-CFC group. Safety events were compared between these two groups. The results showed that allogeneic transfusion(s) in the 266 patients was low, with medians of 2 (interquartile range [IQR],0-5), 0 (IQR 0-0), and 0 (IQR 0-1) units for red blood cells (RBCs), fresh-frozen plasma (FFP), and platelets (PLTs), respectively. Ninety-seven of 266 LTs (36.5%) were performed without RBCs transfusion, 227 (85.3%) without FFP, and 190 (71.4%) without PLTs. There were no significant differences in thrombotic, thromboembolic, and ischemic adverse events occurrence between the CFC group and the non-CFC group (11/156 patients vs. 5/110; p = 0.31). The authors concluded that in LT, ROTEM-guided treatment with fibrinogen concentrate and/or PCC did not appear to increase the occurrence of thrombosis and ischemic events compared to patients who did not receive these concentrates.

In a similar retrospective study in our department we have been able to show haemostatic management following an A5 based ROTEM algorithm, reduced FFP transfusion leading to blood products administration according to the intraoperative needs, obviously reducing relative transfusion risk and cost. We compared three successive patient groups who underwent LT. In the first group, fifteen patients were empirically transfused with FFP/Blood Products (BPs) based on standard lab tests and clinical bleeding signs. In the second group, eighteen patients were transfused with FFP/BPs based on ROTEM values and in the third group, 31 patients were transfused with FFP/BPs based on a specific algorithm based on A5 ROTEM values, facilitating decision making for transfusion triggers in the first 5 minutes of the test. We found a statistically significant difference in FFP transfusion between the first two groups and the third one. Group one & two had mean values of FFPs transfused 14,93 and 11,53 respectively, while in Group three only 4,46 units.

Conclusion

Haemostatic monitoring based on SLTs is a representation of an artificial system not very close to "in vivo" situations. They are clotting times that measure the enzymatic activity of coagulation factors from a start signal until the formation of fibrin (stop signal). They have two main indications: Detection of factor deficiencies (congenital/acquired) and anticoagulant treatment monitoring. They also suffer from two blind spots (FXIII & FvW assessment), but in this case, it may be covered by other special tests. Their main weakness is that they interpret only the "cascade" model of the coagulation procedure, reinstituted as an artificial system (no cells; Ca^{2+},pH,and ^{o}C are not incorporated) and with long turnaround time. In the surgical setting of perioperative coagulopathy (i.e. trauma, cardiac, liver surgery, obstetric PPH, e.t.c.), SLTs offer no prediction, no detection and no coagulation management guidance. On the contrary, Viscoelastic Haemostatic Assays is a Point-of-Care monitoring procedure offering the most promising support in early and individualized decision making for the correct type and quantity of blood product/factor/substitute needed to be transfused with impact in overall morbidity, mortality and cost.

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AN UPDATE ON UNILATERAL SPINAL ANESTHESIA

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Introduction

Spinal anesthesia is a safe and economical method, which can performed in a rapid and relatively simple way. It is associated with a lower incidence of postoperative nausea and vomiting (18%) compared to general endotracheal anesthesia (30%), as well as with a lower rate of postoperative pain compared to general anesthesia which makes it more convenient for use in out-patients and in single-day surgery settings. However, some complications do occur after spinal anesthesia, such as the problems with urination and hours long „immobility", which negatively impacts patient comfort and length of stay in the recovery room after operation. Other typical unwanted side effects of spinal anesthesia are the episodes of hypotension, as the consequence of accompanying sympathicolysis, or more rarely bradycardia. The risk of hypotension occurring due to vasodilation in lower portions of the body certainly requires great care in the selection of spinal anesthesia for high-risk cardiovascular patients (especially those with aortic stenosis and coronary vascular disease).

Unilateral spinal block is not associated with these disadvantages typical of bilateral spinal anesthesia, and provides the patient with all the benefits of this anesthesiology procedure. The success of the technique depends on a number of factors. In addition to the type of local anesthetic, its concentration and dose, the baricity of the injected solution, it depends as well on the shape and thickness of the spinal needle, speed of injection, patient position during the injection and period of time after the injection.

In order to achieve unilateral spinal block, 0.5% hyperbaric bupivacaine should be used, injected at 0.33 ml/min or at a slower rate. During the injection and in the 20 minutes to follow, the patient should lie in the position of lateral decubitus on the side of the planned surgery, with his knees flexed towards the chest. An injection of 5 mg (1 ml) hyperbaric 0.5% bupivacaine induces 1-hour block up to T12, and 7.5-10 mg (1.5-2 ml) extends the block up to the level of T6. During the fixation period of 20 minutes, cephalic extension of the block can be supported or prevented by the elevation or descent of the operating table head rest.

History

Most studies of unilateral spinal anesthesia were performed near the middle of the 20th century. Even then, at the very beginnings, the authors were able to clearly identify the benefits of this procedure in patients with cardiovascular comorbidities because of lower-degree sympathicolysis. The degree to which sympathicolysis was confined to a single side of the body in the context of unilateral spinal anesthesia was for the first time investigated and evaluated by Tanasichuk et al., comparing the changes in skin temperature and skin resistance in both legs, before, during and after the performance of spinal anesthesia. It was therefore possible to demonstrate strict sympathetic unilateral spinal anesthesia („real spinal anesthesia"), the degree of success of which depends on a variety of factors.

After the advancements made in general endotracheal anesthesia, the interests in spinal anesthesia gradually waned with time, so that further studies were not undertaken until 1980, when the „renaissance of regional anesthesia" was witnessed. At that time, the control of intrathecal distribution of local anesthetics depended primarily on their baricity and patient position , but the produced success rates were not outstanding at all.

Local anesthetics

The choice of a local anesthetic for spinal anesthesia depends on the indications, preferences of individual anesthesiologists and the results expected by surgeons. In out-patient surgery, short-term blocks are required (lasting for 2 hours at the most). In the past, hyperbaric lidocaine was used for this purpose, with a rapid onset but short-term action, and it was therefore extensively used, but it turned out that it caused an increased incidence of postoperative transitory neurologic symptoms (TNS). Long-acting hyperbaric tetracaine caused less TNS, but was not shown to be a convenient agent either due to a very low success rate for sensory unilateral spinal anesthesia. Not until bupivacaine, which very rarely causes TNS (0.7-1.3%), could be achieved sufficiently high motor block or sensory block success rates. Although bupivacaine is a long-acting local anesthetic, the length of its action can be adequately controlled and possibly shortened by appropriate dose adjustments. That was the reason why bupivacaine or its L-isomer levobupivacaine (in use since 2000) was the preferred anesthetic in most of the recent studies of unilateral spinal anesthesia. Ropivacaine, with a similar low rate of TNS events as bupivacaine, is suggested as another possible option. In its hyperbaric form it allows for a more rapid recovery from bilateral spinal anesthesia and enables earlier patient discharge from the hospital. The first comparative studies of unilateral spinal anesthesia performed using bupivacaine, levobupivacaine or ropivacaine in out-patient surgery settings have produced almost identical results. The use of short-acting hyperbaric prilocaine for

unilateral spinal anesthesia has so far produced unsatisfactory results. At present, there is no published relevant information about short-acting 2-chlorprocaine.

Impact of local anesthetic baricity

The baricity of a local anesthetic describes its density at the body temperature of 37°C and its behavior after being injected into the spinal canal; a hyperbaric solution descends to the bottom (the lowest spot available), while hypobaric and isobaric solutions remain close to the injection site. However, this „descent" of a hyperbaric solution is much more pronounced and more independent of the patient position compared to hypobaric or isobaric solutions. It is not surprising, therefore, that hyperbaric bupivacaine solution has been primarily used for the study of unilateral spinal anesthesia.

Impact of injected dose and concentration of local anesthetic

The success rate of unilateral spinal anesthesia depends for the most part on the dose of injected local anesthetic. Only a very low dose and concentration of tetracaine (4.4 mg 0.1%, compared to 9 mg 0.5%) can produce one-sided spinal spinal anesthesia (67% vs 0%), although with the failure rate of 17%. Although higher doses can always produce adequate analgesia, they are rarely accompanied by unilateral sensory block only. As the consequence, anesthesiologists are faced with the dilemma whether to increase the doses of anesthetic which would produce more reliable effects of anesthesia but also a higher proportion of bilateral blocking on the one hand, or to reduce the doses of anesthetic and achieve only unilateral sensory blocking but with higher rates of failure. Moreover, the success rate of sensory unilateral block is increased from 25% to 90% by volume reduction of injected 0.5% hyperbaric bupivacaine (2.5 ml vs 1.4 ml).

Many augmentation strategies for intrathecal analgesia have been proposed. With the addition of clonidine (0.5-1.0 μg/kg BW) the block can be prolonged for up to 2-3 hours. A meta-analysis by Popping *et al.* concluded that the concomitant use of an opioid such as fentanyl intrathecally allows the reduction in the dose of local anesthetic, while augmenting its analgesic potency thereby decreasing its adverse effects.

It has also been proven that the addition of dexmedetomidine intrathecally significantly extends the analgesic effect in unilateral spinal anesthesia. Dexmedetomidine (DEX) is a potent, selective α_2 adrenergic agonist and when given intrathecally, it exerts its analgesic effect via stimulating spinal α_2 receptors. Wu *et al*., in their meta-analysis showed that addition of intrathecal DEX significantly increased the duration of postoperative analgesia and reduced analgesic consumption. The increase induration of postoperative analgesia is dose dependent but with increase in the incidence of bradycardia.

As the analgesic effect produced by intrathecal α_2 adrenergic agonists and intrathecal opioids is through different pathways, their combination would lead to additive effects. Therefore, by using low dose of both DEX and fentanyl the incidence of adverse effects of both drugs could be reduced while greatly prolonging postoperative analgesia. This would be beneficial in high-risk elderly patients as it reduces the need for postoperative opiates or NSAIDs.

The results of Sohair A. Megalla study demonstrated that adding intrathecal DEX 6μg to bupivacaine–fentanyl mixture in high-risk elderly patients receiving unilateral spinal anesthesia for major orthopedic surgery provides significantly longer postoperative analgesia with mean time to first analgesic request in FD group of 522.79±59.0 min compared with 207.37±20.19 min in F group, with *P*=0.0001. DEX enhanced the onset of sensory and motor blockade, but without statistical significance. Hemodynamic stability was observed in both groups. Pruritis was recorded in group (12%) compared with none in F group. Sedation was more in FD group.

Similar results were seen by Routray *et al*., who observed prolonged postoperative analgesia when they compared adding either 5 μg DEX or 25 μg fentanyl to 15 mg bupivacaine. They reported time to first analgesic request of 299±33.92 min with DEX. This was much lower than our results probably owing to the synergistic effect offered by the addition of α_2 agonist to opioids. Mahendru *et al*. also compared adding 25 μg fentanyl or 5 μg DEX to 12.5 mg bupivacaine for orthopedic surgery. DEX showed prolonged sensory and motor blockade, less postoperative analgesic requirement, and good hemodynamic stability.

In the study, dose of fentanyl was 20 μg. Reuben *et al*. stated that the least dose of intrathecal fentanyl needed to provide satisfactory postoperative analgesia in elderly patients undergoing revascularization procedures was 20 μg.

Kim *et al*. observed increasing intrathecal fentanyl dose more than 25 μg did not further increase duration of analgesia. Early respiratory depression was reported by Varassi *et al.* after administration of 50 μg, but not 25 μg of intrathecal fentanyl. Moreover, itching was more common after doses of at least 25 μg.

Age-related reduction in the cerebrospinal fluid, degenerations in the central and peripheral nervous systems, and anatomical changes in the dorsal and lumbar spine may contribute to increased sensory and sympathetic block levels in the elderly.

On the contrary, Hoda *et al.* studied adding 20 μg fentanyl to low-dose bupivacaine 6 and 8 mg in elderly patients for hip surgery. Although the reduced dose of bupivacaine led to more stable hemodynamics, the duration of spinal anesthesia was only 123 and 136 min, respectively.

A study by Ben David *et al*. used mini-dose bupivacaine 4 mg plus 20 μg fentanyl and demonstrated effective anesthesia sufficient for hip surgery in elderly patients with mean operative time between 50 and 110 min. Using a small dose of local anesthetic may prevent hypotension but unfortunately it may not provide acceptable anesthesia.

A dose of 6 μg DEX was used in study of Sohair A. Megalla. The idea behind adding intrathecal DEX is to produce a high drug concentration in the vicinity of α_2 adrenoreceptors present in the spinal cord, thereby blocking the conduction of C and Aδ fibers, hyperpolarization of postsynaptic dorsal horn neurons, and intensifying local anesthetic-induced conduction block. Based on a meta-analysis by Abdallah *et al*., there is no single dose

recommended for intrathecal DEX, and it may vary between 3 and 15 μg when added to local anesthetic in spinal anesthesia.

Wu *et al*. in their meta-analysis demonstrated average prolongation of sensory block duration of 43 min for up to 5-μg DEX versus 102 min for more than 5-μg DEX. With increase in dose to 10 and 15 μg, risk of bradycardia is increase.

Both groups in our study showed hemodynamic stability. Alonso *et al.* showed that when intrathecal fentanyl is added to hyperbaric bupivacaine in elderly patients undergoing orthopedic surgery, it results in greater hemodynamic stability and allows the use of a lower dose of local anesthetic thereby reducing the need for intravenous ephedrine during surgery.

Al Mustafa *et al*. found maximum sedation score of 2 in their patients when they added 5 or 10 μg of DEX to 12.5 mg of bupivacaine. When administered via an intrathecal or epidural route, α_2 agonists show analgesic effect without deep sedation, as supraspinal central nervous system sites are not exposed to high drug concentrations.

Unilateral spinal anesthesia offers more hemodynamic stability when compared with conventional spinal, as hypotension is reduced four-folds. Unfortunately, none of the patients in our study had strictly unilateral spinal block, some sensory and motor blockade was present in the contralateral limb but at a much lower level.

Cohan *et al*. calculated the dose of hyperbaric intrathecal bupivacaine according to the patients' height, where those shorter than 155 cm received 1.1 ml, from 155 to 170 cm received 1.5 ml, and taller than 170 cm got 1.8 ml and were kept on the desired side for 10 min.

There was still sensory and motor blockade in the opposite limb. Determining the optimal time period for the patient to remain in the lateral position is difficult as the anesthetic drug may still have some spillover effect even if the patient is placed for 30–60 min in the lateral position, especially with hyperbaric bupivacaine doses 12–20 mg. Use of lower doses such as 5–8 mg hyperbaric bupivacaine and maintaining lateral position for 10–15 min may prevent migration of the anesthetic drug to the nonoperated side but at the expense of the duration. Animal studies found evidence of neurotoxicity when DEX was given epidurally without local anesthetic in rabbits in a dose of 6.1 μg. Yet other studies proved intrathecal DEX to possess neuroprotective effects by virtue of its presynaptic α_2 adrenoreceptor inhibition. By inhibiting catecholamine release, vasospasm is reduced and spinal cord perfusion is enhanced. It showed a neuroprotective profile comparable to methylprednisolone when given intrathecally within 8 h of spinal cord injury in rats.

Conclusion

Unilateral spinal anesthesia is a cost-effective, readily available and simple technique. Isolated unilateral block involves only sensory, motor and sympathetic functions on one side of the body and it is able to afford all the spinal block benefits, without any typical side effects seen with the bilateral block approach. The absence of hypotension makes unilateral spinal anesthesia especially convenient for the patients with a higher cardiovascular risk (for instance, those with aortic valve stenosis or coronary vascular disease). An increasing number of surgical procedures are nowadays performed as single-day surgery. Until recently, spinal anesthesia has not been considered convenient for the purpose, not only because of a higher incidence of intraoperative hypotension and postoperative urinary retention, but also due to prolonged postoperative hospitalization before discharge. This is not the case with unilateral spinal anesthesia: motor functions are rapidly regained, the incidence of urinary retention is extremely low, and patients can usually be discharged sooner than with general anesthesia or bilateral spinal anesthesia. The addition of 6 μg intrathecal DEX to hyperbaric bupivacaine–fentanyl mixture seems to be a better choice for long-duration orthopedic procedures in high-risk elderly patients, as it offers prolonged postoperative analgesia, stable hemodynamics, minimal adverse effects, and better patient satisfaction.

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CERVICAL EPIDURAL ANESTHESIA: IS IT A SAFE ALTERNATIVE FOR MASTECTOMY?

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Mastectomy for carcinoma breast is usually done under general anesthesia. However, there is growing interest to do this surgery under regional (cervical epidural and upper thoracic) anesthesia. The advantages are less intra-operative blood loss, less intra-operative surgical stress and better postoperative analgesia. All these factors help to decrease morbidity and mortality in such patients.

Cervical epidural anesthesia (CEA) involves the administration of local anesthetics (LA) into the epidural space resulting in the block. CEA has been used for carotid artery, thyroid, breast, airway, upper limb and other head and neck surgeries.

The reason for choosing CEA in most comparative studies involved assessment of physiological parameters of respiration and circulation including: circulatory hemodynamics and heart rate variability, spirometry parameters, diaphragm function and combination there of.

Cervical epidural space (CES) extends from the fusion of spinal and periosteal layers of the dura mater at the foramen magnum to lower border C7. The CES itself contains fat the dural sac, blood vessels and connective tissue. CES is narrow with a width of 3-4 mm as compared with 5ü6 mm in lumbal spine. Among the various methods of epidural space identification, hanging drop (HD) method and loss of resistence (LOR) tehnique were most commonly used for locating the CES. Access to the CES can be made with the patient sitting, prone or in lateral decubitus.

Most studies observe side effect of CEA. CEA in patients can decreases tidal volume, forced vital capacity, forsed expiratory volume in the 1st second (FEV1) and vital capacity (VC). The effects on the circulatory sistem result from the sympathetic blockade along with changes to baroreflex sensitivity. Heart rate decreases from the blockade of cardio-acceleratory fibers and also reflexively from diminished venous return through intracardiac stretch fibers. Variable decrease in arterial pressure, ejection fraction and cardiac index can also be observed. The most common and possibily an expected side effect of CEA is bilateral sensory and motor block of upper extremites.

Considering the potential procedural risks, and its effects on cardio-respiratory systems, the practice of CEA suggests an unnecessary patient exposure, which could be easily avoided by better anaesthetic and analgesic choices. The evidence and observations suggests that the clinical use of CEA must have a strong rationale-mostly supported by unique patient demands and surgical requirement and CEA is a safe alternative for mastectomy, in extensive carotid artery surgeries and possible oral-hypopharyngeal cancer surgeries.

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ANAESTHETIC PRACTICE FOR CAROTIDE ENDARTERECTOMY OVER 30 MONTHS IN TERTIARY TEACHING HOSPITAL IN BOSNIA AND HERZEGOVINA - RETROSPECTIVE REVIEW

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Abstract

Since 1970, Carotid endartrectomy (CEA) has emerged as the best treatment option in the prevention of cerebral infarction in patients with high-grade carotid artery stenosis. Given an average 5% reduction in long-term risk of stroke or death following CEA, there is a need to keep major cardiovascular events at the time of surgery lower than 4 to 5%. Most patients present with a 'vulnerable brain', from previous cerebral ischaemia and pathophysiologies that include diffuse atherosclerosis, coronary artery disease, chronic lung disease and diabetes mellitus. In this context, does the choice of anaesthetic technique – regional vs general anaesthesia – make any difference. *The aim* of this article is to present the advantages and disadvantages of anesthetic techniques through the experience of the University Clinical Center of Republic of Srpska. *Methods:* A retrospective analysis includes data on 485 patients from electronic medical records operated for carotid disease for 36 months (2015-2018. years) at the Clinic for Vascular surgery of the UKC Republic of Srpska, Banja Luka. The following data were collected and analyzed: demographic, use of general (GA) or regional anesthesia, conversion from regional in general anesthesia, shunt insertion, length of hospital stay and 30 day mortality. Anesthesia for all study patients was performed with one of two anesthetic techniques: general balanced endotracheal anesthesia (GA) or regional anesthesia, cervical superficial block without sedation (RA). Statistical data processing was done using the SOFA statistic (1.4.6) of the program. *Results:* The study includes 485 patients in our institution for carotid disease, 320 (65.8%) men and 165 (34.4%) women. The average age of the patient is 69.91 years. Of the 485 carotid endarterectomies, RA was used in 326 (67.2%) patients, GA was used in 159 (32.8%). 17 patients from the RA group were converted to GA (1 claustrophobia, 1 pain, 15 disrupted neurological status). The indications for placing the protective shunt were different. There were a total of 44 patients in both groups, 25 (15.7%) in the GA group and 19 (5.8%) in the RA group. The length of hospital stay was similar among groups GA 4.55 days vs. RA 4.68 days. The total 30 day mortality in the analyzed data was 15 patients (3.09%), in the GA group 7 patients (4.4%), in the RA group of 8 patients (2.4%). *Conclusion:* Our study shows that there is no significant statistical difference in the length of hospital stay and 30 days of mortality between CEA in general and regional anesthesia. The advantages of regional anesthesia are an awake patient- "gold-standard" of brain monitoring and a significantly lower price.

Key words: carotid endarterectomy, anesthesia, general, regional, outcome

Introduction

Stroke is the most common cause of neurological damage in adults and one of the leading causes of mortality in the developed world. In the United States, when viewed separately from other cardiovascular diseases, the stroke occupies the third place among all causes of death after heart and cancer [1]. On average every 40s, someone experiences a stroke and every 3-4 minutes someone dies as a result of a stroke [2]. Ever since 1970, carotid endarterectomy (CEA) is the best treatment for the prevention of stroke in symptomatic patients with high carotid arterial stenosis [2]. Symptoms include transient ischemic attacks (TIAs) and cerebral hypoperfusion that can provoke syncope. The relationship between carotid alerting symptoms and stroke is still unclear. Less than 10% of all strokes had TIA, and most patients with carotid stenosis had no warning signs before the neurological event. When we have in mind that the average reduction in risk of stroke and death is 5% after CEA, there is a need to reduce the incidence of major cardiovascular events in the perioperative period to less than 4 to 5%. Patients who come to surgery due to carotid blood vessels stenosis usually have a large number of associated diseases in the form of diffuse atherosclerosis, ischemic heart disease, chronic lung, renal disease, and diabetes.

There are currently two types of procedures in addition to the pharmacological therapy for the treatment of carotid disease: open carotid surgery and stent insertion. Meta-analysis [4] wich included seven randomized controlled trials published between 1998 and 2006 found that open carotid surgery was associated with a similar degree of stroke or death, but also less procedural failures and restenosis after 1 year, and greater incidence of damage cranial nerves after 30 days of surgery. The authors concluded that open carotid surgery remains the "gold standard" of treatment. Stent placement may be a preferred alternative to high-risk patients for open carotid surgery [5].

Contemporary anesthesiology circles have a continuous and open debate about the choice of anesthetic techniques for these procedures, and whether the choice of anesthesia technique can have an effect on the outcome of treatment. For now, in most institutions, the choice of anesthesia technique is guided by local clinical practice of surgeons and anesthesiologists, as well as the condition and motivation of patients.

The aim of this article is to show the advantages and disadvantages of anesthesia techniques through the experience of the University Clinical Center of Republic of Srpska.

Methods

The retrospective analysis includes data from electronic data chart of 485 patients operated for carotid disease in the period of 36 months from 01.01. 2015 to 31.12. 2018. at the Clinic for vascular surgery, UKC Republic of Srpska, Banja Luka. The following data were collected and analyzed: demographic, use of general (GA) or regional anesthesia, conversion from regional to general anesthesia, shunt insertion, length of hospital stay and 30 day mortality.

Anesthesia for all study patients was performed with one of two anesthesia techniques: general balanced endotracheal anesthesia (GA) or regional anesthesia, cervical superficial block without sedation (RA). Statistical data processing was done using the SOFA statistic (1.4.6) of the program.

The results

The study includes 485 patients in our institution for carotid disease, 320 (65.8%) men and 165 (34.4%) women. The average age of the patient is 69.91 years, ASA score II and III. Of the 485 carotid endarterectomies, RA was used in 326 (67.2%) patients, GA was used in 159 (32.8%). 17 patients from the RA group were converted to GA (1 claustrophobia, 1 pain, 15 disrupted neurological status). The indications for placing the protective shunt were different. There were a total of 44 patients in both groups, 25 (15.7%) in the GA group and 19 (5.8%) in the RA group. The length of hospital treatment was similar among groups GA 4.55 days vs. RA 4.68 days. The total 30 day mortality in the analyzed data was 15 patients (3.09%), in the GA group 7 patients (4.4%), in the RA group of 8 patients (2.4%).

