ISSN 2545-4366
www.e-mja.finki.ukim.mk

MJA

Macedonian Journal of Anaesthesia

A Journal on Anaesthesiology, Resuscitation, Analgesia and Critical Care

Supplement Vol. 8 No 2, May 2024
from VII Macedonian Congress of Anesthesiology, Reanimation and Intensive Care Medicine - Ohrid 2024

Journal of the Macedonian Society of Anaesthesiologists
and Macedonian Society of Critical Care Medicine

Publisher:
Department of Anaes thesia and Reanimation Faculty of Medicine,
“Ss. Cyril and Methodius” University, Skopje, R.N.Macedonia

Apotel® 1000mg/6.7ml

I.V. Paracetamol

БЕЗБЕДНА АНАЛГЕЗИЈА

менаџирање на болка кога сте загрижени за безбедноста

I.V. paracetamol за прв пат во Европа е применет во 2001 година, а денес поради неговата докажана безбедност и ефикасност е прв од избор **аналгетик и антипиретик.**

Предоперативна и Интраоперативна Аналгезија:
Предоперативна анелгезија е дефинирана како третман кој што започнува пред оперативниот зафат се со цел да се превенира воспоставувањето на централна сензибилизација на болка.
i.v. paracetamol е безбеден, добро толериран лек со докажана ефикасност како **предоперативна и интраоперативна анелгезија** за умерена до средна болка при оперативни зафати.
Голем број на клинички студии ја докажуваат ефикасноста на **i.v. paracetamol** како **преодоперативна и интраоперативна анелгезија**.

КЛИНИЧКА СТУДИЈА:
Ефект од **предоперативен i.v. paracetamol** за постоперативни аналгетски потреби кај пациенти кои се подлежни на оперативни зафати. A Sreenivasulu , R Prabhavathi, 2015
Цел: Да се утврди ефикасноста на **предоперативната употреба на 1000mg i.v. paracetamol** кај постоперативните болки и анелгетски потреби кај пациенти подлежни на хируршки зафати.
Метод: 60 пациенти беа поделени во две рандомизирани групи од по 30 пациенти.
На I. Група им беше администрирано **ампула од 1000mg i.v. paracetamol разредена 0,9%NaCl** р-ор 30 минути пред индукција **(ГРУПА П)**,
На II. Група им беше администрирано **i.v. 0,9% NaCl р-ор 100мл** 30 минути пред индукција **(ГРУПА НС)**
Сите пациенти беа индуцирани со i.v. thiopentone 5mg/kg, i.v. fentanyl 2µg/kg, i.v. vecuronium 0.1mg/kg
Постоперативниот резултат на болка беше мерен со **Визуелна Аналогна Скала (ВАС) од "0-10"**. Исто така беше забележувана и **постоперативната употреба на tramadol** како спасувачки аналгетик. Инциденцата на **постоперативно гадење и повраќање (ПОГП)** и други компликации исто така беа забележувани во пост оперативниот период.
Резултатот на постоперативната болка беше забележуван во интервали 15 мин, 30 мин, 1 час, 2 часа, и 6 часа.

Резултат:

Табела 1: *Споредба на средниот резултат на болка (ВАС) помеѓу двете групи*

Интервали	I Група П	II Група НС	*P вредност*
15 мин	2.06 ± 0.63	2.61 ± 0.56	0.0006
30 мин	2.35 ± 1.17	3.84 ± 1.55	0.0001
1 час	2.42 ± 1.12	2.87 ± 0.99	0.0989
2 часа	2.13 ± 1.06	2.52 ± 0.89	0.1219
6 часа	2 ± 0.52	2.52 ± 0.89	0.0549

Табела 2: *Споредба за потребите од tramadol помеѓу двете групи*

Интервали	I Група П	II Група НС	*P вредност*
До 1 час	4 (12.90%)	15 (50%)	0.0002
1-2 часа	3 (9.68%)	2 (6.45%)	0.64
2-6 часа	1 (3.23%)	3 (9.68%)	0.301
Вкупно	**8 (25.81%)**	**20 (64.52%)**	**0.002**