Discussion

In our study, there were more male patients (65.8%), which is also found in many other studies [6,7]. A lower percentage of women undergoing carotid surgery is a common finding in many studies, which may not reflect the prevalence of carotid artery stenosis in women and men. Kapral and associates [8] concluded in their study that the average age at the time of surgery is the same in men and women, and that the older age at the time of the onset of cerebrovascular disease in women may reflect less use of carotid endarterectomy in elderly women.

There is still no scientific evidence to show that any anesthesia technique is superior to the other. The main objectives of anesthesia are maintaining the airway control, oxygenation and cardiovascular stability in a diseased patient, providing good operational conditions and allowing monitoring of cerebral function. Cardiovascular instability is common during CEA due to multiple factors: autoregulation of arterial pressure is damaged after stroke, baroreceptor sensitivity is reduced due to carotid arterosclerosis, the effects of carotid surgery and anesthesia, elderly age, associated illnesses and medication. Cardiovascular instability (hypotension or hypertension) can cause stroke or precipitate cardiac ischemia and heart failure, although it has been thoroughly perceived that most perioperative strokes are caused by thromboembolism. General or loco-regional anesthesia individually with all its variations offer its advantages and disadvantages, without any evidence that any method is better than the other.

In the last few years, regional anesthesia is an often used anesthetic technique in our institution. 62.7% of patients in our study were RA. We use only a cervical superficial block (redirection technice) without sedative drugs. Sedation was used in 66% of patients, and additional infiltration of local anesthetic in 35% of patients in the Davies study and associates on 1000 CEA performed in a superficial or deep cervical block [9]. Regional anesthesia is achieved by blocking the cervical plexus. The technique can be performed blindly, using anatomical or using ultrasound, which in most centers becomes "gold standard". During the clamping of the carotid artery, an anesthesiologist has no insight into the limitation of blood flow through Willis's hexagon. About 10% of patients experience neurological changes after carotid artery clamping [10]. Neurological damage caused by cerebral O_2 desaturation can be monitored by NIRS spectroscopy [11]. This technique is able to predict neurological deficits during CEA 5 to 10 seconds before clinical signs become apparent [12]. Testing awake patient is a superior way of monitoring cerebral blood flow. Tests of awake patients include the ability to tighten a hand or respond to visual or audio stimulus. In spite of the existence of NIRS monitoring if there is doubt about the compromise of cerebral circulation during the operation, the best monitoring is the patient's confirmation that it is good. The use of loco-regional anesthesia of possible reoperation can be performed without the need for additional anesthesia [13]. The performance of CEA in RA has a positive effect on the postoperative neurocognitive outcome [14]. In our study, we only had one case of claustrophobia, which may occur more often, so the protocol for the treatment of unexpected patient reactions should exist. In addition to the listed facts, if cost-effectiveness is considered, if there is a desire for precise monitoring of cerebral physiology, the choice of anesthesia should be RA.

GA in our study was used in 32.8% of patients. General anesthesia for CEA provides easier and better positioning of the patient and offers a quiet operating field with easier and better visualization during the operation. It is an ideal choice for a claustrophobic patient, a patient with neurological diseases or an articular-bone disease. The main advantage of GA is a safe airway, adecvate ventilation and oxygenation. McCholloch and associates [15] in a randomized study of the effects of propofol and sevoflurane on cerebral hemodynamics during carotid endarterectomy have shown that propofol anesthesia offers better hemodynamic conditions during the carotid artery clips period, but there is no evidence that any anesthesia technique of GA is superior. The basic disadvantage of GA in carotid endarterectomies is the lack of adequate monitoring of cerebral function. It is widely accepted that awake patient during RA is "gold standard" which eliminates the need for additional neuromonitoring [16].

Indications for placing the protective shunt were different. Shunt was made in 25 (15.7%) patient from the GA group and 19 (5.8%) from the RA group. Patients in the GA group received a protective shunt while shunt in

the RA group was used in 15 patients due to intraoperative neurological failure while 4 patients received a protective shunt. The data of European Carotis Surgery Trial show very significant variations in the use of a protective shunt for the CEA both between the surgeon and among the countries [17]. 89% of the CEA is performed in Germany with a protective shunt, and only 1% in France [17]. There are only two prospective randomized studies on the routine use of shunt vs non-use of shunt, Gumerlock and Neuwelt in USA and Sandmann et al. in Germany [18]. They included 590 patients and showed a downward trend in perioperative stroke and death in routine shunt use, but without statistical significance [18]. In these studies there were significant variations in the perioperative use of antithrombotic therapy that complicate data and some methodological errors that may affect the validity of study results. The duration of the follow-up period in these studies is limited to only 30 days, so that late complications, restenosis or late stroke can not be assessed. Locati et al. [19] compared selective shunting with routine shunt in 1266 awake patients, but did not find any effect on the outcome. Now days, a large number of patients undergoing CEA have asymptomatic disease, and knowing that the benefit of surgery over drug therapy is lost if the incidence of perioperative stroke and death exceeds 3%, it seems even more important to examine the usefulness of routine use of the protective shunt during CEA large prospective, randomized studies .

There is no significant difference in the duration of hospital treatment for patients in our study, regardless of the anesthetic technique used, GA 4.55 days vs. RA 4.68 days. Although there is a trend of early discharge of RA patients, the difference has not yet become statistically significant [20].

The total 30 day mortality in the analyzed data was 3.09%, in GA (3.4%), in RA (2.4%). The GALA study finds slightly lower percentages of 30-day mortality (GA 1.5% vs. RA 1.1%), but also of no statistical significance.

The price of 2 hours of general anesthesia is the average duration of the CEA, is 200 Euros, and regional anesthesia is 12 Euros.

Conclusion

Our study shows that there is no significant statistical difference in the length of hospital treatment and 30 days of mortality between CEA in general and regional anesthesia. The benefits of regional anesthesia are a patient-gold-standard brain monitoring and a significantly lower price.

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EVALUATION OF THE KNOWLEDGE ON CHRONIC NON-CANCER PAIN AMONG PHYSICIANS FROM PRIMARY HEALTHCARE CENTERS

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Pain is one of the most common reasons for a patient to seek advice from their physician. Chronic pain lasts a long time. It can persist over months or years, sometimes even lifelong, and causes significant impairment of physical, psychological and cognitive functions of the body thus negatively affecting the quality of life of the patient. Chronic non-cancer pain is highly important health issue, yet not enough understood and mostly inadequately treated.

It is likely that physicians in primary healthcare practice are poorly acquainted with the options of recent developments in the therapy of chronic pain of non-cancer etiology.

During 2018, a pilot case study was conducted in 12 health centers in the region of Autonomous Province of Vojvodina. The research was designed as an anonymous questionnaire.

The research included physicians from primary healthcare at the Departments of general medicine, Departments of occupational medicine and Departments of home treatment service. The evaluation was accomplished using Questionnaire *on the Treatment of Chronic Non-cancer Pain for Physicians in Primary Health Care* developed by the *Serbian Association of Pain Research and Treatment (SAPRT)* with an aim of enabling realistic identification and understanding of the treatment of chronic non-cancer pain.

The results obtained in this research are highly important and point out the importance of the treatment of chronic non-cancer pain in our environment.

The analysis of the questionnaire revealed that 29% of physicians reported that 30% of adult population complains of some type of chronic non-cancer pain, mainly females (87.7%) at the age of 61 to 70.

Even 59.4**%** physicians consider themselves poorly informed about possibilities to cooperate with other specialists in the field of chronic non-cancer pain.

Majority of physicians (52.3%) evaluates the pain empirically, whereas only 2.6% use relevant scales and empirical method.

The etiology of the pain was estimated as musculoskeletal and neuropathic by 78.7% and 30.3% of physicians, respectively.

Nonsteroidal anti-inflammatory drugs (NSAIDs) as conventional analgesics are prescribed for the treatment of chronic non-cancer pain by 62.6% of physicians. Most frequently prescribed opioid analgesics are Tramadol (6.2% of physicians) Fentanyl patch (1,3% of physicians), while Hydromorphone has never been prescribed for the therapy of chronic non-cancer pain.

Chronic pain was treated with coanalgesics by 54.2% of physicians, mainly pregabalin, which was prescribed by 35.5% of physicians.

Majority of physicians (89%) considers that patients are moderately satisfied with the treatment of chronic non-cancer pain.

During 2007, The European Commission's Eurobarometer performed a survey „*Health in the European Union*" that encompassed five EU countries. The survey revealed that every fifth inhabitant of Europe suffers chronic pain in the joints (52%), neck (32%), back (66%) or suffers headache (31%). One third of the population suffers pain throughout the year, 1/3 reported an unendurable pain and in 50% of the patients adequate alleviation and cure could be accomplished only after two years [1,2,5].

In Europe, most widely used medication for the treatment of chronic non-cancer pain still implicates NSAIDs (44%), and opioids are used in the range 22.4 - 23% [3,4,6,7]. Neuropathic pain is commonly managed using antiepileptics (50.7%) and antidepressants (28.7%) [8,9,10,11].

The majority of patients (87%) visited their doctors for chronic non-cancer pain during the past six months, 63% of them were treated by a pain management specialist whereas 31% of them have never received any pain therapy. 60% of patients were satisfied with the therapy, and 40% of them reported discontent [12].

Such outcomes are mostly due to inadequate knowledge of the physicians (predominantly in primary healthcare institutions), inadequate information of the patients, fear from administration of certain drugs for pain therapy (both among patients and doctors) as well as the unavailability of some drugs.

In recent decades, there have been substantial advancements in understanding of chronic pain, above all the physiology and pathophysiology of pain signal, enabling novel therapeutic approach and improved treatment of patients with chronic pain. However, chronic pain still remains underestimated and inadequately treated worldwide. Poor assessment of the quality and quantity of pain results in poor pain control and often leaving the patient in a "magic circle" of pain. To that end, diagnostics and treatment of chronic pain requires an organized and comprehensive approach, which is best achievable in relevant centers, clinics and outpatient clinics for pain therapy.

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LONG-TERM MECHANICAL VENTILATION AND DIFFICULT WEANING RESPIRATORY SUPPORT

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Introduction

The first question to be answered is how often mechanical ventilation (MV) is used in intensive care units? P.G. Metnitz and colleagues back in 2009, based on the SAPS 3 study, which included more than 13,000 patients in 299 intensive care units from 35 countries, showed that more than half of the patients (53%) had been subjected to artificial ventilation being admitted at ICU [1].

It should be noted that there is a variety of terminology and definitions in terms of "long-term mechanical ventilation" and "long-term separation from mechanical ventilation." In the work of Nicolo Ambrosino and Michele Vitacca (2018) the following options have been described [2]:

National Association for Medical Direction of Respiratory Care (NAMDRC) [3]: "the need for more than 21 consecutive days of MV for more than 6 h/day".

European Respiratory Society (ERS) Task Force [4]: "the need for more than 7 days of weaning after the first spontaneous breathing trial (SBT)". According to this definition patients may represent up to 14% of those admitted to ICU for mechanical ventilation (MV) accounting for 37% of all ICU costs with a hospital mortality up to 38% [5], being significantly higher compared with simple and difficult weaning [6-8].

Weaning is explained according to New Definition (WIND) study: "successful extubation after more than three SBTs or taking more than seven days". According to this definition, MV accounts for 10% of patients receiving MV with a 29.8% mortality [9].

Factors associated with prolonged weaning are shown in Table 1.

Basic statements long-term mechanical ventilation

Of course, long-term mechanical ventilation is based on a number of basic statements. First of all, this is the so-called concept of protective (safe) mechanical ventilation developed in the last 20 years to a greater extent for patients with ARDS. This concept is based on the following positions [10,11].

1. Target a tidal volume of 6 mL/kg predicted body weight in patients with ARDS (grade 1A vs. 12 mL/kg).
2. Plateau pressures should be measured in patients with ARDS and initial upper limit goal for plateau pressures in a passively inflated lung be < 30 cm H2O (grade 1B).
3. Positive end-expiratory pressure (PEEP) has to be applied to avoid alveolar collapse at end expiration (atelectotrauma) (grade 1B).
4. Strategies based on higher rather than lower levels of PEEP can be used for patients with moderate or severe ARDS (grade 2C).
5. Recruitment maneuvers could be used in patients with severe refractory hypoxemia (grade 2C).
6. Prone positioning should be used in ARDS patients with a PaO_2/FIO2 ratio <150 mm Hg in facilities that have experience with such practices (grade 2B).
7. We make no recommendation regarding the use of noninvasive ventilation (NIV) for patients with ARDS.

Table 1. Factors associated with prolonged mechanical ventilation

Systemic	▪ Chronic diseases, comorbidities ▪ Nutrition and metabolic problems ▪ Severity of illness ▪ Sepsis
Cardio-vascular function **Critical Illness neuromyopathy**	
Respiratory	▪ Unresolved respiratory causes of respiratory failure ▪ Diaphragm weakness or dysfunction ▪ Imbalance between work of breathing and respiratory muscle reserve ▪ Tracheo-bronchial obstruction ▪ Ineffective cough and secretion retention
Complications of management	▪ Ventilator associated pneumonia, infection ▪ Length and modalities of mechanical ventilation ▪ Tracheostomy ▪ Sedation ▪ Lack of early mobilization
Cognitive	▪ Sleep deprivation ▪ Anxiety/Depression
Management setting	▪ Protocols ▪ Staffing (number and professionals) ▪ Personnel training

8. Neuromuscular blocking agents (NMBAs) are used for ≤48 h in adult patients with ARDS and a PaO_2/FiO2 ratio <150 mm Hg.
9. A conservative rather than liberal fluid strategy is applied in patients with established ARDS who do not have evidence of tissue hypoperfusion (grade 1C).
10. In the absence of specific indications such as bronchospasm, using of beta 2-agonists for treatment of ARDS is not recommended (grade 1B).
11. Against the routine use of the pulmonary artery catheter for patients with sepsis-induced ARDS (grade 1A).
12. That mechanically ventilated sepsis patients be maintained with the head of the bed elevated to 30–45 degrees to limit aspiration risk and to prevent the development of ventilator-associated pneumonia (grade 1B).
13. That a weaning protocol be in place and that mechanically ventilated patients with severe sepsis undergo spontaneous breathing trials regularly to evaluate the ability to discontinue mechanical ventilation when they satisfy the following criteria:
    a) arousable;
    b) hemodynamically stable (without vasopressor agents);
    c) no new potentially serious conditions;
    d) low ventilatory and end-expiratory pressure requirements; and
    e) low FIO_2 requirements which can be met safely delivered with a face mask or nasal cannula.

If the spontaneous breathing trial is successful, consideration should be given for extubation (grade 1A).

A weaning protocol recommend in mechanically ventilated patients with respiratory failure who can tolerate weaning.

However, the literature data on the volume of tidal volume, peak inspiratory pressure and other parameters of mechanical ventilation in patients without ARDS are controversial. Therefore, PreVENT research is being conducted. The objective of the trail, therefore, is to de- termine whether ventilation with tidal volumes from 6 down to 4 ml/kg PBW, as compared to ventilation with tidal volumes from 8 up to 10 ml/kg PBW reduces duration of mechanical ventilation in ICU patients without ARDS at onset of ventilation. Specifically, we hypothesize that ventilation with low tidal volumes in- creases the number of days alive and free from ventilation at day 28 [12].

However, I would like to cite data from a literature review on mechanical ventilation in patients with a neurological profile conducted by R. Cinotti and co-authors [13]. Patients undergoing severe brain injury (BI) caused by trauma or intra-cranial haemorrhage display a high prevalence of respiratory complications, longer artificial ventilation period, and high rates of extubation failure, compared to other ICU patients. New data about MV management have been tested in the neuro-ICU setting. It is now clear that PEEP has minor effects on cerebral perfusion pressure. Protective ventilation with low tidal volumes (6–8 mL/kg of ideal body weight), could be safely applied to BI patients, but its benefits has not been formally proven.

Assessing the impact of different levels of PEEP on ICP, changes in blood oxygenation in the bulb of internal jugular vein on the side of the lesion, blood flow velocities in middle cerebral arteries and the resistive index showed that the increase in the level of PEEP up to 15 cmH2O does not lead to substantial increase in intracranial pressure, as well as significant changes in the indices of oxygenation and cerebral blood flow [14].

In a case of alveoli collapse, a recruitment maneuver is used. Today, its three main options are most often used in clinical practice [15]. The first is the individual selection of parameters for the volume-pressure loop, setting the ventilation parameters so that the PEEP value was on 2 cmH_2O above the lower inflection point of a volume-pressure loop, and the plateau pressure was not higher than the upper inflection point on this loop.

The second option is to create a continuous positive pressure in the airways at 40 cm water column for 40 seconds.

And the third option is a step-by-step maneuver of both increasing inspiratory pressure and PEEP, maintaining driving pressure at 15 cmH2O, reaching a peak pressure after recruiting 50 cmH_2O and PEEP 35 cmH2O. After recruitment, PEEP is decreased with titration and a new recruitment maneuver performed after an optimal PEEP is determined (i.e., the PEEP associated with best compliance of respiratory system or best oxygenation). After the new recruitment, PEEP is set at 2 cmH2O above the optimal level.

In the process of long-term mechanical ventilation, it is certainly important to assess the effectiveness of respiratory support, which is based on the principles:

- Satisfactory (sufficient) chest excursion
- Conduct respiratory noise on both sides
- Fulfillment of the "protective ventilation" concept
- Satisfactory (SaO_2≥90%, PaO_2≥60 torr) or sufficient (SaO_2≥95%, PaO_2≥80 torr) oxygenation
- Stable condition of the vital functions of the body.

T. Fham and colleagues wrote in their review "Mechanical Ventilation: State of the Art" that in the early phase of MV, sedation with or without paralysis is often required, especially for patients with shock or ARDS or for those "fighting the ventilator" [16]. Slow metabolism of sedative agents may unduly prolong the duration of MV and lead to detrimental short- and long-term outcomes. Each sedative agent has specific effects, and the appropriate choice of the type and dose of sedative drugs may impact outcome. Data suggest that benzodiazepines are particularly associated with poorer long-term outcomes. Propofol is frequently used because of a relatively short half-life, but there are concerns associated with prolonged infusion. Dexmedetomidine has been proposed as a promising alternative to usual sedation because it reduces the rate of delirium, but results from clinical trials have not been consistent. If sedation cannot be avoided, it is important to carefully monitor the depth of a patient's sedation and to use a sedation protocol, including daily interruption of sedation to avoid a state of deep sedation.

It should be noted that if you need a long mechanical ventilation, the question arises about the timing of a tracheostomy. The proposed benefits include more patient comfort and decreased sedation requirements, hastened weaning, and improved clinical outcomes.

«Recent large randomized controlled trials (RCTs) of tracheostomy timing have shifted the pendulum towards delaying tracheostomy decisions, at least among general medical–surgical and cardiac surgery patients. Despite differing inclusion criteria and definitions of ''early'' versus ''late'' tracheostomy, these trials indicate that the routine

performance of earlier tracheostomies is unlikely to reduce mortality or prevent nosocomial infections. The Early versus Late Tracheotomy Study (ELTS) showed that earlier tracheostomies can decrease mechanical ventilation duration and length of stay in the ICU, but that this did not translate into shorter hospitalizations. Most importantly, in two of these RCTs (ELTS and theTracMan) a surprisingly large proportion of patients assigned to receive delayed tracheostomies were successfully extubated without ever having received the procedure (43 and 54 %, respectively). Therefore, routinely performed tracheostomies earlier than 4 (TracMan) to 8 days (ELTS) may subject many patients to unnecessary procedures, suggesting that tracheostomies should probably be postponed until after 10 (TracMan) to 15 days (ELTS)» [17].

Intensive care unit (ICU)-acquired weakness (ICUAW) develops as a complication of critical illness, and may represent the extreme end of a spectrum of weakness that begins with any serious illness regardless of care location. ICUAW is associated with prolonged mechanical ventilation and ICU stay, as well as increased ICU, hospital, and 1-year mortality. Age, sepsis, longer ICU length of stay, longer duration of mechanical ventilation, and bed rest increase the risk of developing ICUAW.

Overall, approximately 25% of PMV patients in the ICU develop generalized and persistent muscle weakness: approximately one million patients develop the ICU-acquired weakness syndrome (critical illness neuromyopathy) annually [18].

Ineffective cough and secretion retention can play a significant role in weaning failure.

Physiotherapy techniques commonly used for early mobilization and airway clearance are shown in this table (table 2).

Matthias Eikermann and Nicola Latronico found that the most important strategies to prevent muscle ICUAW include: early and aggressive treatment of the underlying disease, early rehabilitation in the ICU where patients receive minimal sedation and NMB, limb mobilization; optimal activation of the respiratory muscles, and early enteral nutrition [19].

Weaning mechanical ventilation

With the improvement of the patient's condition, of course, the question is raised on cessation of respiratory support. Basic principles for weaning from MV that were described by Carl Haas and Paul Loik [20].

Formal discontinuation assessment should be performed during a spontaneous breathing test (SBT) rather than while receiving substantial ventilatory support.

To assess the effectiveness of the withdrawal of respiratory support, it is most advisable to focus on the parameters proposed by N.R. MacIntyre [21].

It is believed that the cancellation of respiratory support will be successful in applying the following statements. The most popular ventilatory strategies that are used to shorten and achieve a more successful weaning from MV in the ICU are as follows:

- Progressive reduction in the level of assistance of Pressure Support Ventilation (PSV);
- Progressive longer periods of SBT through the tube;
- Syncronized Intermittent Mandatory Ventilation (SIMV: the patient can breath spontaneously between ventilator-delivered breaths).
- Neurally Adjusted Ventilatory Assist (NAVA).
- Noninvasive mechanical ventilation (NIV).
- High-flow oxygen (HFO).

After 20 years of research on weaning, the question is whether the results of all these studies have been transferred to clinical practice. Although these data reveal a great variability in clinical practices, it can be concluded that [22]: (1) there has been a slight decrease in the use of the spontaneous breathing trial with the T-piece and an increase in CPAP and trials with low levels of PS; (2) there has been an increase in the use of PS in gradual reduction; (3) there has been a significant decrease in the use of SIMV with or without PS.

F. Frutos-Vivar and A. Esteban in their review on the question "why are we looking for alternative ways to cancel the ventilator?" analyzed opportunities provided by several ventilator modes [23]:

- Noninvasive positive pressure ventilation
- Automatic tube compensation (ATC)
- Automated closed loop system (mandatory minute ventilation)
- Adaptive support ventilation (ASV)
- Automated knowledge-based weaning (SmartCare/PS, MRV…)
- Adaptive pressure ventilation (VSV, PRVC, AutoFlow, VC+)
- Automode (VSV + PRVC)
- Proportional assisted ventilation (PAV)
- NAVA

Joyce Yeung and colleagues in their review on early extubation and the transition to non-invasive ventilation as a strategy of weaning from MV, showed that using of NIV in weaning from mechanical ventilation decreases hospital mortality, the incidence of VAP, and duration of stay at ICU. Thus, NIV as a weaning strategy appears to be most beneficial in patients with COPD [24].

Juliana Ferreira et al. [25] compared two tests of spontaneous breathing (NAVA and PSV) in 20 patients (60

Table 2. Physiotherapy activities and techniques for patients with prolonged mechanical ventilation [2]

Muscle weakness	▪ Passive and active-assisted mobilization ▪ Continuous rotational therapy ▪ Postures ▪ Active limb exercise ▪ Peripheral muscle training ▪ Neuromuscular electrical stimulation ▪ Respiratory muscle training
Cough augmentation techniques	▪ Manual hyperinflation ▪ Percussion and vibrations ▪ Mechanical In-Exsufflation ▪ Percussive ventilation

years old in average). NAVA reduces patient-ventilator asynchrony index and generates a respiratory pattern similar to PSV during SBTs. Patients considered ready for MV cessation may be submitted to an SBT in NAVA using the same objective criteria used for SBTs in PSV.

Reintubation after the withdrawal of respiratory support is another problem. Having conducted a study on 480 patients (243 - the control group and 227 - the main group), M.M. Fernandes and colleagues showed that one-hour rest after a successful SBT reduced the rates of reintubation within 48 h after extubation in critically ill patient [26]. "In both groups, the main reason for reintubation was patients' inability to manage secretions that eventually induced acute respiratory failure. Reintubation within 48 h after extubation was more frequent in high-risk patients [43/392 (11%) vs. 4/78 (5%); p = 0.001], both in the control group [32/202 high-risk patients (16%) vs. 3/41 low-risk patients (7%); p = 0.001] and in the rest group [11/190 high-risk patients (6%) vs. 1/37 low-risk patients (3%); p = 0.001]."

Ratender Kumar Sungh et al. developed a decanulation algorithm which is based on meta-analysis data [27]. This protocolized decannulation algorithm in- corporates easy to use bedside checklist for evaluation of patients deemed fit for decannulation.

Conclusion

In order for the cancellation of respiratory support should be carried out in a less difficult way, thereby the following principles are recommended:

- Routine respiratory support in auxiliary regimens
- "Prevention" of muscle weakness and diaphragm dysfunction
- Timely assessment of the possibility of starting the withdrawn of mechanical ventilation
- Compliance with the recommendations for the mechanical ventilation weaning and personalized protocols for the weaning from mechanical ventilation
- Automation ("intelligent" respiratory support modes)
- Reintubation prevention.

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IMPACT OF PREOPERATIVE ORAL CARBOHYDRATE ADMINISTRATION ON SHORT-TERM CLINICAL OUTCOMES, POSTOPERATIVE COMPLICATIONS AND PROGNOSIS AFTER COLORECTAL SURGERY

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Introduction

Colorectal cancer (CRC) is the third most frequent cancer worldwide. Ten percent of the new cases of cancer account for CRC. The most frequently CRC has diagnosed between 65 and 74 years old. Surgery is the most important treatment in patients with CRC. Elderly people have a higher risk of postoperative complications that implies prolonged hospital stay, higher rates of readmission and mortality [1]. Preoperative nutritional status often is aggravated by cancer disease that predicts adverse postoperative outcomes. Long-term preoperative fasting further affects patient's catabolic state. Numerous perioperative interventions focused on nutritional status and reduction of postoperative complications are established in Enhanced Recovery After Surgery (ERAS) protocol [2]. A part of ERAS protocol is preoperative feeding with carbohydrate oral (CHO) drink in the evening before surgery and in the morning, two hours before anesthesia induction. Preoperative feeding with CHO drink attenuates postoperative insulin resistance and perioperative surgical stress response, improves insulin sensitivity and perioperative patients well-being [3]. Preoperative fasting and surgical tissue damage activate network of inflammatory pathways. CHO drink is advocated in reducing of postoperative inflammatory response. Unfortunately, implementation of new strategies sometimes has difficulties and preoperative CHO drink is not widely accepted.

In this study we evaluated the effect of preoperative CHO drink on short-term postoperative clinical outcomes, on incidence and severity of postoperative complications and postoperative Neutrophil/Lymphocyte Ratio (NLR) as a prognostic predictor after CRC surgery.

Methods

This prospective clinical randomized trial was approved by Ethics Commitee of Cantonal Hospital Zenica and written informed consent was obtained from each patients. A total of sixty consecutive patients with CRC who fulfilled eligibility criteria were recruited in the study. The inclusion criteria involved a diagnosis of CRC followed by open colorectal surgery, an age between 20 and 70 years, an American Society of Anesthesiologist (ASA) grade I and II and body mass index between 20 and 30. The exclusion critera involved history of any type previous cancer treatment, metastatic disease, diabetes mellitus, immunological disease or immunomodulatory therapy, emergence surgery, gastrooesophageal reflux and total score ≥3 according to Nutritional Risk Screening 2002 (NRS-2002). The patients were randomly divided into FAST group (control group) underwent to standard preoperative fasting 8 hours before surgery and CHO group (test group) received 400 mL of carbohydrate drink (ProvideXtra^{R} DRINK, Fresenius Kabi, Deutchland) at 10 pm the evening before surgery and additional 200 mL 2 hours before anesthesia induction. Randomization performed by a nurse blinded to study protocol with an allocation ratio of 1:1 was generated with block randomization. Open radical colectomy under general endotracheal anesthesia was performed in al patients. Anesthesia was induced with propofol 3 mg/kg, fentanyl 3 μg/kg and pancuronium-bromide 0,1 mg/kg. Balanced anesthesia was maintained using sevoflurane minimum alveolar concentration 0.5-1‰, N_2O 50% in oxigen**,** at a total flow of 2 L/min and intermittent bolus doses of fentanyl and pacuronium. At the end of surgery, neuromuscular block was reversed with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg.

Assesment of the short-term clinical outcomes and postoperative complications

Short-term cilinical outcomes: first flatus day, first defecation day, postoperative hospital stay days and weight loss were recorded prospectively beginning on the day of surgery and daily thereafter until discharge. Readmission were evaluated within the first 30 days after surgery. Definitions of complications were predefined and graded by severity according to the Clavien-Dindo classification.

Assesment of the NLR prognostic system

Peripheral venous blood samples were taken at 6 am on the day of surgery and repeated at 6 am on the postoperative day 1, 3 and 5. A count of white blood cells, neutrophil cells and lymphocyte cells were analyzed. The NLR was calculated as: number of neutrophils / number of lymphocyte. The optimal cut off NLR values of 3.0 is recommended for CRC. The stuff who collected postoperative data and taken blood samples were blinded to study protocol.

Statistical analysis

Sample size was estimated using sample size calculator software with 95% confidence interval and power of 80%. The $p< 0.05$ was considered as statistically significant. Categorical variables were analysed by Pearson's $\chi 2$ test and presented as frequency and relative number of cases (percentage). The change in continuous parameters was tested by Levene's Test for Equality of Variances and T-test for Equality of Means. The results was expressed us means and standard deviation

Results

The groups were homogeneous and comparable. Preoperative fasting time was only difference between groups 12.34 hours in the FAST group versus 2.38 hours in the CHO group. Baseline characteristics of the groups are summarized in the Table 1. During the study no patients were excluded from analysis.

Postoperative short-term outcomes were significantly better in the CHO group. First flatus day was 3.77 ±0.52 in the CHO group versus 4.25±0.56 in the FAST group (p<0.04). First defecation day was 3.55±0.46 in the CHO group versus 4.84±0.90 in the FAST group (p<0.01). Postoperative hospital stay was shorter in the CHO group 8.32±1.0 days than in the FAST group 9.70±1.5 (p<0.01). Readmission rate was lower in the CHO group but there was no statistically significant among the groups. Weight loss during hospitalization was significantly higher in the FAST group 5.3±1.2 versus 2.9±1.6 kg in the CHO group (p<0.001)

The incidence of postoperative complications Clavien-Dindo grade I, II, III and IV was significantly lower in the CHO group (Table 2). Two reoperations were re-

Table 1. Baseline characteristics of the participants according to the groups

Group parameters	FAST group n=30	CHO group n=30	p value
Male/Female	16/14 (53.3/46.7)	13/17 (43.3/56.7)	0.733[a]
Age (year)	66.5 ±14.6	63.3 ±10.1	0.342[b]
Body weight (kg)	75.3 ±12	79.0 (±10)	0.562[b]
Body Mass Index (kg/m^2)	24.7 ±1.6	25.8 (±4.5)	0.594[b]
Nutrition Risk Score-2002 II/I	17/13 (57/43)	16/14 (52/48)	0.866[a]
ASA I/II	10/20 (33/67)	2/18 (40/60)	0.605[a]
Tumor localisation			
Right hemicolon	6 (21)	9 (30)	
Left hemicolon	14 (46)	12 (40)	
Rectum	10 (33)	9 (30)	0.995[a]
Duration of surgery (minutes)	136.6 ±2.89	127.2 ±39.4	0.418[b]
Fasting time (hours) year	12.34 ±2.1	2.38 ±0.5	0.0001[b]
Blood loss			
<300 millilitres	26 (84)	25 (80)	0.713[a]
>300 millilitres	4 (16)	5 (20)	

Data expressed as a mean and ± standard deviation or a number (percentage); p<0,05 considered statistically significant; [a], indicate p values were according x^2 test; [b], indicate p values were according *t* test; FAST group, the participants underwent to preoperative fasting; CHO group, the participants received preoperative carbohydrate oral drink; ASA, American Society of Anesthesiologists

Table 2. Incidence and severity of postoperative complications according to the groups

Complications	FAST group n=30	CHO group n=30	p
	n (%) of patients		
Clavien-Dindo grade I	10 (33.9)	3 (10.0)	0.04
Transient elevation of serum kratinine> 100µmol/L	7 (23.3)	3 (10.0)	0.05
Transient confusion	3 (10.0)	0 (0)	0.01
Clavien-Dindo grade II	14 (47.6)	3 (10)	0.01
Pneumonia	6 (20.0)	2 (6.7)	0.05
Uroinfection	2 (6.7)	1 (3.3)	0.59
Wound infection	3 (10.0)	0 (0)	0.01
Delirium	2 (6.7)	0 (0)	0.28
Deep vein thrombosis	1 (3.3)	0 (0)	0.32
Clavien- Dindo grade III	5 (16.5)	0 (0)	0.01
Anastomotic leakage	1 (3.3)	0 (0)	0.32
Ileus	1 (3.3)	0 (0)	0.32
Abdominal wall dehiscence	1 (3.3)	0 (0)	0.32
Reoperation	2 (6.7)	0 (0)	0.28
Clavien- Dindo grade IV	4 (13.3)	0 (0)	0.05
Lung failure requiring ICU	2 (6.7)	0 (0)	0.28
Septic shock	1 (3.3)	0 (0)	0.32
Multiorgan failure	1 (3.3)	0 (0)	0.32
Clavien- Dindo grade V	1 (3.3)	0 (0)	0.32
Death of patient	1 (3.3)	0 (0)	0.32

p<0,05 considered statistically significant according x^2 test; FAST group, the participants underwent to preoperative fasting; CHO group, the participants received preoperative carbohydrate oral drink;

Table 3. The Neutrofil/Lymphpcyte Ratio according to the groups and time

Parameter	Time	FAST group n=30	CHO group n=30	p
		mean±standard deviation		
White blood cells	Preoperative	6.58 ±0.48	6.36±0.58	0.223
	Postoperative day 1	14.04±1.46	12.03±1.26	0.01
	Postoperative day 3	12.61±2.37	10.30±2.23	0.01
	Postoperative day 5	11.76±1.28	8.84±1.08	0.001
Neutrophil cells	Preoperative	3.71±0.28	3.90±0.12	0.441
	Postoperative day 1	11.5±1.80	9.2±1.90	0.01
	Postoperative day 3	9.82±1.20	7.1±1.64	0.01
	Postoperative day 5	8.82±0.46	5.32±0.18	0.01
Lymphocyte cells	Preoperative	2.01±0.49	2.12±0.45	0.180
	Postoperative day 1	1.35±0.59	1.83±0.53	0.01
	Postoperative day 3	1.50±0.72	2.24±0.73	0.01
	Postoperative day 5	1.82±0.58	2.14±0.62	0.01
Neutrophil / Lymphocyte Ratio	Preoperative	1.59±0.82	1.56±0.46	0.281
	Postoperative day 1	8.7±6.80	5.2±4.20	0.001
	Postoperative day 3	6.5±3.82	3.0±1.56	0.001
	Postoperative day 5	4.8±2.10	2.4±1.00	0.001
Neutrophil/ Lymphocyte Ratio >3 n (%)	Postoperative day 1	22 (73.9)	15 (52.5)	0.001
	Postoperative day 3	18 (58.4)	12 (40.0)	0.001
	Postoperative day 5	14 (47.5)	8 (26.1)	0.001

p<0,05 considered statistically significant according *t* test; FAST group, the participants underwent to preoperative fasting; CHO group, the participants received preoperative carbohydrate oral drink;

quired in the FAST group because of postoperative ileus in one patient and anastomotic leakage in another patient. Both of them required mechanical ventilation after reoperation. The patient with anastomotic leakage had multiple organ failure and died.

The postoperative NLR value was statistically significant lower in the CHO group. The number patients with postoperative NLR >3.0 is presented in Table 3.

Discussion

The presented study sugested that CHO drink used in the evening before open colorectal surgery and 2 hours before induction of anesthesia provided better short-term clinical outcomes, reduced incidence and severity of postoperative complications and reduced value of NLR prognostic system.

Some studies did not find efficacy of preoperative CHO on postoperative hospital stay or recovery of gastrointestinal function [4,5]. The reasons are various methodology and study protocols, differences in study population or surgical procedures. In intention to homogenize study population and avoid influence of malignant disease on nutritional and immunological status of patients in this study evaluation by the NRS-2002 score was conducted before randomization. The patients with NRS ≥3 were considered at nutritional risk and stress metabolism induced by malignant disease who were excluded from the study.

Presented study revealed earlier postoperative return of gastrointestinal function and lesser weight loss due to abbreviation of preoperative fasting. Preoperative CHO drink improves perioperative insulin sensitivity, reduces inflammatory response and skeletal muscle catabolism after surgery, alleviates a degree of anxiety and pain [6]. In the CHO group postoperative hospital stay was reduced mainly because of faster recovery after surgery, shorter time of first flatus and less postoperative complications. Mathur et al., did not find benefit of CHO drink on length of hospital stay after major abdominal surgery. In that study various type of surgical procedures and anesthesia technique were included that induced different level of surgical stress response and polluted opposite results to our study [7].

Decreased incidence and severity of postoperative complications was recorded in this study, after CHO loading. Minor postoperative complications occurred in the CHO group while minor and major complications were noted in fasted patients. Better control of postoperative insulin resistance and glicaemia is related with lower rates of infectious complications and faster wound healing [8].

NLR is used in clinical practice as a test to evaluate the cell-mediated immune response to various stresses, including cancer disease. NLR is associated with short-term postoperative immune function. An increased NLR presents low immunocompetence in cancer patients. The cutoff NLR values of 3.0 is recommended for CRC. NLR >3 showed the worse treatment-related outcome [9]. In presented study, NLR>3 remained at all postoperative investigated time points in the patients with standard preoperative protocol. To our knolwedge, impact of CHO drink on NLR prognostic system did not evaluated previously. The use of CHO drink reduced NLR and value above cutoff was recorded only on the postoperative day 1. These results strongly suggest that CHO drink changes systemic inflammatory status, indirectly measured throughout NLR and may improve prognosis of CRC patients. For more precise statements further investigations are needed.

In conclusion, preoperative CHO drink is a simple, safe and cheap method to improve postoperative short-term clinical outcomes, reduce incidence and severity of postoperative complications and and may improve prognosis after CRC surgery.

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PREOPERATIVE NUTRITIONAL OPTIMIZATION FOR MAJOR ABDOMINAL SURGERY

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Introduction

There is an accumulation of data supporting positive effects of nutrition on surgical outcomes [1]. However, insufficient attention has been paid to nutritional preparation of surgical patients.

The two main implications of preoperative nutritional optimization are:

- Surgical stress response
- Malnutrition or risk of malnutrition

Surgical stress and injury produce specific metabolic and hormonal changes known as "metabolic stress response". Their main characteristics are water and salt retention and mobilization of energy reserves. The intensity of stress response is in a positive correlation with the degree of tissue injury [2]. Even though this is a survival mechanism for preserving plasma volume and organ function, an exaggerated response produces significant catabolism and immune dysfunction. Furthermore, patients with prolonged stress or in *malnutrition* do not have the ability to respond to this metabolic challenge. This has already been pointed out in Studley`s [3] study where patients with greater preoperative weight loss demonstrated an increased postoperative mortality rate after the surgical treatment of peptic ulcer. A multivariate analysis of patients undergoing major abdominal surgery for gastrointestinal cancer [4] showed that malnutrition presents an independent risk factor for postoperative complications along with low serum albumin, advanced age of patients and pancreatic surgery. A meta-analysis of Zhong et al.[5] conducted on 15 randomized trials and 3831 patients demonstrated that nutritional support reduces the incidence of infectious and non-infectious complications and length of hospital stay. The majority of studied trials were in gastroenteric cancer surgery.

What can be done?

Up to 65% of patients preparing for gastrointestinal surgery are malnourished with two thirds becoming malnourished during hospitalization [6]. Decline in nutritional status of these patients is present due to [7]: gastrointestinal and metabolic abnormalities, drug or treatment-related side effects, patient-related factors.

The main goals of preoperative optimization for major abdominal surgery can be abbreviated in reverse order as **PASTE**:

- To **E**valuate patients for preexisting malnutrition
- To **T**reat malnutrition
- To minimize **S**tarvation
- To support **A**nabolism for recovery
- To **P**revent postoperative malnutrition

The first step – **EVALUATE** patients with preexisting malnutrition or patients at risk of malnutrition.

The evaluation of nutritional status is achieved through nutritional screening and nutritional assessment. Nutritional screening has to be considered in all patients on hospital admission, according to European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines from 2002 [8]. There are different screening tests for different patient populations, one of the most abundant being nutritional risk screening (NRS-2002). According to the prospective study of Schiesser et al. [9], in a consecutive series of patients undergoing various elective gastrointestinal surgeries, postoperative complications were significantly more frequent in patients with nutritional risk (40%) versus patients without nutritional risk (15%; $p<0.01$).

After the screening, the patients with or at risk of malnutrition require further assessment and initiation of nutritional therapy.

The second step – **TREAT** malnutrition

The first goal of nutritional therapy is to maintain nutritional care and prevent postoperative complications while the second is the improvement of the nutritional status and functional recovery [10]. Nutritional therapy should be started as early as it appears that patient is in malnutrition or at risk of malnutrition [11]. Moreover, if it is believed that the patient will not be able to eat or maintain oral intake for longer periods, nutrition support should be indicated.

Different provision methods of nutrition therapy can be used alone or in combination with:

- Oral diet (regular diet, therapeutic diet, fortified food, oral nutrition supplements (ONS))
- Enteral nutrition (EN)
- Parenteral nutrition (PN)

The effect of preoperative ONS and EN on enhanced postoperative surgical outcomes after abdominal surgery has been documented [12]. In this meta-analysis using ONS (250-600kcal)/day from 7 days to 10 weeks or tube feeding (831-2852kcal)/day <11days, postoperative complications were significantly reduced (wound dehiscence, postoperative ileus, respiratory and other infections).

The third step – Minimize **STARVATION**

According to Cohrane review [7] and meta-analysis [13], preoperative fasting from midnight neither reduces gastric content nor raises Ph of gastric fluid compared to the preoperative pathway where patients were allowed fluids up to 2h preoperatively. Different national and society guidelines [14,15] recommend the intake of solid food 6h and clear fluids 2h before anesthesia.

Moreover, it was shown that preoperative fasting induces metabolic stress and produces insulin resistance [16].

Sato et al.[17] found that decreased insulin responsiveness is associated with higher morbidity and mortality. The introduction of preoperative oral carbohydrate fluids attenuates postoperative insulin resistance[18] and corresponds to decreased length of hospital stay[19,20]. Due to the encouraging results, changing preoperative fasting paradigm and introducing preoperative oral carbohydrate fluid started to be a part of ERAS protocols for elective colonic surgery[15], pancreaticoduodenectomy[21]and rectal/pelvic surgery[22].

The forth step – Support **ANABOLISM** for recovery

Whole body proteins are constantly synthesized and degraded where anabolism presents a situation in which synthesis outweighs degradation. In the ERAS era, prehabilitation has become a special point of interest as a tool for achieving anabolism. Prehabilitation encompasses exercise, nutrition and psychological preparation of the patients for the forthcoming surgery. In a systematic review and meta-analysis of patients undergoing colorectal surgery, nutritional prehabilitation with or without exercise significantly decreases hospital stay[23]. However, prehabilitation in the form of resistance exercise does not produce positive muscle balance in the fasted state[24]. It is suggested that exercise together with higher dietary protein intake can positively impact protein balance[24].

The fifth step – **PREVENT** postoperative malnutrition

All the steps previously mentioned constitute the final step of preoperative optimization.

Conclusion

Preoperative nutritional optimization for abdominal surgery has already proved its importance in the way of reducing length of hospital stay, postoperative complications and mortality. Nevertheless, some of the conservative approaches are still to be revealed and applied. On the other hand, new evidence about muscle mass and the pathways of stimulating anabolism are emerging.

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NUTRITIONAL THERAPY IN SEPTIC PATIENTS

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Sepsis is a condition characterised with massive catabolism, loss of muscular mass and progredient hypermetabolism. This condition can decrease patient's health over long period of time, so it is of great importance to start early with nutritional support. Nutrition had been observed over long period of time as a support for patients suffering from critical condition. Today, nutrition is considered to be a therapy which can directly improve outcome of sepsis. This change of terminology is a result of numerous studies that support previous constatation. On the other hand, as any other form of therapy, nutritional therapy has its own indications, recommended doses, composition, type of application and duration of therapy. Keeping this in mind, nutritional therapy, as a term, should be used instead of nutritional support. [1,2,3]

Major changes occur in organism during any critical condition, including sepsis. Increased proteolysis, glucolysis and glyconeogenesis, elevated levels of proteins of acute phase can all be noticed during sepsis. As a result of increased need for oxygen and deterioration of perfusion, anaerobic metabolism becomes predominant lactate levels become elevated. Urea and creatinine can be elevated as well as a result of protein catabolism. All these processes impose two questions. Firstly, can protein catabolism be decreased by increasing energy intake via glucose. Secondly, considering increased protein catabolism in these patients, will increase of calorie and amino acid intake improve their outcome. All these logical questions impose logical hyphotheses that increasing calories and amino acids intake when treating critical conditions can decrease catabolism and improve outcome in these patients. [1,4]

It is of great importance to determine type of application of nutritional support for patients with critical ill. Enteral therapy is recommended in most guides. According to European society for enteral and parenteral nutrition, in the case of a hemodynamically stable, critically ill patient with a functionally preserved digestive tract, early enteral nutrition should be started (within 24 hours) using appropriate nutrition. It is also suggested that parenteral nutrition should be included later, only after the seventh day. [5,6] However, there is a different opinion which suggest that in order to reach nutritional goal, parenteral nutrition should be added on fourth day of enteral nutrition.

Wischemayer suggests that nutritional therapy in septic patients whould be divided in two phases. First phase, nutritional therapy in acute phase of sepsis (first 24 to 96 hours in Intensive Care Unit (ICU)), and second phase until releasing patient from hospital and later during recovery. [8] In first phase, early enteral nutrition is advised with 1g/kg/day protein intake and 15kcal/kg/day non-protein energy intake (in patients with normal Body Mass Index (BMI) score). Parenteral nutrition in patients with normal BMI score should be started between third and seventh day of nutritional therapy only if less than 60% of recommended EN calories intake was reached. In malnourished patients, parenteral nutrition should be started immediately upon admission to ICU with 1.2 g/kg/day protein intake and 15 to 20 kcal/kg/day total caolories intake. If enteral therapy is not possible.

After 96 hours from admission in ICU, it is recommended to increase enteral intake of proteins and amino-acids (1-2 g/kg/day) and non-protein intake 25-30 kcal/kg/day (ideally guided by indirect calorymetry). During recovery, protein and energy intake should be increased. In case that peroral intake is possible, increased protein intake, divided in two or three meals, is advised. Parenteral nutrition should be postponed up to 3 to 7 days if patients are well nourished and if enteral intake of proteins or calories is less than 60% of recommended intake. In malnourished patients, parenteral nutrition should be started immediately upon admission to ICU with 1.2 g/kg/day protein intake and 15 to 20 kcal/kg/day total caolories intake. Additional parenteral nutrition should be started upon admission in ICU in malnourished patients with protein intake of 1.2 g/kg/day and total calories intake of 15 to 20 kcal/kg/day. If enteral nutrition is not possible. Nutritional risk scores should be used this time as well. Nutritional therapy continues for months or even years after the release of patients from hospital. During this period, peroral intake of proteins should be between 1.2 and 2 g/kg/day with energy goal between 4000 and 5000 kcal/day. These recommendations are based upon a Mnnesota study about starving. There are some results that suggest that there are no benefits from increased calories intake.[9]

Even though there are some different opinions, we may conclude: 1. Evaluation of nutritional risk is needed upon admission of patients in hospital and/or ICU (NUTRIC or NRS). 2. Enteral nutrition has advantages in well nourished patients. 3. Parenteral nutrition is of great need in malnourihsed patients. 4. Protein intake should be carefully monitored. 5. Nutritional therapy continues after releasing patients from hospital care.