Табела3: *Споредба на ПОПГ помеѓу двете групи*

ПОГП	
I Група П	II Група НС
0	4

Заклучок: Предоперативна администрација на **1000mg i.v. paracetamol** кај пациенти подлежни на оперативен зафат обезбедува **статистички задоволителна анелегизија**, и ја **намалува постоперативната употреба на tramadol**. Оттука **1000mg i.v. paracetamol** може безбедно да се администитрира како превенција при оперативни зафати.

i.v. Paracetamol + јак опоид	МНОГУ ЈАКА БОЛКА
i.v. Paracetamol + слаб опоид	ЈАКА БОЛКА
i.v. Paracetamol + NSAID i.v. Paracetamol + rescue medicine	УМЕРЕНА БОЛКА
i.v. Paracetamol + rescue medicine	СЛАБА БОЛКА

Мултимодално менаџирање на постоперативна болка
I.V. Paracetamol е атрактивна компонента за мултиодално менаџирање на болка.

- **Синергистичко делување**
- **Зголемување на аналгетски ефект**
- **Значително намалување на болка**
- **Редукција на дозата на опоидни лекови за - 40% во првите 24 часа**
- **Намалување на несаканите ефекти поврзани со монотерапија на NSAID и опоидни лекови**
- **Ублажување на акутна и хронична болка**

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WHEN EARLY RECOVERY REALLY MATTERS

Дистрибутер за Македонија

FARMA TREJD

Macedonian Journal of Anaesthesia

A Journal on Anaesthesiology, Resuscitation, Analgesia and Critical Care

Publisher:
Department of Anaesthesia and Reanimation
Faculty of Medicine
"Ss. Cyril and Methodius" University
Skopje, R.N.Macedonia

Proofreading:
Daniela Nacevska Stojcevska

Graphic adaptation:
Arbëria Design

Printing:
Arbëria Design

The articles presented in this Supplement have undergone proofreading.
But still they were not subject to peer review.
They are based on materials and discussions presented during the Congress.
While efforts have been made to ensure their accuracy and integrity, readers are advised that they have not been subjected to the rigorous scrutiny typically applied in peer-reviewed scientific literature

CONTENT

ANTIBIOTIC STEWARDSHIP IN THE ICU: WHY? WHAT TO DO? WHAT TO AVOID

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Abstract

Responsible, educated use of antibiotics is crucial in the ICU with its high incidence of infections, resistant bacteria and vulnerable patients. Antibiotic stewardship (ABS) strategies like mandatory guidelines, restriction and approval, mandatory education before using reserve antibiotics, pathogen and resistance surveillance etc. should be established to "preserve the miracle of antibiotics" (J.G. Bartlett, D.N. Gilbert, B. Spellberg, 2013), and reduce side effects and associated mortality. This article focusses on the available evidence for applying Antibiotic or Antimicrobial Stewardship principles in the ICU, i.e. optimizing pharmacokinetics, narrowing, shortening and deescalating therapies, and avoiding wrong or unnecessary therapies.

Material and Method

Literature research of PubMed/ MEDLINE, Cochrane Database and Google Scholar.

Key Words: *Antibiotic bundles, antibiotic prophylaxis, antibiotic resistance in the ICU, deescalation of antibiotic therapies, individualized dosing, pharmacokinetics of antibiotics, procalcitonine, short(er) antiinfective therapies, therapeutic drug monitoring (TDM).*

Presentation of the Problem and Introduction

Increasing antibiotic resistance is an important issue in the ICU. Multi- Drug- Resistant bacteria (MDR) with Extented Spectrum Betalactamases (ESBL) and Extended-Drug-Resistant Bacteria (XDR) with carbapenem-resistance due to different classes of carbapenemases (OXA48, metallo-betalactamases) are a growing problem in the ICU (1, 2). Pan-Drug-Resistant-Bacteria (PDR) with resistance against any available antibiotic therapy emerge and are a realistic clinical scenario (3). There`s a well-known correlation between antibiotic overuse and resistance (4-6).