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RAPID DIAGNOSIS OF INFECTIOUS DISEASES: FROM FAST TO FASTEST

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Since it has been reported that the incidence of nosocomial infections in the intensive care units (ICU) is about 2 to 5 times higher than in the general in-patient hospital population, that therapies for infectious diseases are not universally successful, as well as morbidity and mortality in intensive care units (ICUs) remain high, fight against pathogen agents is constantly faced with numerous challenges.

Based on reports of European Centre for Disease Prevention and Control in 15 countries of EU, out of all 87,337 patients staying in an ICU for more than two days, 6,995 patients (8.0%) presented with at least one healthcare-associated infections (HAI) [1]. Among patients staying in the ICU for more than two days, 5.5% were affected by at least one episode of pneumonia with *Pseudomonas (P.) aeruginosa, Staphylococcus (S.) aureus*, *Klebsiella* spp. and *Escherichia coli* as the most frequently isolated microorganisms; ICU-acquired bloodstream infections (BSIs) occurred in 3.5%, mostly due to coagulase-negative staphylococci, *Enterococcus* spp., *S. aureus* and *Klebsiella* spp. infection. However, of most concern is the high percentage of antimicrobial-resistant isolates in selected bacteria associated with ICU-acquired HAIs [1].

Regarding these facts, today, accurate and rapid methods are imperative for detection of infectious agents in timely manner. In recent years, new trends in medical microbiology and molecular biology are design and establishment of rapid molecular and immunochromatographic (IC) kits - point of care tests (POCTs) for detection of the pathogen agents directly in the patient's material [2]. Prompt diagnosis of infection with optimal sensitivity and specificity and the fact that POCTs are applicable for the *bench to the bedside* use are the major advantages of these kits. Besides, the use of reliable POCTs in daily clinical practice bring many other benefits such as cost-effectiveness, user friendliness, equipment free testing, treatment decision guiding and improving patient satisfaction with health care system [3]. Regarding the most common causative agents, the advantages of two POCTs for direct detection of microorganism in patient's specimens should be pointed out [4]. The most prevalent causative agent of pneumonia in ICU patients - *P. aeruginosa,* can be identified directly in sputum and throat swab samples using a POCT with monoclonal antibody against the outer membrane protein F (OprF) conjugated with colloidal gold. Compared to multiplex-polymerase chain reaction (M-PCR), the sensitivity and specificity of this POCT are 84.8% and 100%, respectively while compared to the culture-based method, the sensitivity of the strip is 91.6% and the specificity is 93.2%. Additionally, early diagnosis of *S. aureus* which represents a major cause of bacteriemia is of great importance to prevent serious complications. Immunochromatographic BinaxNOW *Staphylococcus aureus* (BNSA) test is rapid (hands-on-time = 30 min), simple and inexpensive way to identify *S. aureus* from blood culture broth when Gram stain indicates the presence of Gram positive cocci [5,6]. The shortcoming of this test is its inability to differentiate between MRSA and MSSA as well as false-negative results obtained in patients already treated with antibacterial drugs.

On the other hand, "revolution" in the diagnosis of infectious diseases has been made with the introduction of simultaneous detection of multiple organisms, resistance genes, and differentiation of pathogenic from non-pathogenic strains and isolates in a single closed tube system by multiplex PCR. This rapid, accurate, and cost-effective diagnostic assay can be used for detection of pathogens directly in patient's material [7-13].

Molecular methods are becoming more widely used for the detection of respiratory pathogens, in part because of their superior sensitivity, relatively rapid turnaround time, and ability to identify pathogens that are slow growing or difficult to culture [14]. More extensive panels like FilmArray™ (Biofire, BioMerieux, USA), a multiplex PCR for viruses and bacteria, might be better suited for ICU patients [15]. The greatest advantage of this test is that it gives the results without prior DNA/RNA extraction. However, the results are presented in qualitative way, which represents the main disadvantage. For example Multiplex Real-Time PCR based on TaqMan® technology, Fast Track Diagnostics, Luxembourg, for detection of 33 pathogens could be ideal for fast detection of 21 viruses and 12 bacteria including the most frequent causative agents of ICU-acquired pneumonia such as *S. aureus*, *Klebsiella* spp. and *Haemophilus* spp. in 4 hours.

Recently, for detection of many different pathogen strains in blood in just a few hours, different rapid molecular methods have been developed to speed up establishing the diagnosis. In the first place, MALDI-TOF MS (matrix-assisted laser desorption ionization time-of-flight mass spectrometry) Sepsityper kit can be used to analyze directly positive blood cultures in real time and provide definitive species identification within 20-60 min, with identification rate of 85.5% [16]. Molecular methods that focus on the detection of pathogenic bacteria in severally ill patients directly from whole blood like Lightcycler SeptiFast (Roche Molecular Systems) and SepsiTest (Molzym, Germany) may further reduce the time to result of bacterial detection in comparison to BC [17]. Moreover, other methods such as Nanoparticle Probe Technology (Nucleic Acid Extraction and PCR Am-

plification) Nanosphere's Verigene can be used not only for identification of pathogens but also for detection of drug resistance markers: antimicrobial resistance genes, *mecA* – methicillin resistance, *vanA/B* – vancomycin resistance, NDM,CTX-M, VIM, IMP, and OXA genes of KPC – carbapenem resistance [7]. The big advantage of these direct techniques is that they have improved sensitivity to detect the cause of the sepsis in comparison to BC [18].

To conclude, we can highlight that ICU patients have the highest prevalence of HAIs and since they are highly vulnerable patient population associated with the use of invasive devices, treatment is big challenge especially if we take into account the burden of antimicrobial resistance. Prompt and accurate diagnosis of HAIs followed by appropriate therapy is crucial in the prognosis and survival of these patients. New approach with application of immunodiagnostic and molecular kits would significantly improve the treatment of these patients in terms of early pathogen detection and choice of effective antimicrobial drugs. However, at a time when a large number of commercial rapid tests are offered, each clinical laboratory must decide on an individual experience which tests are the most economical and the most appropriate to introduce into the routine work.

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MULTIDRUG RESISTANCE IN ICU

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Antimicrobial resistance (AMR) is one of the most serious global public health threats in this century. The World Health Organization (WHO) has long recognised the need for an improved and coordinated global effort to contain AMR. In 2001, the WHO Global Strategy for Containment of Antimicrobial Resistance has provided a framework of interventions to slow the emergence and reduce the spread of antimicrobial-resistant microorganisms;[1] In 2012, WHO published The Evolving Threat of Antimicrobial Resistance – Options for Action[2] proposing a combination of interventions that include strengthening health systems and surveillance; improving use of antimicrobials in hospitals and in community; infection prevention and control; encouraging the development of appropriate new drugs and vaccines; and political commitment. Following the indication of a primary role for surveillance, in April 2014, WHO published the first global report on surveillance of AMR collecting experiences from national and international surveillance networks.[3]

A number of studies have been performed to assess the burden of infection in critical illness. The Intensive Care Over Nations (ICON) audit showed that more than one-third of the patients develop an infection during their intensive care unit (ICU) stay. The Extended Prevalence of Infection in Intensive Care (EPIC) II study showed that 51 % of patients were considered to be infected while in ICU. The infection was of respiratory origin in 64 % of cases. *S aureus* (20.5 %) was the most frequent organism isolated, despite the overall predominance of Gram-negative organisms as a group: 62.2 % (*E. coli*, *Enterobacter s*pp., *Klebsiella* spp., *Pseudomonas* spp. and *Acinetobacter s*pp.). [4]

The impact of antibiotic resistance in terms of mortality and of the public health cost is quite difficult to estimate, and there are few studies addressing this issue. The US Center for Disease Control and Prevention (CDC) conservatively estimated that, in the US, more than two million people every year are affected with antibiotic-resistant infections, with at least 23 000 dying as a result of the infection.[5]

In Europe each year, the number of infections and deaths due to the most frequent multidrug-resistant bacteria (*S. aureus*, *Escherichia coli*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) was estimated at ~400 000 and 25 000, respectively, in 2007.[6] A team of European researchers estimates that more than 33,000 people in Europe die each year from antibiotic-resistant infections, and that the growing health burden of these infections is similar to that of influenza, tuberculosis, and HIV combined. [7]

In Europe, the overall crude economic burden of antibiotic resistance was estimated to be at least 1.5 billion euros with more than 900 million euros corresponding to hospital costs.[5]In the US, the CDC estimated the cost of AMR as $55 billion per year overall: $20 billion in excess for direct healthcare costs, with additional society costs for lost productivity as high as $35 billion a year.[4].

Antimicrobial resistance is occurring everywhere in the world, compromising our ability to treat infectious diseases, as well as undermining many other advances in health and medicine. The goal of the draft global action plan is to ensure, for as long as possible, continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them. To achieve this goal, the global action plan sets out five strategic objectives(WHO):

- to improve awareness and understanding of antimicrobial resistance;
- to strengthen knowledge through surveillance and research;
- to reduce the incidence of infection;
- to optimize the use of antimicrobial agents;
- develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

Antimicrobial resistance happens when microorganisms (such as bacteria, fungi, viruses, and parasites) change when they are exposed to antimicrobial drugs (such as antibiotics, antifungals, antivirals, antimalarials, and anthelmintics). Microorganisms that develop antimicrobial resistance are sometimes referred to as "superbugs". As a result, ineffective and infections persist in the body, increasing the risk of spread the medicines become to others.Antimicrobial resistance occurs naturally over time, usually through genetic changes. However, the misuse and overuse of antimicrobials is accelerating this process. [8]

A group of international experts brought together by a joint initiative between the ECDC and the CDC, was tasked with creating a standardized international terminology to describe acquired resistance profiles in multidrug-resistant organisms. MDROs have been divided into three categories depending on their resistance profile: 1. MDROs—non-susceptible to at least 1 agent in 3 antimicrobial categories; 2. extensively drug-resistant (XDR) organisms—non-susceptible to at least 1 agent in all but

2 or fewer antimicrobial categories; and 3. pan-drug-resistant (PDR) organisms—non-susceptible to all agents in all antimicrobial categories.Infections by MDROs were associated with worse clinical outcomes compared with their susceptible counterparts.While higher mortality associated with MDROs may be related to the virulence of the pathogen and a weak (comorbidity, age, etc.) or severely ill host (organ failure status, etc.), it is also important to highlight that delays in effective antimicrobial administration are also associated with high mortality.[4]

Table 1. CDC Assessment of Antibacterial Resistance Threats [9]

Urgent Threats
▪ Clostridium difficile
▪ Carbapenem-resistant Enterobacteriaceae (CRE)
▪ Drug-resistant Neisseria gonorrhoeae
Serious Threats
▪ Multidrug-resistant *Acinetobacter*
▪ Drug-resistant *Campylobacter*
▪ Fluconazole-resistant *Candida* (a fungus)
▪ Extended spectrum beta-lactamase-producing Enterobacteriaceae (ESBLs)
▪ Vancomycin-resistant Enterococci (VRE)
▪ Multidrug-resistant *Pseudomonas aeruginosa*
▪ Drug-resistant nontyphoidal *Salmonella*
▪ Drug-resistant *Salmonella* Typhimurium
▪ Drug-resistant *Shigella*
▪ Methicillin-resistant *Staphylococcus aureus* (MRSA)
▪ Drug-resistant *Streptococcus pneumoniae*
▪ Drug-resistant tuberculosis
Concerning Threats
▪ Vancomycin-resistant *Staphylococcus aureus* (VRSA)
▪ Erythromycin-resistant Group A *Streptococcus*
▪ Clindamycin-resistant Group B *Streptococcus*

Threats that are urgent or serious require more monitoring and prevention activities, whereas those considered concerning require less. The CDC declared in 2013 that the human race is now in the "post-antibiotic era," and in 2014, the World Health Organization (WHO) warned that the antibiotic resistance crisis is becoming dire.9

Over recent years, a new, comprehensive recommendation on classification of infections caused by Gram-positive and emerging Gram-negative multidrug-resistant pathogens has been launched. *E. faecium, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa* and *Enterobacter* spp. (ESKAPE) pathogens account for more than 80 % of infectious episodes in the ICU. As this acronym seems to help to highlight the problem of MDROs, some authors claim a change to "ESCAPE" is warranted (*E. faecium, S. aureus, C. difficile, A. baumannii, P. aeruginosa* and *Enterobacteriaceae* spp.) in order to highlight the importance of *C.* difficile and incorporate not only *Enterobacter* spp. but also other *Enterobacteriaceae*spp. (namely, *Escherichia coli and Proteus* spp.) because of the increasing levels of antibiotic resistance (including extended-spectrum β-lactamases, carbapenemases and aminoglycoside resistance) and decreasing levels of fluoroquinolone susceptibility among these organisms. [10]

One of the key aspects of avoiding the spread of resistant strains is early detection with the use rapid diagnostic tests. Shortening the turn-around time of positive blood culture identification and susceptibility results is essential to optimize antimicrobial treatment in patients with severe infections. Rapid diagnostic tests implemented in the current clinical practice should also consider an adequate workflow of information within a multidisciplinary working group approach that can process quickly and correctly the results from the microbiology laboratory to the bedside of the patient.The basis for all infection control measures is the accurate and timely laboratory identification of MDROs. This will also deliver important information for regional and national containment strategies and hospitals. The implementation of rapid tests and the development of microbiology laboratory reference services is an urgent requirement.[10]

Antimicrobial stewardship (AMS) programs

Antimicrobial stewardship (AMS) programs aim to provide assistance with optimal choice, dosage, pharmacokinetic–pharmacodynamic (PK/PD) characteristics and duration of antibiotics in order to reduce costs, adverse events and the development of resistance. Antimicrobial stewardship has been defined as "the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance." The goal of antimicrobial stewardship is 3-fold.The first goal is to work with health care practitioners to help each patient receive the most appropriate antimicrobial with the correct dose and duration. Joseph and Rodvold wrote about the "4 D's of optimal antimicrobial therapy": right Drug, right Dose, De-escalation to pathogen-directed therapy, and right Duration of therapy. The second goal is to prevent antimicrobial overuse, misuse, and abuse.The third goal is to minimize the development of resistance. [11]

There are 2 major approaches to antimicrobial stewardship, with the most successful programs generally implementing a combination of both. The front-end or preprescription approach to stewardship uses restric-

Table 2. Example of ASP approach

Strategy and drug	Pharmacodynamically optimized dose
Prolonged infusion of β-lactams	
Piperacillin-tazobactam	3.375 g IV every 8 h for 4 h (prolonged infusion)
Meropenem	1 g IV for 360 min every 6 h (contiunuous infusion)
Doripenem	500 mg IV every 8 h for 4 h (prolonged infusion)
Increased frequency dosing of quinolone	
Ciprofloxacin	400 mg IV every 8 h
Adjusting antimicrobial dosage to achieve specific recommended blood level	
Vancomycin	Maintain trough above 10 mg/L to prevent development of resistance
Use of high-dose therapy to overcome high MICs	
Cefepime	2g IV every 8 h (3-h infusion)

IV = intravenous; MIC = minimum inhibitory concentration

tive prescriptive authority. Certain antimicrobials are considered restricted and require prior authorization for use by all except a select group of clinicians. Clinicians without authority to prescribe the drug in question must contact the designated antimicrobial steward and obtain approval to order the antimicrobial. The back-end or postprescription approach to stewardship uses prospective review and feedback. The antimicrobial steward reviews current antibiotic orders and provides clinicians with recommendations to continue, adjust, change, or discontinue the therapy based on the available microbiology results and clinical features of the case.[11]

Conclusions

Infections with MDROs are already a threat in a number of countries. It is expected that in others with existing low level of MDROs, the number of infections due to MDR, XDR and even PDR organisms will rise. These infections are associated with an increased consumption of healthcare resources manifested by a prolonged hospital stay and an augmented mortality. In order to reduce antibiotic resistance rates, a strategy minimizing the use of broad-spectrum antibiotics and ensuring prompt antibiotic administration should be adopted. The development of rapid diagnostic tests will help by both shortening duration of therapy and allowing prompt-targeted therapy. The implementation of more accessible therapeutic drug monitoring will help to optimize drug administration and enable a more personalized approach to treatment. Some points require further investigation in clinical trials, such as the heterogeneity of patients admitted to ICU and the need for new drug development.

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AVOIDING PITFALLS IN ANTIBIOTIC THERAPY: THE ANTIBIOTIC STEWARDSHIP APPROACH

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Problem

Worldwide increasing resistance against antibiotics is a big clinical issue in our daily work, especially in the ICU. Multi-Drug- Resistance is not limited to India and the Middle East anymore, but it is emerging in Europe, especially in south-eastern countries. There is not only a problem of Multi-Drug - Resistant (MDR) bacteria with Extended- Spectrum-Beta- Lactamases (ESBL) but meanwhile of Extended- Drug -Resistant Bacteria (XDR) with carbapenemases – up to 66,9% of infection isolates in Greece.[1]

Pan- Drug- Resistant- Bacteria (PDR) with resistance against any known antibiotic exist.[2] This development had already been foreseen by Sir Alexander Fleming in 1945.[3]

The fact that there has been very little development of antibiotics with new mechanisms of action due to a lack of economic incentives during the last 15 years, worsens the situation.

Antibiotic Stewardship

A strong correlation between antibiotic overuse and the growing resistance is well established, in accordance with the saying "the more you use it, the quicker you lose it." As 2/3 of nosocomial infections are endogenous, we select MDR/ XDR bacteria by antibiotics and spread it on other patients by a lack of hand hygiene. With the rise of Carbapenem- Resistant Enterobactericeae, the increasing use of second- line treatment options will induce new resistances. International and German studies show that 20-50% of antibiotic therapies in hospitals are inappropriate. In up to 20% of antibiotic therapies severe side effects like Clostridium difficile infections (CDI) occur.[4,5]

To impede the spread of resistance many interventions were started in the past 10 years, summarized as "Antibiotic Stewardship Programs." ABS aims to "preserve the miracle of antibiotics" (Bartlett 2013), reduce the side effects of antibiotic therapies, as well as morbidity and mortality, shorten antibiotic therapies and hospital stay and minimize costs.

The plainest definition of this approach is the following:

What is Antimicrobial Stewardship?

Using the **right** antibiotic
at the **right** time
at the **right** dose
for the **right** duration

The White House National Action Plan for Combating Antibiotic-Resistant Bacteria

General structures and interventions of Antibiotic Stewardship (ABS)

To reach its goals, ABS implements structures and interventions summarized by the keywords: Investigation, education and enablement, restriction and pre- approval (antibiotic policies, SOPs), surveillance. Between 2007 and 2018 several editorials and guidelines have been published.[6-10]

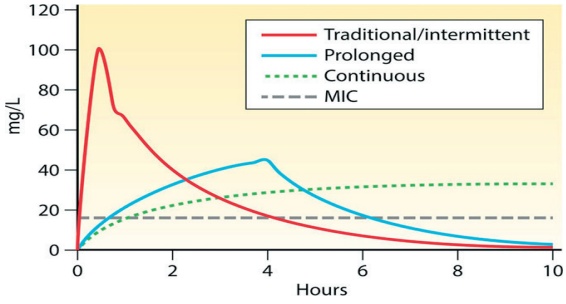
- **Select a Team**: ABS expert, physician, clinical pharmacist, clinical microbiologist, support of hospital administration, go to the bedside, perform multidisciplinary rounds and councils
- **Obtain baseline information on antimicrobial use:**
  - Institutional pathogen spectrum
  - Institutional susceptibilities
- **Density of use:** Monitor RDD / 100 patient days (Recommended Daily Doses)
- Implement **Antibiotic prescribing policies:** Standard operating procedures for your environment, according to the specific pathogen spectrum and susceptibilities. Implement standard length of therapy. Write down the date of stop when starting.
- **Restriction and pre- approval**
- **Monitoring:** adherence to SOP (Point Prevalence Analysis)
- **Audit and feedback**
- **Education/ Enablement:** appropriate use
- **ABS time out on day 3:** Stop? Change? Continue? How long? Cultures?
- **De-escalation:** Clinical improvement/ results of culture
- **Surveillance of nosocomial infections, benchmarking of NI and density of antibiotic use** with comparable hospitals (national programs)

It is of special interest to initiate an ABS approach in the ICU due to the high density of antibiotic use. Detailed descriptions of ABS implementation in the ICU have been published.[11-13]

Implementing an Antibiotic Stewardship program is effective and save

A meta- analysis of 32 trials investigating the effect of Antibiotic Stewardship shows a significant reduction of MDR gram- negative bacteria, MRSA und CDI.[14] Thus, there is evidence for decision makers that the implementation of ABS interventions reduces the medical and economic burden of infections with antibiotic- resistant bacteria and of CDI in hospital inpatients.

In a 2017 Cochrane database review of 58 RCTs and 163 NRS the authors found an increased compliance to prescribing policies, a reduction of unnecessary antibiotic use, a shorter duration of treatment (- 1,95 d in 14 RCT), a reduced length of hospital stay (- 1,12 d in 15 RCT) and reduced incidences of CDI, MRSA, MDR gram-negatives. All these findings were statistically significant. There is high quality evidence (28 RCT, 15827 patients) that implementing the afore-mentioned interventions will reduce antibiotic use without adversely affecting mortality.[15]



The ABS approach in daily routine - Pitfalls to avoid

No prolonged perioperative prophylaxis

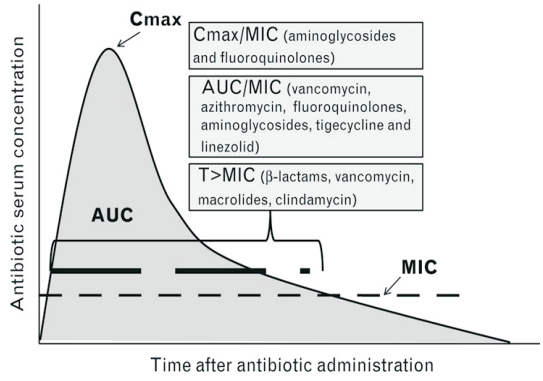
Perioperative antibiotic prophylaxis (POP) is always "single shot only". Some (low- quality) evidence suggesting benefits of a prolonged POP exists only in cardiac surgery. For any other clean or clean- contaminated procedure there is evidence and the firm recommendation not to give additional prophylactic antimicrobial doses after closing the surgical incision, also if the patient has a drain in place.[16] Antibiotics should be given repeatedly only during surgery, in accordance with the duration of the procedure and the half-life- time of the substance. Broad- spectrum antibiotics should never be used for POP. Though this is clear and simple, we know it is one of most frequent inappropriate uses of antibiotics in clinical practice.[4,5] It is useful to implement a written policy (SOP) with the surgical partners and to monitor the adherence.

Individualized dosing may be the key in the critically ill: TDM

It has been shown that critically ill patients may suffer from inadequate antibiotic exposure because of physiological changes as altered fluid status, augmented renal clearance, extracorporeal circulation, and impaired renal / hepatic function.[18,19] The European Committee on Antimicrobial Susceptibility Testing has recently (1.1.2019) changed its definition of "I" in the antibiogram from "intermediary" to "susceptible, increased exposure". These theoretical approaches are relevant to the problem of "hit hard" and "get to the point" of antibiotic therapy. TDM is well established for Vancomycin (AUC/ MIC is decisive) and aminoglycosides (C max/ MIC is decisive), with measurement of through- and peak- levels to establish low toxicity and efficacy, but not yet extensively available for Pip- Taz and Meropenem. Yet, it may be useful in the critically ill or in morbidly obese patients.[20,21]

Time-dependence of beta- Lactams, prolonged infusions

The PK- PD issues are relevant for the clinical use of beta- lactams in critically ill patients. Efficacy is related to fT> MIC. 100% fT > MIC of the dosage interval is the optimal exposure in critically ill patients.[17] Several meta- analysis between 2015- 2018 have addressed the question whether the difference between classical bolus infusion, prolonged infusion (> 3hrs) or continuous infusion is of clinical relevance. A recent high quality- evidence (22 RCT, 1876 patients) meta- analysis by Vardakas et al.[18] demonstrated that prolonged or continuous infusion of Piperacillin- Tazobactam and Meropenem provides significantly better survival than bolus infusions (RR 0,70; 95%CI 0,56-0,87). For cephalosporins statistical significance was not reached. There is no evidence whether prolonged or continuous infusion is better. The difference in survival was more significant in gram- negative than in gram- positive infections, in MDR than in highly susceptible bacteria and when APACHE score was > 22. Thus, for severe infections, low susceptibility, and on the ICU, prolonged infusions of Pip- Taz and Meropenem after a loading bolus are recommended. The use of continuous infusions leads to problems of drug-stability and incompatibility. Therapeutic Drug Monitoring (TDM) should be available as you risk the antibiotic serum level being lower than MIC all the time (fT > MIC = 0)



I – Susceptible, increased exposure*: A microorganism is categorized as "Susceptible, Increased exposure*" when there is a high likelihood of therapeutic success because exposure to the agent is **increased by adjusting the dosing regimen or by its concentration at the site of infection.**

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Redefining susceptibility testing categories **S, I** and **R.**

Gunnar Kahlmeter and the EUCAST Steering Committee

The role of fluoroquinolones (FQ)

As FQ have a big intracellular volume of distribution they are less susceptible to ICU- related changes in the volume of distribution than the hydrophilic beta- lactams. This seems ideal to address the afore-mentioned problems. But FQ are clearly related to the increasing incidence of MRSA and ESBL, as they are excreted with the sweat on the skin and contribute to inducing bacterial resistance. Furthermore, Ciprofloxacin shows low activity against S. aureus and there is increasing resistance of E.coli in Europe (ECDC). Finally many warnings about side effects have been issued between 2016 and 2018, so that they may no longer be considered as first choice substances. [22-25]

Class 3 cephalosporins and the correlation to CDI and ESBL incidence

In many countries Ceftriaxone is used as first- line therapy for moderate- severe CAP despite its poor activity against S. aureus. The density of use of class 3 cephalosporins correlates strongly with the incidence of ESBL and CDI. There is recent evidence that this might be an explicit problem of Ceftriaxone because of a 50% not- metabolized hepatobiliary excretion with very high bowel concentrations. This leads to selection of resistant bacteria. Cefotaxime proved to be better in a clinical trial[26] and in microbial research[27] and may also be preferable with respect to the afore-mentioned problems of individual dosing range and fT>MIC (3x1g -6x 2g/d).

Shorten antibiotic therapy courses

A lot of high quality evidence demonstrates that shortening antibiotic therapy courses is a safe and useful ABS intervention, even in gram- negative sepsis.[28-32] Nevertheless there are exceptions like osteomyelitis, spondylodiscitis, endocarditis or S. aureus bacteremia.

Table. Infections for which short-course therapy has been shown to be equivalent in efficacy to longer therapy

Disease	Treatment, Days	
	Short	Long
Community-acquired pneumonia [1-3]	3-5	7-10
Nasocomial pneumonia [6,7]	≤8	10-15
Pyelonephritis [10]	5-7	10-14
Intraabdominal infection [11]	4	10
Acute exacerbation of chronic bronchitis and COPD [12]	≤5	≥7
Acute bacterial sinusitis [13]	5	10
Cellulitis [14]	5-6	10
Chronic osteomyelitis [15]	42	84

Combination treatment: De- escalate

Even the 2016 Surviving Sepsis Campaign guidelines[33] state early narrowing of antibiotic therapy, once the patient improves or the pathogen is identified. A prospective observational study[34] and a systematic review of 2 RCT and 12 cohort studies[35] found that de- escalation of empirical therapy in the ICU leads to lower mortality and was a protective intervention. Even in uncomplicated S. aureus bacteremia (MSSA and MRSA) the ARREST trial (36) did not detect any benefit (but more adverse effects) of adjunctive rifampicin, as long as there was no non- removable foreign body with the risk of biofilm.

Investigating bloodstream infections with carbapenemase- producing Enterobactericeae the INCREMENT (retrospective cohort) study suggest that only critically ill patients with a high mortality score enjoyed improved survival from combination therapy.[37]

PCT

Subject to controversial data and discussions for many years, PCT is no "magic bullet". But there is recent evidence from a meta- analysis (26 RCT, 3336 patients PCT guided therapy, 3372 patients control), that PCT- guidance may not only be safe to shorten antibiotic therapies in critically ill patients[38], but actually reduces mortality[39]. Yet, the meta- analysis included respiratory infections only.

Take home message

- Worldwide increasing resistance
- ABS interventions are effective and safe
- Create interdisciplinary team, local guidelines. Perform surveillance, audits
- ABS time out on day 3 for any antibiotic therapy, define length of therapy at the start
- Use penicillin- derivatives first- line, BLI not always necessary
- Use FQ second line only (CDI, ESBL, warnings / restrictions)
- Cefotaxime might be better than Ceftriaxone
- Spare Carbapenems if possible
- Use PI for Pip/ Taz and Meropenem in the the critically ill
- Use beta- lactam TDM for selected patients
- De-escalate as soon as possible (clinical improvement)
- Combination therapy only in septic shock or under special conditions
- Shorten therapies, it is safe
- PCT guided therapy reduces side effects and mortality

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NEUROINVASIVE WEST NILE VIRUS INFECTION IN THE INTENSIVE CARE UNIT

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Introduction

West Nile Virus (WNV) is a zoonotic arbovirus of the Flaviviridae family. It is transmitted from infected birds to humans via mosquito vectors. Numerous outbreaks of human WNV disease have been reported globally since it was first identified in Uganda in 1937. [1]

The incubation period for WNV disease is typically 2 to 6 days but ranges from 2 to 14 days. About 70-80% of individuals infected by WNV are asymptomatic. Approximately 20-30% have "West Nile Fever" (WNF) presenting as fever, headache, tiredness, body aches, nausea, vomiting, occasionally with a skin rash and swollen lymph glands, without neurologic manifestations. Although neuroinvasive disease accounts for less than 1% of WNV cases, it can result in severe neurological sequelae and high mortality rate between 10% and 30% for patients with neuroinvasive WNV disease, or <0.1% of all infected patients . West Nile virus is most often diagnosed by: IgG and IgM antibody determination in cerebrospinal fluid (CSF) or serum by enzyme-linked immunosorbent assay (ELISA); viral detection by reverse transcription polymerase chain reaction (RT-PCR) assay. In patients with neuroinvasive disease, CSF examination generally shows lymphocytic pleocytosis, but neutrophils may predominate early in the course of illness. Brain magnetic resonance imaging is frequently normal, but signal abnormalities in the basal ganglia, thalamus, and brainstem may be seen in patients with encephalitis, and in the anterior spinal cord in patients with poliomyelitis. [2,3]

Neuroinvasive WNV disease can manifest as: West Nile meningitis (WNM), West Nile encephalitis (WNE), or myelitis with acute flaccid paralysis (AFP). Changes in cognitive status, muscle weakness, motor neuron disease (flaccid paralysis and hyporeflexia), cranial nerve palsies (most commonly facial nerve palsy), Guillain-Barre like syndrome (GBS), or movement disorders (e.g., myoclonus, tremor, parkinsonism) are various manifestations of the central nervous system (CNS) disease. [1,4,5,6]

Older age (over 50 years) and medical co-morbidities have been associated with higher rate WNV-related morbidity and mortality. Most patients with WNM and no focal neurological deficits have full recovery, but with frequent subjective complaints of prolonged fatigue and weakness. Unlike WNM, patients with WNE have a significant mortality rate (~20%). Patients who survive WNE frequently experience persistent movement disorders (tremors, bradykinesia) for months to years. AFP has the worst overall prognosis and a high mortality rate, which can reach 50% when neuromuscular respiratory failure occurs. [7,8]

The aim of this paper is to present cases of the patients with WNV disease hospitalized in the Intensive Care Unit of the Clinic for Infectious diseases, Clinical Center in Nis, Serbia, from August 2018 until October 2018.

Patients and methods

Specimens of ten patients suspected of being infected with WNV during outbreak in 2018 were tested at Institute for virusology, vaccines and serums – Torlak. Enzyme-linked immunosorbent assay (ELISA) was used for detection of WNV-specific IgM and IgG antibodies in sera (10 specimens) and cerebrospinal fluid (4 specimens). Eight patients had encephalitis and two patients had fever with headache.

Results

Demographic data of the patients, characteristics of the disease, CSF and serology analyses results are given in Table 1 and Table 2.

Table 1. Characteristics of the WNV infection patients and the disease outcome

Patient №	Age (years)	Sex	Form of disease	Comorbidities	Lethal outcome
1.	59	Female	WNF	Arterial hypertension	No
2.	59	Female	WNE	No	No
3.	78	Male	WNE	COPD	No
4.	82	Female	WNE	Diabetes, arterial hypertension, absolute arrhythmia	Yes
5.	65	Male	WNE	Diabetes	Yes

Two patients were from city of Niš (one of them was travelling before the disease onset to Srebrno jezero, a lake near city of Smederevo and travelling status of the other Niš inhabitant is unknown), one patient was from Drenovac village (near city of Paraćin), one patient was from Parunovac village (near city of Kruševac), one patient was from Donje Vidovo village (near city of Paraćin).

Patients who had WNF complained of fever, headache, exhaustion. Patients who had encephalitis and survived presented with fever, disarthry, disorientation, confusion. Instability, sopor and dispnoea were additional symptoms

Table 2. Serology results and cerebrospinal fluid characteristics of the WNV infection patients

Patient №	Serum ELISA WNV		CSF ELISA WNV	CSF cytological and biochemical findings	
	IgM	IgG	IgM		
1.	+	+	Not performed	Not performed	
2.	+	-	Not performed	Not performed	
3.	+	-	Not performed	Neutrophils /mm^3	30
				Lymphocytes/mm^3	58
				Proteins (g/l)	1.65
				Glucose (mmol/l)	3.7
4.	+	+	+	Neutrophils/mm^3	95
				Lymphocytes/mm^3	41
				Proteins (g/l)	2.37
				Glucose (mmol/l)	4.5
5.	+	+	+	Neutrophils/mm^3	23
				Lymphocytes/mm^3	25
				Proteins (g/l)	4.3
				Glucose (g/l)	3.9

of the patients who died. Three cases with encephalitis were associated with respiratory failure and subsequent mechanical ventilation treatment, two of them had lethal outcome. The period of time from symptom onset to hospitalization ranged from 3 to 7 days. The length of hospital stay ranged from 5 to 52 days. Computed tomography finding were normal in all the patients with encephalitis. Electroencephalography (EEG) findings revealed generalized non-specific slowing of electrocerebral activity.

All the patients with encephalitis received manitol and corticosteroids as therapy against brain swelling and prophylactic anticonvulsive therapy. They were also treated with acyclovir for presumptive herpes encephalitis and antibiotics for presumptive bacterial CNS affection. The patients with respiratory failure were mechanically ventilated. Additional therapy was based upon preventing and treating intensive care unit stay complications.

Discussion

The interpretation of the findings of this case series is limited because of small number of cases and the fact that two patients were from the central-west part of Serbia. However, knowing the fact that one resident of city of Niš infected with WNV was actually travelling to northern part of Serbia supports the fact that Northern and Central-West parts of Serbia were regions with the majority of patients from the Serbia WNV outbreak. [9]

Between 2014 and 2018, European countries reported locally-acquired WNF cases. WNF follows a seasonal pattern with most cases acquired in the European countries between July and October, with the case numbers usually peaking between mid-August and mid-September. [(10)] It is estimated that by October 2018, 29 people have died from West Nile fever in Serbia, with 286 cases registered by medical authorities. [9]

One of the largest prospective studies providing neurological symptoms data among American patients with WNV CNS disease revealed that 93% presented with a significant neurological deficit detectable by clinical examination, with 49% having some form of weakness, 35% with tremor, and 16% with cranial neuropathy [1]. Another American study showed that males were 63.6% of the cohort and females 36.4% with a median age of 62. Mortality was 7.31% for encephalitis and 1.5% for other CNS involvement. The encephalitis cohort had more comorbidities. Younger patients (<62) were 73% less likely to die and those with respiratory failure were 84% more likely to die. [11]

Patients with WNV neuroinvasive disease can present with a multitude of EEG abnormalities ranging from non-specific slowing, epileptiform activity, focal slowing, triphasic waves and frontal intermittent rhythmic delta activity. An anterior predominance of EEG changes was observed in more than half of those with epileptiform discharges and/or focal slowing. [12]

Serologically confirmed West Nile virus meningitis and encephalitis produce similar degrees of CSF pleocytosis and are frequently associated with substantial CSF neutrophilia. Patients with encephalitis have higher CSF protein concentrations and are more likely to have lethal outcome. CSF findings is only a modest predictor of disease outcome, with patient age adding important independent prognostic information. [13]

The first reported outbreak of WNV infection in humans in Serbia in August to October 2012 presented 58 patients, mean age 61 years, from Belgrade and its suburbs; of whom 52 had neuroinvasive disease: 8 had meningitis, 44 had encephalitis. 13 patients with encephalitis developed AFP and respiratory failure. Age over 60 years and immunosuppression (including diabetes) were independently associated with the development of encephalitis. 35 patients fully recovered and 9 patients died. The presence of AFP, consciousness impairment, respiratory failure and immunosuppression (without diabetes) were found to be associated with lethal outcome. [14] A study of an outbreak in Vojvodina, Serbia, 2015, which involved 22 (69%) males and 10 (31%) females aged from 31 to 65 years showed that there were 16 (50%) febrile individuals, 27 (84.4%) with positive meningeal signs, 17 (53.2%) with pathological neurological signs, and 10 (31.3%) with consciousness disorders. Cardiovascular comorbidities dominated in 7 (21.9%) of the cases. Full recovery was accomplished in 87.5 % of the cases. In most cases, after the administered symptomatic therapy, the complete recovery of patients was achieved. [15] Still unpublished data from Infectology Departement of Clinical Center of Kragujevac (the 2018 outbreak), which encountered 37 cases, showed that 35 patients with WNV had encephalitis among which 30 cases presumably had mild or moderate form of encephalitis and 5 patients had severe encephalitic forms with respiratory failure and lethal outcome. More than 80% of patients were males from rural parts of central-west Serbia. As viewed in literature, CSF pleocytosis, irregular EEG finding, impairement of consciousness and neurologic deficit are present in our patients with WNE. Lethal outcome was also associated with higher degree of consciousness impairment, respiratory failure, older age and comorbidities.

Conclusion

Patients presenting with signs of central nervous infection between July and October should be tested for West Nile Virus infection.

Since there is no established antiviral treatment for West Nile Virus infection, neuroinvasive forms of disease are treated by means of supportive therapy in an intensive care setting.

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SPECIFICITY OF ANESTHESIA IN GERIATRICS

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In recent years a growing interest has revolved around the impact of surgery and anesthesia on the elderly. The process of ageing is complex and under constant influence by numerous factors, for which reason the way human age is extremely individual [1]. Ageing is a physiological process, where the structure and functional capacity of organs and tissue progressively degenerates over time. The ageing process is extra-ordinarily complex, and is constantly influenced by numerous factors; such as life style choices, environment, genetics, social network and chronic diseases [2]. Often patients receive several drugs for their chronic diseases, which may have negative connotations. Polypharmacy can be associated with increased risk of adverse drug reactions, problematic drug interactions, and medication errors [3]. The geriatric surgical population with its unique physiology and response to surgical insult poses challenges in perioperative assessment. It is now well established that frailty is a strong predictor of perioperative complication and mortality in surgical patients. Moreover, the older population has the highest incidence rate for 60% of operations compared with other age groups. These patients often are with multiple comorbidites, malnutrition, heart failure, diabetes, chronic obstructive lung disease, kidney impairment, dementia. frailty, and little reserve. 50% of patients aged over 70 suffer from one chronic disease, and 30% present more than one [4].

In 1989, Rosenberg coined the term sarcopenia to refer to the age-related loss in skeletal muscle mass and size. Several mechanisms are involved in the development of sarcopenia, including alterations in sex hormones, protein synthesis, proteolysis, neuromuscular integrity, endocrine issues (insulin resistance), an increase in muscle fat content, changes in physical activity, and inadequate nutrition [5]. Recently, it has been suggested that primary sarcopenia be used to define sarcopenia that is caused by aging itself, and that secondary sarcopenia be used to define sarcopenia that is caused by disuse (immobility, physical inactivity, or prolonged bed rest), disease (associated with advanced organ failure, inflammatory disease, malignancy, or endocrine disease), and/or inadequate nutrition and malabsorption (inadequate dietary intake of energy or protein, gastrointestinal disorders, or use of medications that cause anorexia. [5] Sarcopenia is believed to be caused predominantly by atrophy and loss of skeletal muscle fibers, mainly type II fibers [6].

Pharmacokinetics

The normal aging process results in changes in body composition and essentially all tissues. These changes significantly influence the pharmacologic effects and dosing of analgesic and anesthetic medications. As the body ages, there is a shift in body mass from muscle to adipose tissue. This progressive adiposity is also associated with a loss of lean body mass and a decrease in total body water, making appropriate dosing of medications challenging. The expansion of adipose tissue increases the reservoir of lipid-soluble agents, contributing to the protracted clearance and increased duration of action for benzodiazepines, volatile agents, narcotics, and sedative-hypnotics. In addition, the decrease in total body water decreases the volume of distribution for water-soluble medications, resulting in higher average and peak plasma concentrations [7]. The variability in pharmacodynamics and kinetics is high; usually, smaller doses are needed for clinical effect compared to the adult population, and the duration of action is prolonged. Therefore dosing should be carefully titrated by the principle: "start low – go slow" [8].

All opioids, i.v. agents and benzodiazepines, exhibit an age-related increase of their t 1/2b elimination half-life, resulting in a prolonged duration of action. This is attributable to an increased volume of distribution for lipophilic drugs because of the increase in body lipid content in the elderly, and a reduction in organ-based elimination [9]. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. Originally conceived of in 1991 by the late Mark Beers, MD, a geriatrician, the Beers Criteria catalogues medications that cause side effects in the elderly due to the physiologic changes of aging [10].

General anesthesia

Anesthetic management needs to be individualized for elderly patients. For example, when using propofol in the elderly, a lower induction dose is needed; the slower blood-brain circulation results in a slower onset and delayed maximal cardiopulmonary depressive effect. As a result of less compliant vasculature, the elderly are also more prone to develop hypotension with this agent. The use of inhalational anesthetics also needs to be adjusted in the elderly. For every decade after 30 years of age, there is a 7% increase in the potency of inhalational agents.

Induction agents The dose requirement for induction agents is also reduced in the elderly. A contracted blood volume coupled with reduced protein binding leads

to a higher free-drug concentration. Prolongation of arm–brain circulation time dictates that induction agents should be administered more slowly than in the younger patient. Inhalational agents The MAC value of all inhalational anaesthetic agents is reduced by 20–40% from young adult values.

Neuromuscular blockade However, the time of onset and the duration of action are both prolonged because of a reduction in cardiac output and reduced metabolism, respectively. Antagonism of neuromuscular blockade with antiholinesterase drugs tends to be similar to younger adults.

Airway management

A history of previous difficult intubation is a very important predictor of difficult airway management. Elderly patients may be unable to provide information about previous difficulties, thus compromising safety in airway management. The edentulous state of the elderly patient may make airway maintenance during mask ventilation more difficult than in younger adults. Anatomical characteristics of elderly patients such as limited head and neck movement may impair visualisation of the vocal cords during laryngoscopy and impede tracheal intubation.

Cardiovascular implications

Ageing is associated with a reduction in the carotid baroreceptor response to a fall in blood pressure. Both i.v. and inhalational anesthetic agents further impair this response, and also depress cardiac and vascular smooth muscle contractility. Etomidate is an exception in that it spares myocardial contractility. Arterial hypotension is the most common hemodynamic complication of general and regional anesthesia. Regional anesthesia produces a drug-induced sympathectomy that produces a drop in blood pressure of >25% in 25–50% of elderly patients. The choice of vasopresor used to correct hypotension lies between a mixed α and β-adrenoceptor agonist such as ephedrine, or a pure α -agonist such as Phenylephrine. α -agonists increase blood pressure via peripheral arterial and venous vasoconstriction, b-agonist activity increases cardiac output by increasing heart rate and contractility.

Respiratory implications

Pulmonary function is most notably affected by anatomic changes in the elderly. Kyphosis, vertebral compression, calcification of the costal cartilage, and contracture of the intercostal muscles lead to decreased chest wall compliance. Loss of intercostal muscle strength alone can decrease maximum inspiratory and expiratory force by as much as 50%. The loss of the elasticity of the lung parenchyma collapses small airways, leading to increased alveolar compliance with uneven ventilation and air trapping. Although total lung capacity remains unchanged, there is a mild increase in functional residual capacity (FRC; 1%–3% per decade) and an increase in residual volume (5%–10% per decade). Thus, vital capacity decreases 20 to 30 mL per year. Mucociliary clearance decreases, whereas swallowing dysfunction, loss of cough reflex, and oropharyngeal colonization contribute to aspiration. Additionally, the neurologic autonomic response to hypoxia and hypercapnia is decreased by 40% and 50%, respectively [11]. The losses in alveolar surface area results in V|Q mismatch and increased physiological shunt, and consequently a lower PaO2. Changes in lung volumes also contribute to an increased physiological shunt. The large airways increase in size as one ages resulting in an increased anatomical and physiological dead space. The elderly are more likely to suffer apneas, periodic breathing patterns and respiratory depression after administration of opioids and benzodiazepines.

Renal function

Total body water is reduced by 10% to 15% in older patients. Elderly patients are susceptible to acute kidney injury or acute/chronic kidney injury and electrolyte abnormalities. However, the older patient population is unique in that they are at an increased risk of electrolyte disturbances without underlying renal dysfunction, dehydration, and polypharmacy simply as a result of physiologic aging. Elderly patients are also more susceptible to water retention and associated electrolyte abnormalities that are exacerbated in the perioperative period, a time of increased physiologic stress. Positive fluid balance is an independent risk factor for mortality in critically ill patients with acute kidney injury [12]. Creatinine clearance is also reduced. Tubular dysfunction impairs the ability to concentrate urine, leading to electrolyte disturbances. Physiologic changes in the perioperative period include systemic neurologic, hormonal, immune, and hematologic responses. Cognitive decline is a risk factor for dehydration. Increased secretion of antidiuretic hormone, renin, and aldosterone during stress results in fluid retention. Salt and water retention has been associated with increased risk of infection, cardiopulmonary complications, and impaired gastrointestinal function as well as a prolonged hospital stay. [13]

Gastrointestinal and Nutrition

The gastrointestinal tract is one of the systems relatively unchanged functionally by aging. Dysphagia is a common elderly problem leading to aspiration in the perioperative period. This problem may be caused by decreased senses (olfactory, taste), decreased tongue muscle mass and strength, medications and as a result of neurologic disorders and neurovascular disease. Gastroesophageal reflux disease (GERD) is present in about 30% of the elderly. Gastritis and gastric atrophy are the most common gastrointestinal disorders in the elderly, placing them at risk for gastrointestinal bleeding. The stress in the perioperative period, along with the use of NSAIDs that deplete mucosal prostaglandins may incite bleeding and ulceration. If an elderly patient develops a gastrointestinal bleed, upper or lower, independent of cause, then mortality can range from 10% to 25%. The liver decreases in weight and number of hepatocytes with age, impacting pharmacokinetics. Although pancreatic function is not altered by age, the main duct increases in size 8% per decade. Inadequate oral intake is similarly multifactorial because of social, psychiatric, and medical factors. Malignancy and depression are identified as the most frequent causes of malnutrition in elderly patients. [14]

Endocrine system

Endocrine system activity reduces with age, causing impaired glucose homeostasis, decreased thyroxine production, decreased production of renin, aldosterone and testosterone, decreased Vitamin D absorption and increased plasma concentration of antidiuretic hormone. The consequences include diabetes, thyroid dysfunction, decreased sodium retention, increased potassium absorption, and osteoporosis.

Hematological and immune system

Reduction in marrow production and in T-cell function, together with poor dietary intake and poor vitamin absorption, predispose to anemia and autoimmune disease. Anticoagulants are commonly prescribed for patients at risk of arterial or venous thromboembolism. The most common indications are atrial fibrillation, venous thromboembolism, and presence of mechanical heart valves. The clinical guidelines and protocols are helpful in deciding the plan of anesthetic management tailored to each patient. [15]

Fluid management

Hypovolemia was considered a major factor in morbidity resulting from hypotension during anesthesia. Hypovolaemia may occur preoperatively because of factors such as self imposed fluid restriction, and occult blood loss in the case of extracapsular hip fractures, in which 500–1000 ml blood can be lost into the fracture site. Over hydration may also occur and has greater impact because of reduced cardiorespiratory reserve. A urinary catheter is essential in the monitoring of fluid status but is only useful if accompanied by accurate charting of fluid balance. Venous access may be easy to achieve, yet rapidly lost because of the thin fragile vessel walls. Pressure over the tip of the cannula may easily tear the vessel wall. Poor fixation will also prejudice the useful life of the i.v. system.