Sir Alexander Fleming is quoted to have understood this problem as early as 1945 by saying "The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism.". Nowadays we all know the quote "the more you use it, the quicker you lose it". Problems on the ICU are just the tip of the iceberg in the light of antibiotic overuse in lifestock, water pollution in antibitic-producing countries like India and China and growing travel activities. Efforts to "preserve the miracle of antibiotics" are necessary in a generalized and universal approach (7). Nevertheless, patients on the ICU are the most vulnerable to resistent bacteria and in time critical settings like sepsis and septic shock, an effective empiric treatment may come too late. On the other hand,

overtreatment in the ICU may increase local resistance, according to the "listen to your hospital" principle in the Tarragona strategy (8). Hence, local guidelines should be implemented. Institutional pathogen spectrum and institutional susceptibilities must be monitored at least once a year and treatment guidelines adapted to changements of the latter (9, 10).

Do-s and Don`t-s

As banal as it sounds, it is important not to give antibiotics to every critically ill patient without a clear idea what to treat. If infection is suspected, we should have a clear idea of the focus, the patient`s risk factors and the pathogen spectrum to be expected. The suspicion of infection must be based on clinical examination, oriented imaging and microbiological samples. A practical algorithm, when and how to start with antibiotics or to withhold them can be found in (11). Fever alone is not a reason to give antibiotics. An overview about differential causes of fever is given in (12).

If we decide to give antibiotics to a newly admitted patient in the ICU, a "5 days bundle" should be implemented. Documentation of the clinical rationale for the choice of antibiotics and adherence to local guidelines is mandatory. After 48 hours, a review of the diagnosis, based on results of microbiological cultures and clinical developpment should be performed ("antimicrobial time out"). Between the days 3-5, daily review and deescalation to the narrowest possible therapy spectrum is strongly recommended (13).

Pharmacokintetics

The pharmacokinetics of antibiotics are among the most interesting problems in intensive care. Due to the fact that most antibiotics, especially the preferably used beta-lactams, are hydophilic, correct dosing in critically ill patients is very difficult. Extracorporal circulation, renal failure, cardiac failure, hepatic failure, altered albumine levels etc. may increase the volume distribution and decrease the clearence of a drug at the same time (14). So, it is very difficult to know if under- or overdosing occurs, and individualized dosing has been suggested. Underdosing is probably more common in the ICU (15, 16, 17). An overview about the complexity of this topic, together with practical advice on the adaptation of dose regimes according to different classes of antibiotics and different sites of infection, is given in (18).

Therapeutic drug monitoring is mandatory for aminoglykosides and vancomycine and has been suggested for beta-lactams like piperacillin-tazobactam and meropeneme, as well as for linezolide (17, 19, 20). Unfortunately, this is not widely and promptly available. Hence, it is not generally recommended, but for special cases with prolonged therapy, narrow therapeutic windows, suspected toxicity, extracorporal circulation like ECMO etc. (11).

By now it is clear that, when using betalactams, we should prefer prolonged infusions for at least 3 hours or continuous infusions with TDM over short term infusions in critically ill patients. A meta-analysis by Vardakas et al. found a significantly better survival (all cause mortality) for piperacillin-tazobactam and meropeneme in pneumonia, urinary tract infections and intraabdominal infections with and without septic shock. No difference could be established between prolonged (3, 4, 6 hours) and continuous infusions (21). These findings are explained by the time- dependent (fT > MIC) efficacy of betalactams (22).

Among the betalactams, penicillines should be preferably used. Cephalosporines, especially Ceftraxone due to its biliary secretion, have a significantly higher incidence of ESBL induction and Clostridium difficile associated diarrhoe (CDAD) (23, 24).