Temperature

The elderly may also lack the metabolic and muscular reserve to bring their body temperature back to normal levels. Passive measures such as reflective drapes and warmed i.v. fluids prevent heat loss but will not return a hypothermic patient to normotermia. Warm air systems and warming mattresses are more useful in this respect.

Postoperative Delirium (POD)

POD occurs shortly after surgery and is an acute change in cognitive status characterized by fluctuating attention and consciousness as well as abnormalities in memory and perception. It is estimated that the incidence of POD in older adults occurs between 36.8% and 73.5%. Although common, this well-recognized clinical entity is associated with a prolonged hospital stay, delayed functional recovery, and increased morbidity and mortality. [16]

Analgesia

Therefore, in the elderly, it is recommended to use a balanced (or multimodal) analgesic approach, which can minimize the adverse effects of opioids. Using a combination of local anesthetics, acetaminophen, non steroidal anti inflammatory drugs (NSAIDs), steroids, and non-traditional analgesic agents is safe and efficacious in this age group [17].

Peripheral Nerve Blocks

Properly done, this approach is an excellent anesthetic in the elderly. The use of peripheral nerve block offers better postoperative pain control, decreased opioid requirement, and increased patient satisfaction. One potential downside of this approach is a documented higher risk of permanent nerve damage in elderly patients.

Regional Anesthesia (Spinal and Epidural Anesthesia)

Several studies have speculated on the potential benefits in selecting regional anesthesia instead of general anesthesia. One advantage is that local anesthetics can be infused to provide good postoperative analgesia to facilitate mobilisation and accelerated recovery with possible earlier discharge from the hospital. However, disoriented demented patients often require additional sedation with benzodiazepines to ensure optimal cooperation during surgery under regional anesthesia and this may reduce these benefits. In addition, hemodynamic depression is common with epidural and spinal anesthesia due to vasodilatation and this type of anesthesia may not be a good choice in the presence of severe cardiac disease.

Day case surgery: anesthetic considerations?

The risk of perioperative major complications and mortality is low in elective surgery; however, elderly patients have an increased risk of cardiovascular and respiratory events, more serious complications and increased perioperative mortality. Major morbidity and mortality is associated with ASA physical status and age. Cardiovascular and respiratory events, postoperative delirium and postoperative cognitive dysfunction (POCD) increase with increasing age. Effective planning avoiding prolonged pre-operative fasting and facilitating early discharge to the home environment may reduce the risk of cognitive impairment. Although regional anesthesia may be the preferred anesthetic technique for minor surgery, anesthetic technique has not been shown to have an important impact in the elderly on the risk of cognitive deterioration. Day case surgery should be seen as an alternative in the elderly patient. The elderly patient may further benefit from this approach since they can return home to recuperate in familiar surroundings. The planning and organisation for day case surgery of the elderly patient must involve all parties: anesthetist, surgeon and the entire health care staff in order to secure a good quality of care and safety

Summary

The older population is rapidly growing and living longer, and this growth is expected to drastically increase surgical demand for both elective and emergent cases. The elderly population undergoes significant changes of numerous organ systems as a result of the aging process; their tenuous homeostasis can be drastically unraveled by minor changes in the perioperative period. The perioperative management of the elderly population is complex and requires a multidisciplinary team focusing on education, frequent assessment, functional status, and quality-of-life outcomes as well as traditional outcome measures. Regional anesthesia with or without supplementary sedation should be chosen whenever feasible. Anesthetics and analgesics should be administered in age-adjusted doses. Perioperative management must be tailored to physiologic changes of ageing, which affect respiratory, cardiac and renal function, as well as guidelines for preventing infection and thrombotic events. Day case surgery may be a superior option for the elderly patients scheduled for minor or intermediate surgery avoiding prolonged hospitalisation and thus change of environment. Appropriate planning, pre-operative preparations and assessment, but also the post-discharge recovery and rehabilitation must be arranged.

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ANESTHETIC CHALLENGES IN CANCER PATIENTS

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Cancer is a leading health problem worldwide. According to epidemiological data, approximately 40% of people have a chance to develop cancer during their lifetime. Cancer is the most common cause of death from disease in children aged 1-14 years.

The aim of this lecture is to present specificity of cancer patients, the major effects of cancer treatment that the anesthesiologist should consider perioperatively and the possible effects of different anesthetic techniques and agents on cancer recurrence.

The major effects of cancer treatment and anesthesia

Recent advances in cancer therapy include combinations of different treatment modalities as well as novel approaches that affect anesthetic care. Surgery, chemotherapy and radiotherapy are the most common modalities used to treat a patient with cancer. To prepare the best perioperative management plans for cancer patients, the knowledge of acute and long-term side effects caused by these methods of treatment is required of anesthesiologists. Children require anesthetic input throughout their disease process, for short procedures, for central venous access insertion, anesthesia to facilitate radiotherapy and for surgical procedures.

Surgery

Many cancer patients undergo surgical resection of their primary cancers for curative intent or may need surgery as part of palliative treatment of an advanced-stage cancer. Alternatively, cancer patients may require emergency procedures, often due to complications related to their oncology disease and ongoing pharmacotherapy, or surgeries unrelated to their malignity.

The anesthetic plan will depend upon preoperative findings. Preoperative evaluation of patients with cancer includes considerations of the pathophysiologic effects of the disease and the recognition of the potential adverse effects of cancer treatment. Correction of nutrient deficiencies, anemia, coagulopathy and electrolyte abnormalities may be needed preoperatively.

Chemotherapy

The development of anticancer agents is a rapidly evolving and growing field, comprising not only the classic cytotoxic chemotherapy drugs but also the new molecular targeted agents.

Chemotherapy agents, used either as monotherapy or in combination, have cardiovascular side effects, including heart failure, arrhythmias, hypotension or hypertension, coronary ischemia or pericardial disease. The anthracyclines, drugs used to treat leukemia, lymphoma and breast cancer, are implicated in cardiotoxicity. Cardiac toxicity manifesting as cardiomyopathy occurs in 1% to 5% patients treated with epirubicin, doxorubicin or daunorubicin. The myocardial depressant effect of the commonly used anesthetic agents may be compounded by the previous exposure to chemotherapy agents, even in patients with apparently normal cardiac function. This is the reason why all these patients should be treated as high risk for potential cardiac events during anesthesia.

Bleomycin is an anti-cancer drug used to treat Hodgkin's disease and germ cell tumors. Bleomycin induced interstitial pneumonitis that can progress to pulmonary fibrosis is the most commonly encountered pulmonary complications of chemotherapy.

The methotrexate and platinum-based chemotherapy agents are nephrotoxic. They can cause either acute or chronic renal failure. The nephrotoxic process is augmented by dehydration and concurrent use of non-steroidal anti-inflammatory drugs. Careful fluid optimization and dosage of analgesics are imperative perioperatively.

Gastrointestinal toxicity is common after the administration of chemotherapy drugs. Side effects which include nausea, vomiting, mucositis and diarrhoea lead to dehydration. In these cases, prescription of fluids and electrolytes is indicated before surgery. Rapid sequence induction of anesthesia should be considered. Furthermore, it should be known that laryngoscopy may exacerbate the mucositis and lead to severe bleeding.

Most chemotherapy drugs affect bone marrow and the peripheral blood cells. It leads to myelosuppression which is usually reversible within six weeks of cessation of chemotherapy. Transfusion of blood products may be required in the cases of anemia caused by myelosuppression and urgent surgery. Neutropenia is associated with infections postoperatively. To avoid severe complications, broad-spectrums antibiotics must be administered. For patients with thrombocytopenia platelet transfusion must be balanced against the prothrombotic state that cancer induces. A patient with pancytopenia should be consulted by a hematologist before surgery.

Anticancer therapy can cause a number of neurotoxic side effects including peripheral neuropathy and encephalopathy. The most common agents with neurotoxic side effects are vincristine and cisplatin. Cisplatin neurotoxicity may extend several months beyond discontinuation of treatment, so performance a regional anesthesia and

administration of local anesthetics and epinephrine in patients being treated with cisplatin chemotherapy may produced a clinically significant injury. However, the major problems for anesthesiologists are associated with the effects on the autonomic nervous system: the development of orthostatic hypotension and vocal cord palsy. Many chemotherapeutical drugs can cause encephalopathy. Preoperatively a full neurological examination to detect any neurological damage should be conducted.

Radiotherapy

Radiotherapy is frequently used in combination with chemotherapy. Radiotherapy causes tissue damage through the production of oxygen-free radicals. As a consequence, they can cause delayed wound healing, induration of the skin, vascular stenosis, myocarditis, pneumonitis and pulmonary fibrosis.

Anesthesiologists are faced with the challenge of management of patients with head and neck cancer. Airway management of these patients is difficult because of the site and size of the tumor. Previous treatment with radiotherapy could also lead to a limited neck extension and rigidity of the oropharyngeal tissues. This makes ventilation with a face mask and laryngoscopy difficult. Radiotherapy for the head and neck leads to a difficult central venous access. Furthermore, mucositis as a consequence of radiotherapy can be exacerbated by tracheal intubation.

Radiation induced pneumonitis is common due to the susceptibility of lung tissue to damage. Severity of disease is related to the total volume of lung exposed to radiation, the total radiation dose and the size of the individual fractions of dose given. Previous chemotherapy, previous radiotherapy and withdrawal of steroids are recognized risk factors for radiation-induced pneumonitis.

The effect of general anesthesia on cancer recurrence

Data from laboratory and animal experiments suggests that anesthesia and anesthetics may contribute significantly topro-tumor environment and affect long-term outcomes after cancer surgery. Anesthesia impairs many immune functions, including functions of neutrophils, macrophages, dendritic cells, T cells and natural killer (NK) cells. NK cells are important in the destruction of tumor cells. Many other factors in the perioperative period, including the inflammatory and endocrine metabolic stress response are suggested to promote a micro metastatic process, which results in poor long-term oncologic outcomes.

An animal study demonstrated that opioids, volatile anesthetics, thiopental and ketamine could inhibit NK cells activity and cause cancer metastasis. Volatile agents may have direct effects on cancer cells and they are associated with immune modulation and could potentially increase the ability of tumor metastasis. Opioids have different effects on the immune response and the reason is unclear. Endorphin increases NK cells cytotoxicity and favors anti-inflammatory cytokines. Therefore endorphin has been considered as a possible anticancer therapeutic agent. Exogenous opioids suppress the immune function. They inhibit humoral and cell-mediated immune functions and increase tumor growth rate.

However, there is some evidence that propofol may have an anticancer effect. Different studies made in vitro established a lot of mechanisms how propofol acts as an anticancer agent: it inhibits tumor size, cell viability, induces cell apoptosis or inhibits invasion and angiogenesis of cancer. Propofol-based total intravenous anesthesia is suggested to have anti-inflammatory features and to be advantageous compared with inhalation anesthesia.

To conclude, general anesthetics do not cause the development of cancer directly. However, immune suppression induced by anesthesia could lead to a faster progress of cancer, but evidence is not convincing and large cancer-specific randomized clinical trials are required for further investigation.

The effect of regional anesthesia on cancer recurrence

There is hypothesis that regional anesthesia and analgesia may influence cancer recurrence and there are few retrospective studies suggesting benefit from the use of perioperative regional anesthesia in patients with breast cancer and prostate cancer. Few others did not in colon cancer, prostate cancer and cervical cancer. The reason for this benefit is unclear, regional anesthesia and analgesia reduce neuroendocrine stress response to surgery, reduce or eliminate general anesthetics, provide excellent analgesia and minimize or eliminate the need for opioids that have been implicated in potentiating tumor cell survival and angiogenesis. Local anesthetics are suggested to have anti-proliferative and cytotoxic effects on cancer cells. Alternatively, local anesthetics may directly stimulate NK cells activity. According to the latest literature there is insufficient data to make any firm conclusions.

It must also be determined whether the pro-tumor effect of anesthetics and opioids observed in the laboratory are likely to make an impact on survival in patients in the real world receiving potent anticancer chemotherapy, molecular-targeted therapies and hormonal therapies that are prescribed to cancer patients. On the other hand, it could be argued that if making a relatively minor change to anesthetic practice has the potential to reduce cancer recurrence even to a small extent, it is logical to do so. Prospective studies are needed to answer these questions. Current data do not call for a drastic change in the perioperative management of cancer patients.

In conclusion to provide the best treatment for cancer patients, cooperation of anesthesiologists with oncologists and surgeons becomes imperative.

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PERIOPERATIVE CONSIDERATION FOR NEUROSURGICAL GERIATRIC PATIENT

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Introduction

Aging is defined as a comprehensive, progressive and irreversibile biological process characterized by the declining possibilities of an organism for adaptation to everyday living situations. Despite all medical measures and procedures, the older population has higher morbidity and mortality compared to younger. With the improvement of living standards and health care, the share of the elderly in the population also increases.

Anesthesia and surgery in geriatric patients is different, often more complex than in young patients. All members of the perioperative team should take into account the physiological features of aging and their association with pathology and applied diagnostic and therapeutic procedures. Every anesthetist must know that there is a great variety in the aging of both the systems and the body as a whole, and the surgical team to seek

Less stressful interventions in tIt he elderly.

Important manifestations of aging

Aging leads to a gradual decrease in functional reserves of organs and systems, basal metabolism is reduced, prolonged the duration of postoperative hypothermia. Due to the accumulation of body fat, the deposition of lipidsoluble medicinal products is more pronounced, the longer the time of redistribution and slower elimination, so the effect of anesthetics is prolonged. The volume of blood is reduced, which in combination with dehydratation significantly affects a higher concentration of anesthetics. The elimination of kidney drugs is reduced, progressive kidney reduction occurs, as well as the reduction in the number and function of nephron, conditions for the development of renal insufficiency are created. Liver weight has been reduced to 35%, but the preservation of the function is good considering the large reserve of liver parenchyma.

There are significant changes in the cardiocirculatory system, reduced elasticity of the blood vessels, cardiac hypertrophy, reduced catecholamine response, development of cardiac insufficiency. The chest in elderly patients loses its elasticity, reducing, the minute respiratory volume and perfusion of gases through the alveolocapillary membrane. The respiratory response to hypoxia has been reduced, the cough reflex is getting weaker and the risk of aspiration increased, which together can significantly reduce pulmonary function.

Disorders of the central nervous system

Aging is associated with a significant change in brain morphology, physiology, and biochemistry. The size and weight of the brain decreases with age, the loss of the cortical gray mass becomes more pronounced, leading to cerebral atrophy. Conversely, the physiology of cerebral circulation is well preserved, so cerebral blood flow (CBF) is at the expense of reduced brain mass. This indicates that cerebral autoregulation and hypoxia reactions have a good response, while the proces of neurotransmission is more disturbed.

The most common form of disordered brain function of elderly hospitalized patients is delirium. It is in acute organic syndrome of transient character, characterized by a disturbance of consciousness and cognition, and can develop relatively rapidly and persist for hours, days, weeks. Many drugs, many conditions and complications can increase the risk of delirium occurrence.

Preoperative assesment

The assesment of the functional status of a neurosurgeon patient is even more difficult, primarily due to altered sensory, neurological deficits, limited mobility. Problems encountered by anesthesiologist during neurosurgical intervention.

- time extended operations
- different position of patients during surgery and following the problem of positioning
- tymely assessment of excessive blood loss
- neurosurgeon complications during surgery
- cardiovascular disorders due to surgical complications near vital centers
- venous and arterial air embolism
- early postoperative neurosurgical assessment

The effect of aging on the respiratory system is manifested by the development of hypoxemia and hypercapnia in the perioperative period, the pulmonary function must be corrected by appropriate drugs, inhalation, breathing exercises. It is often necessary to perform lung function tests and perform an adequate assessment of respiratory parameters before surgery. The elderly are more susceptible to dehydration and their response is poor, and it is necessary to make correction of the electrolyte and especially hyponatraemia. Patients who receive antiaggregation and anticoagulant therapy should perform adequate preoperative preparation in accordance with the basic disease and urgency of surgical treatment. Diabetes mellitus is a comon disease in elderly patients, and these patients have a higher incidence

of cerebral ischaemia in the perioperative period, so glycemic correction is necessary. Antihypertensives should be taken regularly during the perioperative period, consideration should be given to the reduction of the dose on the day of surgery, and some should be discontinued (ACE inhibitors and diuretics).

Neurological status

The goal of the neurological assessment is to determine the location and size of the lesion of the nervous tissue, and to determine the level of consciousness. If a patient with a changed state of consciousness and symptoms of intracranial hypertension (headache, nausea, vomiting) should take all measures to treat and prevent further increase in intracranial pressure.

Arterial gas analyzes are very important because they indicate hypoxia and hypercapnia that can cause cerebral vasodilatation and exacerbate intracranial hypertension. In patients with changes in the last cranial cave with implantation of the brainstem, there may be weakened airway reflexes and loud wires, so the extubation is only performed when they are fully awake with all the methods of preventing bronchial aspiration.

The main conditions in neurosurgery

Brain tumors

In brain tumors, both malignant and benign, primarily meningeomas, treatment can depend on many operational technical problems when removing tumors (increased blood loss, proximity to vital centers, prolonged surgery). Clinical signs of increased intracranial pressure usually occur very late or do not occur at all. Brain atrophy and increased volume of cerebrospinal fluid cause small peripheral edema around the tumor, and the frequency of epi attacks is less due to decreased brain irritation.

Intracranial spontaneous bleeding

The most common causes of intracranial haemorrhage are rupture aneurysms or arteriovenous malformations. First and basic anesthesiological measures and procedures are to provide rest and sedation of these patients. There is often high blood pressure and is usually reactive hypertension due to an increase in intracranial pressure. These patients are affected by complications such as rebleeding, hydrocephalus, vasospasm. Cerebral vasospasm, brain ischemia and neurological deficiency are the main postoperative problem and the cause of morbidity and mortality. For the prevention of vasospasm consider the use of Ca-channel blockers and 3H therapy (hypertension, hemodilution and hypervolemia).

Head trauma

The clinical picture of patients with cerebral trauma can sometimes be slightly dependent on the age of the patient, but the aetiology of the injury and the prognosis of treatment can be quite different. By type of injuries, chronic subdural hematomas are more frequent, as opposed to epidural, and there is a higher incidence of intracranial bleeding in the field of brain contusion. This can be interpreted by more frequent use of antiaggregation and anticoagulant therapy, expressed by degenerative changes in cerebral blood vessels, also by brain atrophy. The main goal is to prevent cerebral perfusion pressure and prevent intracranial hypertension.

Chronic subdural hematomas

These are very common in elderly and mortality is twice as high as in young people. Cerebral atrophy affects the clinical manifestation, since a significant amount of blood can be accumulated in the subdural space without causing an increase in intracranial pressure. This is the reason for the long and subdued history of the disease that occurs as a result of seemingly small and often forgotten injuries. The diagnosis is based on a CT scan and is treated with surgical intervention. Goal is the decompression of the spinal cord.

Spinal surgery

Aging is accompanied by degenerative changes on the spinal column, which involve both bones and soft tissues. The spine column becomes less mobile due to altered bone architectility, reduced elasticity of ligaments, dehydration of the intravertebral disc, atrophy of the paravertebral musculature. Because of the high incidence of osteoporosis in the geriatric population, it is more susceptible to traumatic fractures that can cause neurological deficits, and due to compression of the nerves and severe pain.

Common surgical procedures on the lumbal section are flavectomy, laminectomy, dysctomy and foraminectomy. Spine fixation with the help of various materials, tiles and screws is often accompanied by complications due to the lenght and complexity of the operation, the patient's position, the large blood loss. The most common cause of dysfunction of the cervical spinal cord is myelopathy, surgical intervention is necessary, and the primary

Intraoperative specificites

Careful exanimation of the airway in the erderly is necessary because the incidence of difficulty intubation is more frequent, especially in people with spondyloarthritic changes and partially or completely immobile neck. The endotracheal tube should be well fixed and further blocked by a tamponade in the oral cavity, which is particularly important in the elderly due to lack or losse teeth.

For rapid infusion, it is necessary to set up two intravenous lines and often a central venous catheter, especially in patients with some tumors and intracranial hemorrhages. Routine monitoring is necessary and involves ECG, pulse oxymetri, capnography, blood pressure measurement, temperature, diuresis, arterial gas analysis, neuromuscular monitoring.

The lower limit for ceebral autoregulation may be higher in hypertensive elderly patients, and this is particularly important in surgery with vascular tumors when we tend to hypotension to reduce acute blood loss. It is necessary that blood pressure and heart rate do not exceed more than 20% deviation from normal preoperative values. The elderly are more susceptible to hypo-

thermia, maintaining the body temperature is of great importance, facilitating early recovery of the patient, preventing postoperative trembling and reducing the consumption of oxygen.

Blood loss

The possibility of blood loss during neurosurgical surgery is significant, and elderly people are difficult to manage to increase the minute volume. These patients are often burdened with cardiovascular disease and blood loss can often be increased due to the inappropriate position of the body during neurosurgical operations, especially spinal surgery. Induced hyponension in order to reduce blood loss is not recommended in the elderly because it is more likely to develop brain ischemia.

Administration of infusion fluids

The goal of infusion fluid administration is to prevent hypoosmolarity, hypovolemia, hypervolemia, amd hyperglycaemia. Administration of fluids should be performed with iso-osmolar fluid, primarily crystalloids, and hypotonic solutions should be avoided, which may create conditions for the development of brain edema. In order to reduce the volume of the brain and reduce intracranial pressure, osmotic diuretics (manitol 0.5-1.5 g/l) and diuretics (furosemide 0.01–0.015 mg/kg) are used.

Position of patients

Neurosurgical operationes can be performed in a different positions, on the back, stomach, in the lateral, sitting or half-sitting position. Regardles of the position of the body, normal circulatory volume should be provided, avoid abdominal compression, avoid increased pressure in the airways, maintain the head in a neutral position

Conclusion

The geriatric population is constantly growing and an increasing number of elderly people show different neurosurgical pathologies that significantly affect the quality of their lives. Proper treatment of these patients includes several factors that are crucial for their treatment.

- Careful preoperative preparation and consideration of all comorbidity
- Planing of surgical treatment and adequate anesthesia
- Careful maintenance of intraoperative cardiovascular stability, respiratory function, intravascular volume and electrolyte balance.
- Postoperative treatment in an intensive care unit.

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THE MANAGEMENT OF SPINAL INJURY IN PEDIATRIC PATIENTS

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Abstract

Spinal cord injury (SCI) in the childhood is devastating and life-treating injury which is fortunately relatively rare in this age group, but takes meaningful psychological and physiological consequences. Pediatric patients with spinal trauma have very different characteristics from their adult counterparts. Traumatic SCI should be highly suspected in the presence of abnormal neck or neurological examination, a high-risk mechanism of injury or distracting injury even in the absence of radiological abnormality. The management depends upon the age, severity, level of injury and degree of neurological damage.

Neurological recovery in pediatric SCI seems to be better and faster than in adults. Life expectancy in children after SCI is significantly reduced due to complications.

Introduction

Spinal injuries in children are rare and account for a low proportion of all childhood injuries. In pediatric patients spinal trauma is quite different from those in adults due to extensive differences with regards to anthropometrics, biomechanics, injury patterns, clinical presentation, imaging analysis and management principles [1]. Timely identification and appropriate treatment in order to prevent further neurologic damage and deformity are crucial for the potential recovery in pediatric patients with spinal cord injury (SCI) [2]. More than half of children and adolescents with spinal trauma have associated injuries, most commonly involving the appendicular skeleton, head, neck and thorax. Pediatric SCI presents unique challenges due to ongoing physical and psychosocial development.

The medical, psychosocial and societal costs of severe pediatric SCI can be vastly disproportionate to small percentage of SCI in the childhood.