Fluoroquinolones have the advantage of beeing lipophilic drugs, but many restrictions and side-effects limit their use (25). From the ABS point of view, it is important to know that they are beeing secreted with the sweat which may lead to resistant bacteria on the skin.

Evidence for Shorter Therapies

There is a lot of evidence that shorter therapies of 5- 8 days instead of 14 days are effective and safe for infections like community-aquired (CAP), hospital-aquired (HAP) and venrilator-aquired (VAP) pneumonia, for primary and secondary peritonitis and many more infections (11, 26). Even for Gramnegative sepsis non-inferiority of 7 or 8 vs. 14 or 15 days of antibiotic therapy has been shown (27, 28).

There are some exceptions like S. aureus bacteriemia, but even for complicated infections like necrotizing fasciitis, osteomyelitis and cellulitis, shortening antibiotic courses by 50% (i.e. osteomyelitis 42 days instead of 84 days) was save in several trials (11, 26). So, this is a simple and save intervention to significantly reduce antimicrobial exposure of single patients and the environment on our ICU wards.

Deescalation is Safe.

As stated in (11) it may sometimes be clinically indicated to start an empiric combination therapy of two antibiotics, especially in septic shock. Nevertheless, after 48-72 hours, with clinical improvement of the patient's state or after obtaining the results of the microbiological samples, early deescalation should be mandatory. This is also stated by the surviving sepsis campaign guidelines. They recommend against any routine use of combination therapies for ongoing treatment, even in sepsis (29). A prospective observational study on 712 patients with sepsis and septic shock underlined this recommendation (30). Of course, other guidelines on the treatment of special infections like endocarditis or S. aureus infections with non removable foreign bodies have to be followed. A meta-analysis of studies with weak level of evidence (2 RCTs not designed for the question of deescalation and 12 cohort studies) stated that deescalation of antimicrobial therapy has a "protective" effect on patients (31). Nevertheless, as stated by Kollef in an editorial, deescalation has to be part of a broader Antimicrobial Stewardship strategy (32). The key message is that we have to ask ourselves every day in every patient, if combination therapy, broad spectrum therapy or antibiotic therapy at all, is still indicated and that we must not continue an antimicrobial therapy just to "finish a therapy course" or because it "worked clinically".

Procalcitonin for Antibiotic - Therapy Guidance

Several reviews and meta-analysises found that using Procalcitonin levels for therapy-guidance and control is safe. It helps to end antibiotic therapies earlier, to detect failure of antibiotic therapy, and to think about alternative diagnosis if PCT is low. In a meta-analysis by Wirz et al. on

ICU patients with infection and sepsis (11 RCT: 2252 pts. PCT- guided, 2230 control, sepsis of any type), the PCT- guided therapy group had a lower 30-days mortality (33, 34). Improved survival and lower antibiotic exposure were also found in a meta-analysis by Schuetz et al. on respiratory infections (35). Huang et al. found evidence that using PCT for antibiotic discontinuation reduces as well antibiotic exposure as the short-term mortality in the special setting of critically ill patients (36). PCT for discutinuation of antibiotics produced an antibiotic-sparing effect of 1.67 days (n = 3404; median – 1.66 days; 95% CI – 2.36 to – 0.96; I2=71%; p<0.01) and a reduced short-term ICU mortality with a RR 0.86 (n = 3414; 95% CI 0.76–0.98; I2=0%; p<0.05).

So, the strategy of using PCT to end antibiotic therapies earlier, should absolutely be implemented in our ICUs. The different cut-offs are beyond the topic of this article.