Epidemiology and etiology

Among pediatric trauma victims the incidence rate of SCI ranges from 1% to 2%.The most common associated injury to spinal trauma is head injury, which contributes to the high mortality rate [3]. Spinal injuries as a common constituent of polytrauma are relatively rare in polytraumatized pediatric patients [4]. Spine fractures accounting for only 5% of all pediatric fractures. Up to60%–80% of pediatric SCI occur in the cervical spine [3,5]. The upper cervical area was twice as frequently injured in the younger child while thoracolumbar level injuries are more common in the older children. Lower cervical spine injuries are equal to both groups. Young children are more prone to spine injuries due to anatomic and biomechanical differences in the growing spine including a more horizontal facet orientation, greater elasticity of the soft tissues, unformed muscles and relatively greater head size compared to the body [6]. Children below 8 years have the fulcrum of movement to the upper cervical spine with the maximum movement at C2/3, with growing age, at about 5–6 years, it shifts to C3/4 and in adolescents it shifts to C5/6 as in adults [1]. This is explanation for the findings that the majority of SCI occur between C0 and C2 in young children whereas older children, like adults have their injuries more commonly in the subaxial cervical spine [1]. The thoracolumbar injuries in children often presents with multiple levels of fractures of the endplate. The reported incidence of multilevel spine injury ranges from 6% to 50% in pediatric patients [7]. By the time a child reaches 11 to 12 years of age, injuries to the cervical and thoracolumbar spine resemble those seen in the adult population [7].

The pattern of SCI in children is related to age and to the mechanism of injury. Traffic-related incidents are a leading cause of injury across all age groups, while older children sustain spinal trauma in sporting activities [1]. In neonates, the common causes of cervical spine injury are obstetrical complications. Spinal trauma occurs in 1 of 60,000 births and it is followed with high mortality rate [1]. Child abuse should always be taken into account in infants and young children injured under unexplained circumstances. Cervical seat belt syndrome is recognized as a separate entity, where small children are placed in an adult three-point seat belt and sustain a cervical spine injury due to hyperflexion of the neck [3].

Diagnostic assessment

SCI should always be suspected if a child is with head injury, unconsciousness, torticollis and neck pain/stiffness and neurological damage [1]. Search should be made for associated injuries to the chest, abdomen and pelvis [1]. Unique pediatric injuries include fractures through the synchondrosis, apophyseal injuries and SCI without radiographic abnormality (SCIWORA) [3]. In pediatric population SCI are often incomplete and improvement may occur very late, whereas complete lesions usually do not recover [1].

Standard trauma series X-rays include cervical spine AP, lateral, and open-mouth views and thoracolumbar spine AP, lateral [1]. The NEXUS (National Emergency X-Ra-

diography Utilization Study) allows avoid X-ray imaging in evaluation of cervical spine if all of defined low-risk five criteria are absent. Low-risk criteria are: tenderness, neurodeficit, loss of alertness, intoxication and distracting painful injury [1]. It has to be remembered that most of pediatric spinal injuries are ligamentous in nature without osseous component [1]. Computerized tomography (CT) shows a better bony architecture and magnetic resonance imaging (MRI) shows a better soft tissue anatomy. If a child has persistent neurological symptoms MRI is helpful to reveal ligamentous or disk injury and to show the neural elements in great details and it is invaluable tool for evaluating patients with SCIWORA [1].

Initial treatment and complications

Initial assessment should follow rules of pediatric advanced life support and advanced trauma life support [8]. Any child in whom a spinal trauma is suspected should be regularly immobilized during transport and initial evaluation [3].

Most pediatric spinal injuries can be treated conservatively [1]. Surgery is usually indicated for grossly unstable injuries, non-reducible dislocations,progressive deformities and for decompression of the neural tissue [1]. Available literature doesn't give any evidence to support the use of neuroprotective approaches that include hypothermia and steroids [9]. The use of methylprednisolone was considered most arguable because there are very different opinions about using it in initial treatment of SCI. Disagreements about the optimal type and timing of prophylaxis of deep vein thrombosis also still exists, even though the existing guidelines on anticoagulation prophylaxis are rather extensive.

Pulmonary complications may be life-threatening in the acute phase of injury [5]. Deep venous thrombosis, autonomic dysreflexia, hypercalcemia, heterotopic ossification, spasticity, neurogenic bowel and bladder, scoliosis, syringomyelia, and neuropathic pain may be secondary complications to spinal trauma [5]. Almost all children with SCI before their growth spurt develop spinal deformation, the younger the patient is, the bigger is the likelihood of developing paralytic or neuromuscular scoliosis [1]. Post-traumatic syringomyelia is quite common complication in SCI patients [1].

Conclusion

Appropriate management of spinal trauma in children requires an understanding the immature spine has distinct anatomic and biomechanical characteristics compared to adults which result in different injury patterns. A high index of suspicion, systematic evaluation and treatment of pediatric spine injuries can limit morbidity and lead to an improved outcome.

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ADVERSE EVENTS IN PEDIATRIC ANESTHESIA. LESSON LEARNED FROM CLINICAL TRIALS

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The Anaesthesia PRactice In Children Observational Trial (APRICOT) study was a prospective, observational, multicenter, cohort study of children undergoing elective or urgent anesthesia procedures in 33 European countries.[1] The study identified the incidence, management, and outcome of perioperative severe critical events that required immediate intervention to prevent the occurrence of disability or death. This study revealed a higher incidence of respiratory severe critical events than previously reported in the literature, and – more importantly – a large variability in the practice of pediatric anesthesia at the 261 participating centers and 33 countries. These results warrant a thorough analysis before drawing any conclusion.

The final APRICOT exported dataset included 30,874 participants and 31,127 anesthetic procedures, with 188 children having more than one anesthetic procedure during the 2-week inclusion period. 1478 children (4·8%) had severe critical events. The total number of reported severe critical events occurring during or immediately after anesthesia was 1,637 (5·3% of the 31,127 procedures), with 1,335 children having one severe critical event, 127 having two, 14 children having three, and two having four. The estimate incidence of perioperative severe critical events was 5.2% (95% CI 5.0-5.5).

The publication of APRICOT was accompanied by a commentary[2] that questioned whether the results are representative, as 27% countries contributed 69% of the cases. There is no doubt that this representation may introduce some bias in the interpretation of the results. Of course, there are serious challenges whenever attempting to generalize findings from one Institution or country to another. However, the APRICOT Study already addressed some relevant questions about the anesthesia practice in children.[3,4]

First of all, who should perform pediatric anesthesia? To answer this question, it is important to define the prerequisites for pediatric anesthesia training and education. The APRICOT results, supported with other evidence from the literature, declare with confidence that a specialist pediatric anesthesiologist must manage anesthesia procedures of children less than 3 years of age with an ASA-PS at least III, as well as of children with a medical history of prematurity, congenital disease, airway hypersensitivity (a composite risk factor with recent upper tract infection less than 2 weeks, wheezing in the last 12 months, asthma diagnosis, and passive smoking), snoring, and a medical condition presenting with fever or requiring medication. Independent of the presence of these risk factors, a specialist pediatric anesthesiologist should manage anesthesia procedures of children less than 3 years of age and must take in charge all healthy children less than 2 years of age.

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PHARMACOGENOMICS IN PEDIATRIC ANESTHESIA: ANOTHER STEP TOWARDS PERSONALIZED MEDICINE

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Introduction

Predicting a patient's response to a particular drug has long been a goal of clinicians. Rapid advances in molecular biology have enabled researchers to identify associations between an individual's genetic profile and drug response. Genotyping methods require small amounts of blood or tissue, and it is not affected by underlying disease or by drugs taken by the patient, and need to be done only once in a lifetime. Statements from professional organizations including the American Academy of Pediatrics and the American College of Medical Geneticists state that the use of established pharmacogenetic tests to improve the use of drugs in minors is ethically appropriate [1,2]. However, with the development and increased use of multiplex platforms for pharmacogenetic tests and the advent of clinical whole-exome sequencing, the likelihood of identifying pharmacogenetic variants unrelated to any current or planned therapies increases. Guidance from professional societies does not directly address this scenario, and a consensus on how to balance the risks and benefits of disclosing these results is yet to be determined [3].

Pharmacogenetics and pharmacogenomics, same or different?

The history of pharmacogenetics stretches as far back as 510 B.C. when Pythagoras noted that ingestion of fava beans resulted in a potentially fatal reaction in some, but not all individuals [4].

Pharmacogenetics has been defined as the study of variability in drug response due to heredity. In the last two decades, with the fashion for adding the suffix `... omics' to areas of research, the term `pharmacogenomics' has been introduced. While the former term is largely used in relation to genes determining drug metabolism, the latter is a broader based term that encompasses all genes in the genome that may determine drug response. In other words, pharmacogenetics is the study of the molecular mechanisms that underlie individual differences in drug metabolism, efficacy, and side effects. Pharmacogenetics refers to the study of inherited differences (variation) in drug metabolism and response. In contrast, pharmacogenomics refers to the study of the many different genes that determine drug behavior. The distinction however, is arbitrary and according to many both terms can be used interchangeably. On the other hand, according to Behrooz[5], they are distinct entities. Much of the research in field of pharmacogenetics has been evaluating the association of single nucleotide polymorphisms with how individuals metabolise drugs. Pharmacogenomics is a more recent, broader term which may be regarded as the application of pharmacogenetics to the whole genome and across populations, encompassing proposed outcomes such as generating drug-response profiles unique to each individual based on their genetic make-up, examining the effect of drugs on gene expression, and the eventual utilization of genomic principles in the development and trialing of new drugs.

Important facts about polymorphism

Anesthetists and other clinicians have concentrated on genetic variability that alters drug metabolizing enzymes to explain variation in responses to drug therapy. The first documented example of inherited variations in anaesthetic drug effects was plasma cholinesterase which will result in prolonged muscle relaxation after succinylcholine [6]. However, it is now apparent that genetic variability can affect many other important proteins such as transporter proteins and receptors. Rapid advances in molecular biology and the Human Genome Project have led to the identification of millions of novel polymorphisms in recent years. Further, our understanding of the drug transporters, drug metabolizing enzymes, and drug receptors and other elements involved in drug pharmacokinetics and pharmacodynamics has also greatly improved, enabling identification of novel candidate genes. An increasing number of studies have thus focused on disease expression or the occurrence of adverse clinical outcomes in individuals expressing a specific genotype.

A gene is a hereditary coding unit composed of a specific DNA sequence occupying a specific position or locus within a chromosome (i.e., a long DNA molecule and its associated proteins). Humans have 23 pairs of chromosomes. All genes have a common structure that includes a 5' untranslated region, exons, introns, and a 3' untranslated region. An allele is any of two or more alternative forms of a gene occupying the same chromosomal locus. The most common type of human genetic or allelic variation is the single-nucleotide polymorphism (SNP), a "point mutation" or position at which two alternative nucleotides occur. To date, more than 13 million SNPs have

been identified. Allelic variation may also occur secondary to other types of mutations, including the insertion, deletion, translocation, or inversion of DNA segments. The words mutation and polymorphism can be used interchangeably, but in general, mutation refers to a variation that occurs in less than 1% of the population, and polymorphism refers to a variation that occurs in more than 1% of the population[7]. An individual who expresses an abnormal, dysfunctional copy of a drug-metabolizing enzyme on only one chromosome (heterozygote) may have a clinically insignificant reduction in drug clearance. However, if the same individual were to express abnormal copies of the enzyme on both chromosomes (homozygote), then a clinically significant reduction in drug metabolism is much more likely to occur because of production of a mutated enzyme with little or no activity. Therefore, the effects of a mutation may be additive. Some mutations act in a dominant fashion, so that expression of a single abnormal gene copy is sufficient to result in disease. In contrast, other mutations are recessive in that abnormal gene copies on both chromosomes must be expressed for disease to occur. Gene polymorphisms are labeled using three different nomenclature systems. The first system uses a number to signify the gene locus where a single nucleotide substitution occurs. The letter before the number signifies the nucleotide most commonly found at the gene locus (i.e., the "wild-type" or major allele), whereas the letter after the number represents the nucleotide found in the mutant or minor allele. Therefore, the A118G SNP of the μ-opioid receptor gene codes for the replacement of the nucleotide adenine (A) at base pair 118 with guanine (G). Alternatively, this polymorphism may be written as 118 A/G or 118 A>G.

Drug metabolism is divided into phase I and phase II reactions. Phase I reactions, including oxidation, reduction, and hydrolysis, introduce a polar group into the molecule, whereas phase II reactions conjugate an endogenous hydrophilic substance with the drug, resulting in more water-soluble compounds. Oxidation plays very important role in metabolism for many drugs which is catalysed by the oxidase system and it comprises of cytochrome P450 (CYP) enzymes.

The expression of CYP enzymes is influenced by age, gender, race, disease state, genetics and epigenetic factors. Studies of the maturational patterns of known drug-metabolizing enzymes must be completed across the developmental spectrum, with sufficient sampling across ages, gender, disease states and ethnicities. These studies may be facilitated by new technologies including RNAseq and metabolomics, which enable characterization of a single sample across a spectrum of transcripts and products. Sufficient diversity of sample collection may be facilitated by collaborations across institutions and by leveraging the power of biobank structures. This approach will determine typical trajectories, define at what age children mature to adult patterns and also refine the extent of interindividual variability. Resulting data will facilitate the interpretation and application of adult-derived data and determine the generalizability of pediatric data within children of various ages and clinical presentations.

Many enzyme families directly conjugate drugs or their oxidative metabolites (Phase II reactions). There are 15 human uridine diphosphate glucuronosyltransferases (UGTs), broadly classified into the UGT1 (phenol/bilirubin) and UGT2 (steroid/bile) families. Some drugs are actively transported by transporter proteins, of which membrane transporters may play a key role but most drugs or drug metabolites enter the cells by passive diffusion. These transmembrane transporters are members of the large protein family known as ABC (adenosine triphosphate binding cassette) proteins they do not catalyse biotransformation but affect drug bioavailability and can act in conjunction with intracellular drug metabolizing enzymes. Receptor is the most important target for genetic studies when examining the drug response. Genetic variability influences interactions with receptors and this forms the basis for poor or efficient receptor interactions. The polymorphisms in genes encoding receptors relevant to drug treatment of different diseases cause widespread variation in sensitivity to many drugs. A new class of human GABAA receptor subunit that confers insensitivity to the potentiating effects of i.v. anaesthetic agents on gabaminergic transmission has been identified. Wilke and colleagues identified the gene, symbolized GABRE, coding for class epsilon of the GABAA receptor (gene map locus Xq28) [8].

The Preoperative Period

Midazolam (MDZ) is a short-acting benzodiazepine that reversibly interacts with inhibitory gamma-amino butyric acid (GABA) receptors in the central nervous system. It has sedative, anxiolytic, amnesic and hypnotic properties and is metabolized primarily by CYP3A4/5 in the liver to its active metabolite, 1-hydroxy-midazolam (1-OH-MDZ) [9].

The Intraoperative Period

Induction agents include inhalational and intravenous anesthetics. Volatile anesthetics are excreted unchanged in the lungs (less than 5% are metabolized via CYP2E1), but intravenous anesthetics undergo extensive metabolism by hepatic CYP450 enzymes including CYP2B6, CYP2C9, CYP3A4, and UGT1A9 prior to renal excretion [9].

Inhalational anesthetics

Kayamak et al. [10] reported that a genetic polymorphism in Glutathione S-transferase pi (GSTP1) was associated with increased serum α-gluthanyl transferase (GST) levels, a marker of liver damage resulting from sevoflurane administration. Although this suggests GSTP1 influences the pharmacokinetics and/or pharmacodynamics of sevoflurane, follow-up studies supporting that GSTP1 testing may have clinical utility for guiding sevoflurane dose selection have been lacking. Polymorphisms in the melanocortin 1 receptor (MC1R) gene, however, have repeatedly demonstrated associations with increased desflurane dose requirements in more than one study [10].

Intravenous anesthetics

The main targets for propofol's actions are the genes of gamma-aminobutyric acid (GABA) systems; nACR; dopaminergic, serotoninergic, or noradrenergic pathways or associated voltage-dependent ion channels; or enzymes associated with metabolism and mechanisms. Cytochrome P450 family (CYP450), ATP-binding cassette (ABCB1), serine/threonine-protein kinase 3 (TAOK3), family with sequence similarity 53 member B (FAM53B), and the cannabinoid receptor (CNR1) are postulated to be involved in propofol pharmacokinetics; opioid receptors (OPRM1 and OPRD1), β-adrenoceptor (ADRB1), Catechol-O-methyltransferase (COMT), and ligand-gated ion channel (P2RX7) are postulated to be directly or indirectly involved in the pharmacodynamic response to propofol; nitric oxide synthase (NOS3), GABA type A (GABAA) receptor, NMDA receptors (GR1N3A and GR1N2B), Galanin (GAL), fatty acid amide hydrolase (FAAH), 5-hydroxytryptamine receptor (5HT2A), cholinergic receptors (CHRM2 and CHRNA5), dopamine transporters (DAT and DRD2), casein kinase (CSNK1E), calcium channels, potassium channels (KCNS1 and GIRK) and sodium channels (SCN9A) are also likely involved in the action of propofol [11]. Iohomet. al.[12] determined that polymorphisms in the receptor gene GABRE (GABRE -mRNA358G, 20118C and 20326T) were not associated with systemic clearance ($p = 0.82$, 0.92 and 0.60, respectively) or on time to eye opening ($p = 0.70$, 0.82 and 0.93, respectively). Similarly, CYP2B6 did not show any significant haplotypic association with apparent systemic clearance ($p = 0.48$) or time to eye opening ($p = 0.55$). Khan et al. [13] reported a significant association between the UGT1A9– 1887T/G variant and propofol induction dose: the -1887T/G heterozygote patients required higher induction dose ($p = 0.03$, without correction for multiple testing) than other patients. Mikstacki et al. [14] concluded, from the results of their study conducted in the Polish patients undergoing general anaesthesia, that polymorphisms c.98T>C in the UGT1A9 and c.1075A>C in the CYP2C9 genes did not affect the pharmacokinetic profile of propofol. The mean propofol retention time (MRT) correlated with the patient's body mass index (BMI) ($p < 0.05$). From all the analysed changes, only polymorphism c.516G>T in the CYP2B6 gene and BMI affect the metabolism rate of propofol and may play an important role in the optimisation of propofol anaesthesia.

Ketamine is metabolised to several phase 1 metabolites, including alkylhydroxy-ketamine, nor-ketamine and dihydro-norketamine. CYP enzymes involved in this process are 3A4 (>60% metabolism), 2C9 and 2B6.Norketamine subsequently undergoes phase I liver processing with the aid of 2B6 and 2A6[15].

Neuromuscular blockade

Mei et al.[16] studied whether genetic polymorphisms in certain transporters and in nicotinic acetylcholine receptors had a significant effect on the clinical response to the non-depolarizing muscle relaxant rocuronium in a cohort of 200 Chinese patients. The transporters, the organic anion transporting polypeptides (e.g., SLCO1B1) and the multiple drug resistance I transporter (e.g., ABCB1), are the prominent transporter types in the liver. The SLCO1B1 transporter actively moves drugs into hepatocytes, an important determinant of drug hepatic clearance as the first step in the detoxification pathway), and the ABCBI transporter moves drugs out (exports) of hepatocytes. Mei et al. reported that variants in ABCB1, SLCO1B1, and CHRNA1 did not affect the time of onset of rocuronium[16]. Clinical duration and recovery time of rocuronium were prolonged in patients with the ABCB1 rs1128503TT and the SLCO1B1 rs2306283 AG and GG genotypes.

Narcotic analgesics

Codeine, a well-characterized and frequently used prodrug, requires metabolism by CYP2D6 to generate its active metabolite, morphine. CYP2D6 is a highly polymorphic gene with variations in gene sequence, copy number and pseudogene arrangement. Given typical doses, individuals who are poor metabolizers are unlikely to achieve adequate analgesia, while ultrarapid metabolizers who have multiple copies of the gene encoding active enzyme can accumulate high concentrations of morphine and experience symptoms of overdose. Mothers who have active CYP2D6 secrete morphine in their breastmilk during codeine therapy. In order to protect newborn and infant patients from dangerous and sometimes lethal doses of morphine transmitted through breastmilk, detection of ultrarapid metabolizer status with the mother's genotype, rather than the infant's, is required [3].

Fentanyl, a potent narcotic commonly used during the perioperative period, is metabolized by CYP3A4/5. Patient response to fentanyl is variable, and dose selection is largely empirical. Mieda et al.[17] reported their genome-wide association study in patients undergoing laparoscopic-assisted colectomy aimed at identification of genetic factors associated with fentanyl sensitivity (patient response). A SNP, rs2076222, in the LAMB3 region was strongly associated with post-operative opioid requirements ($p<0.05$). The C allele (rs2076222) was strongly associated with lower sensitivity and/or higher pain sensitivity ($p<0.05$).

Zhang et al.[18] examined whether CYP3A5*3 was associated with postoperative response to fentanyl. They had previously reported that the CYP3A4*1G SNP was associated with postoperative analgesic response in Chinese women undergoing gynecological surgery. They reported a trend that 24-hour postoperative fentanyl consumption was lower in CYP3A5*1/*3 and CYP3A5*3/*3 compared with CYP3A5*1/*1. However, combining CYP3A5 and CYP3A4 genotypes allowed for detection of a significant association between reduced 24-hourpost post-operative fentanyl consumption and CYP3A5*3 carrier status (both heterozygous and homozygous *3 carriers). They also concluded that an interaction between CYP3A5*3 and CYP3A4*1G polymorphisms significantly reduces fentanyl consumption over the 24-hour postoperative period.

Local anesthetics

The main CYP isoforms involved in the oxidation of LAs are CYP3A4 for lidocaine and bupivacaine and CYP1A2 in case of ropivacaine[15].

The postoperative period

The primary target for acute pain control in the perioperative period is the μ opioid receptor in the central nervous system (CNS). Other targets include Na-channel blockade of neurotransmission with local anesthetics (spinal and epidural blockade; peripheral nerve blockade), inhibition of prostaglandin synthesis or prostaglandin complex formation (ibuprofen; ketorolac), κ-opioid receptor blockade (butorphanol), and inhibition of serotonin and norepinephrine reuptake (tramadol). Some agents (acetaminophen) have an unknown analgesic mechanism of action [9].

Morphine sulfate is a pure μ-opioid agonist with primary actions in the brainstem, particularly the medulla, where it promotes analgesia and depression of respiratory centers. The OPRM1 gene codes for the encoding for the μ-opioid receptor. The most frequent and best described SNP in OPRM1 is OPRM1 A118G. Morphine is a substrate of the P-glycoprotein transporter ABCB1, which is an ATP-dependent efflux transporter present in the brain, as well as in the liver, kidney and gastrointestinal tract. ABCB1 is coded by the highly polymorphic ABCB1 gene, which has 38 identified SNPs. P-glycoproteins in brain capillary endothelial cells act as outward transporters for morphine across the blood–brain barrier, reducing cerebrospinal fluid (CSF) morphine concentrations. A C3435T allelic variant of ABCB1, rs1045642, reduces P-glycoprotein transporter function and results in increased CSF morphine concentrations. This variant has been associated also with significant differences in interindividual pain relief achieved by morphine. With drug addiction and chronic opioid use there may also be changes in the structure of the μ-opioid receptor (OPRM1) due to differential expression of mRNA in polymorphic gene variants [9].

Many genetic association studies have examined the impact of SNPs in various target genes related to pain sensitivity and/or analgesic dosing requirements. However, original findings have not always been replicated in other cohorts. Deficiencies in study designs have included small sample size, inappropriate statistical methods, and inadequate attention to the possibility that between-study differences in environmental factors may alter pain phenotypes through epigenetic mechanisms.

Tramadol is a prodrug and metabolized by hepatic cytochrome P450 2D6 (CYP2D6). Its M-1 metabolite, (+) O-desmethyltramadol is an analgesic that has 200-fold more affinity to μ-opioid receptors than tramadol and is largely responsible for tramadol's opioid mediated analgesia. CYP2D6 is deficient in about 7-10% of Caucasians (CYP2D6 PMs).

Non-steroidal anti-inflammatory drugs (NSAIDS) are non-opioid analgesic adjuncts often used to treat acute post-operative pain. Their clinical utility is often limited by interindividual variability of cardiovascular, gastrointestinal and renal side effects. Hepatic CYP2C9 polymorphisms may play a significant role in NSAID efficacy and toxicity. Prostaglandin-endoperoxide synthase 1 and 2 (PTGS1 and PTGS2) encode cyclooxygenase 1 and 2 (COX-1 and COX-2), and genetic variation in either can cause altered pharmacodynamic responses to NSAIDs.

Under normal conditions, paracetamol is extensively conjugated with glucuronic acid and sulphate as part of phase 2 metabolism in order to make it water soluble, preceding its excretion via the kidneys. A total of 5% of the remaining drug undergoes phase 1 oxidation in the liver via the CYP system. Cytochrome P450 2E1 and 3A4 convert paracetamol to a toxic intermediary metabolite, N-acetyl-p-benzoquinoneimine (NAPQI), which is instantly cleared by conjugation with glutathione to form cysteine and other conjugates. Glucuronidation process was first noted to be impaired in sufferers from the inherited bilirubin disglucuronidation condition called Gilbert's syndrome, increasing the risk of paracetamol toxicity in affected individuals[15].

Antiemetics

Post-operative nausea and vomiting (PONV) is the most commonly reported side effect in the perioperative patient. Ondansetron, a selective 5-HT3 receptor antagonist, is used for the prevention of chemotherapy-induced nausea and vomiting or nausea/vomiting secondary to opioid use. Some patients, however, do not respond to ondansetron. Candiotti et al.[19] reported on their study of genetic polymorphisms in hepatic cytochrome CYP2D6 and failure to respond to ondansetron. PONV appears to be multifactorial and include several genomic pathways. Other genes associated with PONV include OPRM1, ABCB1, DRD2 and CHRM3.

Conclusion

A future direction for pharmacogenomic testing in anesthesiology and in the perioperative patient would provide knowledge of genotypes that significantly impact drug efficacy and drug adverse events. Ideally, genotyping would be performed during the pre-operative workup allowing the anesthesiologist to individualize drug and optimal dosing choices throughout the perioperative period. Moving pediatric pharmacogenetics toward clinical implementation will require collaboration between many providers, researchers and institutions.

Limitations

Identification of a positive association between a specific genotype and clinical outcome does not necessarily imply causality. The identified genotype may actually be clinically silent, but linked to one or more other genotypes that individually or collectively form a disease haplotype. Along these lines, several investigators have advocated for building a "haplotype map" of the human genome that will make it easier, faster, and perhaps cheaper to find disease-causing or disease-predisposing genes. Instead of searching through a giant haystack of millions of SNPs, scientists would be searching through bundles of 10,000 to 50,000 bases each. Haplotype mapping may also greatly increase the sensitivity and specificity of predicting how genotypic variation will affect specific clinical outcomes [7].

An additional barrier to clinical implementation of pharmacogenetics for the pediatric patient is the unclear minimum threshold of evidence required prior to introducing pharmacogenetic testing into clinical prac-

tice. In an ideal world, generation of data from modeling and observational studies would be followed by prospective RCTs to determine whether genotype-guided therapy improved outcomes [3]. Broad clinical implementation would only follow in pediatric patients if evidence from these well designed and executed RCTs proved efficacy and demonstrated a favorable cost–benefit ratio. In personalized medicine, and specifically in personalized pediatrics, the gold-standard RCT may be unfeasible for several reasons including sample size limitations, lack of measureable meaningful outcomes (e.g., mortality or significant adverse drug reaction), cost and perceived lack of equipoise based on adult studies and limited pediatric data.

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MECHANICAL VENTILATION IN CHILDREN

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Mechanical ventilation refers to the use of life-support technology to perform the work of breathing for patients who are unable to breathe on their own.

The overall aim of mechanical ventilation is to relieve the distress of dyspnea, reduce the work of breathing, improve oxygenation, and improve CO_2 clearance in order to improve gas exchange.

The art of mechanical ventilation witnessed a revolution during the last three decades for improving the ways to protect the lung from injury as a result of positive pressure. The care for ventilated pediatric patients requires an extensive understanding of respiratory mechanics and pathophysiology of cardiopulmonary diseases. Many of the fundamental principles of respiratory physiology and gas exchange are similar to those of adults, but there are many differences in the anatomy, physiology and pathology with these two populations.

As the adage says, 'children are not small adults', the management of ventilated pediatric patients requires an appreciation of the susceptibility of their lung tissue to developing an injury, congenital anomalies, disease processes specific to pediatric population, and the potential equipment-related difficulties associated with small patients. Each pediatric patient who requires mechanical ventilation represents a unique clinical problem. Regarding the condition of the childs lungs there are different modes of setting a mechanical ventilator that can differ from the standard of adults to better co-operate with the childs respiratory functions. Children in general need frequent therapeutic actions from the health care staff as they are more liable to complications regarding their incomplete or immature systems.

Mechanical ventilation can be lifesaving, but more the 50% of complications in conditions that require intensive care are related to ventilatory support, particularly if it is prolonged. Mechanical ventilation with positive pressure is a technique that has been employed in pediatric intensive care units (PICUs) with increasing frequency. The percentage of mechanical ventilation varies from 30 to 64% in PICUs. Since its introduction into the modern PICUs, mechanical ventilation has undergone continuous evolution. There has been an explosion of new ventilator modes, many of which have been incorporated into routine clinical practice without evidence of their efficacy or their superiority over other modes of ventilation. Currently, pressure modes are generally used for children.

The indications for mechanical ventilation are respiratory failure (pneumonia, bronchiolitis, lung hemorrhage, muscle disease, laryngotracheobronchiolitis), cardiovascular failure together with hypotension (heart failure, myocarditis, spell attack), septic shock, central nervous system disease (meningitis, encephalitis, coma, bleeding, tumor), and safety airway, especially in critical situations like sepsis.

Airway and tracheal tube

While the majority of tracheal tubes placed in critically ill children are for the purposes of facilitating mechanical ventilation, decisions at the time of airway placement may have important implications. Features specific to pediatric patients (e.g. size, anatomy) leave them at particular risk for compromising the security of their airway.

Uncuffed tubes have traditionally been used in children due to historic anatomical surveys revealing the conical shape of the airway during the first several years of life. However, due to the common occurrence of ineffective ventilation and the egress of inhalatory anaesthetics in the presence of a large air leak, cuffed tubes in pediatrics have grown in popularity. Early investigations showed that tubes with high-pressure, low-volume cuffs had similar rates of post-extubation stridor when compared to uncuffed tubes. Despite this information, the choice of tube type in young children remains controversial, as long-term data on airway injury are lacking. Currently, the use of cuffed or uncuffed tubes is considered an acceptable standard of practice. If cuffed TTs are used, cuff pressure should be routinely monitored and kept below 20 cmH_2O. Uncuffed TTs should be sized to allow a leak of ~ 20cmH_2O.

Breathing and Oxygenation

The majority of intubations in the pediatric intensive care unit are performed to facilitate oxygenation, clearance of carbon dioxide (CO_2), decrease the work of breathing, or a combination of these clinical issues. Hypoxemia in ventilated patients is treated in several ways: increasing the fraction of inspired O_2 to increase the partial pressure of oxygen in the alveoli, optimizing alveolar patency via recruitment manoeuvres, and providing adequate PEEP to maintain functional residual capacity (FRC).

The main clinical target involved in regulating CO_2 clearance is alveolar ventilation (minute ventilation, less dead space ventilation). A patient's $PaCO_2$ is directly proportional to CO_2 production by the body, and inversely proportional to CO_2 clearance by alveolar ventilation. Permissive hypercapnia continues to be used regularly

in ventilated pediatric patients in the ICU. Typical strategies aim for a gradual increase in $PaCO_2$ to < 8–10 kPa and allow for a corresponding mild acidosis (e.g. pH 7.25–7.33). This permits patients to be ventilated with lower plateau pressures and tidal volumes in an effort to reduce ventilator-induced lung injury.

Modes of mechanical ventilation

Multiple mechanical ventilation modes are currently used in clinical practice to provide respiratory support for a wide spectrum of patients, ranging from no lung disease to acute lung injury (ALI) and ARDS. To date no data exist to determine the ventilatory mode that provides the greatest benefit with the least risk to an individual pediatric patient. Each new generation of conventional mechanical ventilators brings new ventilation modes and new features. However, despite a multitude of new modes, no study has shown that any mode is better than others in improving survival rates for ALI patients. It should be noted that in reality it might not be possible to demonstrate a significant change in mortality based only on changes in ventilator modes, because of the extremely low baseline mortality rate for intubated infants and children in pediatric ICUs.

Mandatory ventilation

In this mode of ventilaton, all breaths are triggered, limited and cycled by the ventilator.

Volume control - in this mode the machine gives a constant volume every breath (tidal volume), during a set inspiratory time with a set frequency and constant inspiratory flow. The ventilator controls all timing parameters of the breath.

Pressure control ventilation - in this mode the ventilator delivers positive pressure up to a predetermined pressure limit above PEEP during a selected inspiratory time and at a set frequency.

Pressure Regulated Volume Control (PRVC) - a control mode which delivers a set tidal volume with each breath at the lowest possible peak pressure. It delivers a breath with a decelerating flow pattern that is thought to be less harmful to the lung.

Inverse Ratio Ventilation - pressure control mode in which inspiration time is longer than the expiration time (I : E > 1). Mean airway pressure can be increased without increasing peak inspiratory pressure in order to improve oxygenation but limit the possibility of barotrauma. There is a high risk for air trapping. The patient should be deeply sedated and may also be paralyzed as well.

Assisted ventilation

This is essentially identical to the respective controlled modes of ventilation except that the patient's inspiratory efforts trigger the ventilator to deliver assisted breaths using the preselected limit and cycle variables. Assisted ventilation can be provided with either pressure or flow as the limit variable.

Intermittent mandatory ventilation – allows spontaneous breathing between positive pressure breaths with a preset inspiratory time and frequency. The positive pressure breaths may be either pressure or volume limited.

Airway pressure release ventilation (APRV) – provides a continuous gas flow circuit to vary the airway pressure between two different CPAP levels. Airway pressures are decreased or „released" intermittently from the preset CPAP to a lower or ambient pressure. Lung volume transiently decreases, allowing gas to exit the lungs passivelly, thereby augmenting alveolar ventilation.

Mandatory minute ventilation – this mode allows mandatory delivery of a predetermined minute volume that is distributed variably between spontaneous and mechanical breaths and depends on the patient's spontaneous ventilation.

Supported ventilation – is defined as a breath triggered by the patient, limited by the ventilator, and cycled by the patient. Ventilation is spontaneous and the patient initiates and terminates each breath and is only used in patients with adequate ventilatory drives (continuous positive airway pressure, pressure support ventilation, volume support ventilation).

High Frequency ventilation

Because of its potential to reduce volutrauma, there has been a surge of interest in high-frequency ventilation in the past few years. High-frequency ventilation may improve blood gases values because, in addition to the gas transport by convection, other mechanisms of gas exchange may become active at high frequencies. There has been extensive clinical use of various high-frequency ventilators in neonates. Small randomized trials suggest that bronchopulmonary dysplasia may be prevented with high-frequency jet ventilation, but results are inconclusive. The largest randomized trial of high-frequency ventilation revealed that early use of high-frequency oscillatory ventilation did not improve outcome. Although various randomized controlled trials show heterogeneous results, meta-analyses largely confirm the original findings. However, there are trends toward decreases in bronchopulmonary dysplasia/chronic lung disease, but increases in severe intraventricular hemorrhage and periventricular leukomalacia as well as small increases in air leaks with high-frequency oscillatory ventilation or high-frequency flow interrupters. High-frequency ventilation is a safe alternative for infants who fail CMV.

Neurally adjusted ventilator assist

It is novel technique in pediatric ventilation. The theory underpinning NAVA is that the most physiological means of determining the need for minute ventilation arises from the patients own respiratory centre. NAVA uses an oesophageal catheter to measure diaphragmatic electrical activity and uses this information to direct ventilation. It is suspected that coordinating the timing of ventilator breaths based on diaphragmatic electrical activity is superior to current techniques based on sensing changes in circuit gas flow, as there is less of a delay. Diaphragmatic electrical activity also permits some estimation of the magnitude of ventilator breath to deliver. The combination of these features is thought to result in improved patient–ventilator synchrony and may po-

tentially benefit those with neuromuscular conditions in particular.

Despite the promising theoretical advantages of NAVA, more experience and study is needed. Oesophageal catheters designed to monitor diaphragmatic activity are costly and their appropriate positioning can be difficult. In addition, it is unknown whether the intact respiratory centre can appropriately regulate ventilation during critical illness.

Weaning from invasive mechanical ventilation

In children, limited guidance exists regarding weaning and extubation. Two reasons are the short duration of MV and low extubation failure rates (2–20%). Various weaning concepts, including spontaneous breathing trials and closed-loop weaning, have failed to show superiority over clinical judgment. Yet, no single or combination of variables, including respiratory mechanics, gas exchange and patient ability to maintain work of breathing, reliably predicts weaning success.

Complication

Attaching a patient to a mechanical ventilator in intensive care unit is considered a life-saving procedure because of it's ability to assist life continuation by helping the patient to carry out his respiratory activity in oxygenation and CO_2 clearance. It is also highly risky for making these patients susceptible to various complications. Mechanical ventilation can result in important complications including pneumothorax, atelectasis, ventilator-associated pneumonia (VAP), barotrauma, volutrauma, obstruction of the tracheal tube during the intubation period, tracheal edema and tracheal stenosis after the extubation period. In this respect, a patient treated with mechanical ventilation must be followed by the pediatric intensive team and in a PICU.

Conclusion

Mechanical ventilation is the most important measure of respiratory support in intensive care units. Knowledge the specifics in childhood, the choice of an adequate mode of mechanical ventilation and optimizing patient-ventilator interaction are essential to minimizing adverse events. Besides the classic forms underlined the are newer forms od ventilators available which have made major contributions to improving the quality of mechanical ventilation in children.

The practice of pediatric MV is predominantly based on anecdotal experiences, institutional belief and, to a certain degree, extrapolation of adult-based data. This is clearly an unwanted situation for such a commonly practised intervention in the pediatric critical care environment. The most important issue affecting the field of pediatric mechanical ventilation is the need for multicenter, randomized, prospective studies.

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ANESTHESIOLOGICAL PROBLEMS IN PEDIATRIC LAPAROSCOPIC SURGERY

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Use of laparoscopic surgery in pediatric population has been rapidly increasing over the last 20 years, and it's become a standard of care for many of the operations as the thoracic, abdominal and urological surgical procedure. Pediatric laparoscopy offers many advantages over laparotomy, including decreased morbidity, rapid recovery [1] as well as decrease of cost of treatment because of shorter terms of in-hospital treatment, less need for post-operative analgesia [2]. However, laparoscopic surgery does not means minimally-invasive anesthesia: laparoscopic procedures usually do introduce different physiologic effects of the pneumoperitoneum, absorption of CO_2, and positioning required for surgery. Experience in adult laparoscopic surgery does not directly translate into safe surgery in younger patients. Pediatric procedures must be performed with a full understanding of the relevant anatomic and physiologic differences between the pediatric and adult populations.

Physiology and pneumoperitoneum

In a surgical considerations, insufflation pressures less than 15 mmHg minimize pathophysiological effects in adult patients. In infants and young children, pressure effect is dependent both on absolute intraperitoneal pressure and the length of time that the pressure is applied. Also, the physiological effects are increased with decreasing age and weight due to decreased muscle bulk, an increased peritoneal surface area to mass ratio, decreased peritoneal thickness, and decreased organ-specific reserve. The insufflation pressures of 6 to 12 mmHg is typically suffice to visualize intraperitoneal structures of infants and young children, and create operating space as far as the prepubertal abdominal wall is more pliable and the peritoneal cavity is smaller than in adults [3,4]. A primary target of preoperative evaluation in laparoscopic surgery is to evaluate of comorbidities that may impact the ability to tolerate surgery. Preoperative evaluation has to be focused on those medical conditions that may affect the response to physiologic changes associated with laparoscopy and surgical procedure, emphasizing even the particulars. Insufflation of abdomen may pose an important risk in patients sensitive to decrease of ventricular preload. Management of these patients requires preoperative consultation with a pediatric cardiologist and intraoperative care by an anesthesiologist experienced in such conditions.

Cardiovascular effects

Hemodynamic effects of laparoscopic procedure have reported an increase in mean arterial pressure (MAP), systemic vascular resistance (SVR) and central venous pressure (CVP) with a decrease in cardiac output (CO) and stroke volume (SV) and these effects are strictly related to the increase of intra-abdominal pressure (IAP), to the effects of positioning and to absorption of CO_2 [5,6]. Changing of hemodynamic parameters during the laparoscopic procedure depends not only on the IAP value, but also on age. The using higer level of IAP than 12 mmHg during laparoscopic herniotomies in younger children, the cardiac index (CI) could decreased significantly. The following decrease of IAP to 6 mm Hg brought the CI back to the initial level [7]. Also, pneumoperitoneum has both neurendocrine and mechanical effects on cardiovascular physiology. The increase in IAP may cause a catecholamine release and activation of the renin-angiotensin system, increasing this way MAP and SVR. Mechanical effects depend on the patient's preoperative volume status and IAP: compression of arterial and venous vasculature with pneumoperitoneum may increase SVR [8]. Position has variable effects on CO and blood pressure: the head up position reduce venous return to the heart and cardiac filling pressure; head down position, increases venous return. CO_2 has direct and indirect cardiovascular effects: it can directly increase SVR and the associated acidosis can decrease cardiac contractility, inducing sensitization to arrhythmias and causing systemic vasodilatation [9]. In infants and adults, these effects are generally well tolerated by healthy patients, vagal stimulation caused by insertion of the Veress needle or peritoneal stretch with gas insufflation, can result in bradyarrhythmias: it is important to consider that pediatric patients have a major risk of vagal reflexes and bradycardia during abdominal distension that may require emergent desufflation [10].

Respiratory effects

Pneumoperitoneum, positioning and absorption of CO2 could induce changes and effects on pulmonary function and gas exchange. Pneumoperitoneum causes cephalad displacement of the diaphragm, which reduces lung volumes and functional residual capacity (FRC), resulting in atelectasis, increased airway pressure for any given tidal volume and reduction in lymphatic drainage [11]. The trendelenburg position exacerbates these effects. The reduction in FRC and the atelectasis may lead to a ventilation/perfusion mismatch with intrapulmonary shunting and hypoxemia, caused by alveolar

collapse [12]. Application of carboxy peritoneum causes increased IAP readings within 8–12 mm Hg allow laparoscopic procedures to be performed without significant gas exchange disorders in children older than 1 year. Increase of IAP > 12 mm Hg caused significant decrease of dynamic compliance and increase of $etCO_2$. Respiratory mechanics readings correction in pressure controlled ventilation mode allows adequate tidal volume and minute ventilation to be reached at lower PIP and Pmean values in comparison with volume controlled ventilation [13]. High rapidity in absorption of CO_2, makes it necessary to increase ventilator rate: this is much truer in children, whose peritoneum is capable to absorb more gases than an adult one because of the shorter distance between capillaries and peritoneum, and the greater absorptive area in relation to body-weight. This can make it necessary to increase minute ventilation by over the 60% to restore end-tidal CO_2 to baseline levels [14].

The influence of laparoscopic procedure on other systems

Mechanical and neurendocrine effects of pneumoperitoneum may decrease splanchnic circulation, while hypercapnia can cause splanchnic vasodilatation: changes on splanchnic circulation seems to be minimal and with no clinical impact [15]. Cerebral blood flow and intracranial pressure could be increased [16] and the laparoscopic procedure in patients with reduced intracranial compliance has to be generally avoided. Also, renal blood flow could be reduced by the increasing of intraabdominal and intrathoracic pressure, hypercarbia and positioning [17]. Also, laparoscopic procedures may be cause of hypothermia in case of neonates and children. The degree of hypothermia depends on the duration of laparoscopic procedure. There is decrease in temperature of 0.01 degree Celsius of surgical time in minutes and warming of the CO_2 gas used for insufflations can solve this problem.

Anaesthesia for pediatric laparoscopic procedures

The main goal of pre-anaesthetic assessment is to identify ongoing acute or chronic problems that may affect the plan for anaesthesia. These would include previously undiagnosed conditions (congenital abnormalities and difficult airways), and disease-specific complications that precipitated the need for surgery (e.g. concurrent pneumonia due to reflux, atelectasis, renal failure, systemic sepsis) [18].

Recommendations for fasting in the pediatric population are the same used for adults, children should be permitted to intake breast milk not later than 4 hours prior to surgery, and infant formula 6 hours prior. The main monitoring implies monitors of blood pressure, electrocardiography, oxygen saturation, capnography, and temperature before laparoscopy. Also, other monitoring (e.g., continuous intra-arterial pressure, central venous pressure) is applied in patients where it is expected blood loss, and longer duration of surgery.

For most children anxiolysis is necessary and midazolam is the drug of choice. Atropine or glycopyrrolate may be included in premedication in order to prevent the reflex bradycardia induced by abdominal insufflations and to dry secretions blunting airway reactivity. Induction may be intravenous or inhalational. That depends on the ability of the child to tolerate placement of a IV catheter. In practice, the inhalational induction is defined for children in pre-scholar age, and an IV induction for older ones. Among these, propofol is the agent of choice as it provides rapid onset and short duration of action, reduces the bronchospastic response to intubation, and has antiemetic effects. For inhalational induction, sevoflurane is generally most potent inhalational agents have the advantage of decreasing airway responsiveness than desflurane (produce an increase in secretions, coughing, airway resistance, and laryngospasm) [19]. After induction, an orogastric tube should be placed to decompress the stomach and the gut allowing minimizing stomach injury and increasing intraabdominal visibility. In children, endotracheal intubation is often preferred rather than a supraglottic airway, because it provides optimal control of ventilation for elimination of CO_2 and protection against aspiration [20]. In children younger than 8 years old the using of an uncuffed endotracheal tube (ETT) makes it difficult to maintain minute ventilation during the laparoscopy, but the use of a cuffed ETT can allow the use of positive end expiratory pressure (PEEP) and high peak pressure along the airways during pneumoperitoneum [18]. Maintenance of general anaesthesia during laparoscopy may be based on inhalational or intravenous agents as opioids (e.g., fentanyl or remifentanil) if needed. Nitrous oxide is generally not used as it can increase bowel distension, postoperative nausea and vomiting (PONV) [21]. N2O diffuses into air containing closed spaces over time and can lead to bowel distention, and reduce visualization of the abdomen [22]. Neuromuscular blocking agents, administered during surgery, facilitate endotracheal intubation and improve surgical conditions [23]. Pediatric patients requires controlled ventilation, a lung protective and volume targeted ventilation. The strategy uses a target tidal volume in a range of 6–7 mL/kg, predicting use of PEEP to prevent atelectasis and, in case, recruitment maneuvers to revert it [11]. The goals of optimal ventilation strategy should achieve optimal arterial oxygen tension at least inspired oxygen concentration, acceptable arterial CO_2 tension, delivered tidal volumes at least inspiratory pressure. Perioperative fluid requirements depend upon multiple factors such as preoperative volume status, perioperative conditions, patient's age, anesthetic management and nature of the interventions (laparoscopic procedures are associated with less insensible fluid losses than open ones).

Postoperative care

Laparoscopy has been identified as a risk factor for PONV and routine prophylactic multimodal antiemetic therapy (dansetron- 0.1mg/kg body weight and dexamethasone- 0.15 mg/kg body weight), should be utilized in all patients undergoing laparoscopic surgery [24,25]. Postoperative pain after laparoscopic surgery is usually less than the corresponding open procedure, but the degree of pain depends on the specific surgery has been performed. Pain after laparoscopy can often be managed ef-

fectively with acetaminophen, nonsteroidal anti-inflammatory drugs, dexamethasone or opioids. Moreover, it could be useful infiltrate the incision with local anesthetic at the time of wound closure [26] or using caudal or epidural anesthesia or bilateral rectus sheath block [25].

Conclusion

Frequent and consistent communication between anaesthesiologist and surgeon is the one factor that ensures the best possible patient outcomes in respect of recognition and prevention of complications. There are two things that make it more challenging in laparoscopic anesthesia management of children, the CO_2 insufflation which causes pneumoperitoneum and patient position changes (Tredelenberg and Reverse Tredelenberg). Differences in physiological changes that occur mainly on the cardiovascular and respiratory system in which the characteristics of pediatrics two systems are different compared to adults. Anesthetic technique recommended in laparoscopic surgery are general anesthesia with endotracheal tube placement. Management of pain after laparoscopic surgery could be managed with nonsteroidal anti-inflammatory drugs or opioids.

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