Don´t Give Antibiotics in the ICU for…

One of the most important parts of universal Antimicrobial or Antibiotic Stewardship concept is to know, when or for which indications antibiotics are **not** necessary in the ICU. Unfortunately, reality of our daily work is often different. Important points to keep in mind and to implement in daily clinical practice are:

- Do not prolong perioperative antibiotic prophylaxis. Extended prophylaxis for longer than 24 hours is potentially harmful. Prophylaxis after wound closure does not prevent wound infections. “Single shot only” strategy with repetition only intraoperatively, according to the antibiotic`s half life, duration of surgery and blood loss. Do not use broad-spectrum antibiotics for perioperative prophylaxis (37, 38, 39, 40).
- Adequate perioperative prophylxis reduces infectious complications in the ICU (41).
- Only in cardiac surgery, low certainty evidence of a beneficial perioperative prophylaxis for 24 to 48 hours maximum exists (42).
- Don’t give any “prophylactic” antibiotics for central lines (CVC), surgical drains, urinary catheters in place. Do not give an antibiotic prophylaxis before placing a CVC (43). Only severe immunosupression (stem cell graft, recent organ transplantation etc.) may be a rare exception.
- If you think a drain or catheter is the focus of infection, remove it.
- The same is true for intracranial drains and catheters like extraventricular drainage (EVD) and ICP monitors (44, 45, 46).

Conclusion

Twelve years after the editorial by Kollef (48) and nineteen years after a review by the same author (49), challenges still remain the same, and the problems remain actual and urgent.

- Don`t use antibiotics as antipyretics.
- Implement a five-days-bundle.
- Re- evaluate empiric therapy after 48-72 hrs.

- No prolonged perioperative prophylaxis.
- No antibiotic prophylaxis for drains/ catheters.
- Shorten therapy courses.
- Deescalate treatment according to microbiological results or if patient improves.
- Therapy guidance by PCT reduces side effects and mortality.
- Use Penicillin derivatives whenever possible.
- Time-dependent Beta-Lactam effect, so use prolonged infusions.
- Individualized dosing - TDM in selected patients.
- Antibiotic Stewardship programs are safe.

All general considerations about the implementation of ABS programs are also true on the ICU (11).

Nevertheless, ideally such programs should be implemented in a broader approach for the whole hospital (9, 10) and on a national scale for the outpatient setting (6, 7).

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LESSER-KNOWN EFFECTS OF LIDOCAINE

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Abstract

Objectives: Recent evidence about the various effects of lidocaine and its wide range of usage as a local anesthetic, antiarrhythmic drug, pain-relief drug and other properties, completes its portfolio.

The aim of this article is to present the known and unknown effects of lidocaine.

Method and Result: A systematic search of the available literature, Internet data, Medline and Cochrane databases was done. It resulted in finding 30 sources with data about lidocaine that were consulted. They were organized as: history of lidocaine, pharmacological properties of lidocaine, mode of application, the mechanism of the therapeutic effect and dosage of lidocaine. There was a huge diversity of applications of lidocaine with different effects and modes of action.

Discussion: Lidocaine with its properties involving strong analgesia, long duration of action, and stability of the compound, is the most popular local anesthetic widely used in all types of regional anesthesia. In addition to the existence of newer local anesthetics, lidocaine is still popular for various types of blocks in regional anesthesia, as well as an antiarrhythmic agent.

The parenteral use of lidocaine has shown antinociceptive, antithrombotic and anti-inflammatory effects. It has also been found that it provides better postoperative pain relief, has opioid sparing effect, decreases acute pain, prevents chronic postsurgical pain, and has antihyperalgesic effects. Furthermore, it plays an important role in the maintenance of the immune function and has an antitumor effect. It was found useful in the treatment of respiratory distress syndrome. All these lesser-known effects cannot be explained with its known mechanism of action (sodium channel inhibition).

This study discusses the effect of lidocaine on pathophysiological events and alternative mechanisms of action.

Key Words: *antitumor effects, immune function, inflammation, lidocaine, pain.*

Introduction

Lidocaine is the first local anesthetic from the amino amide class**.** Since the moment of its synthesis until today, it has become the most popular drug with a wide range of usage as a local anesthetic, antiarrhythmic drug, pain-relief drug and other properties.

The re-survey in the past returned us to the early 1943 year. When Europe was engaged with the Second World War, in a Swedish chemical laboratory at the Institute of Chemistry at Stockholm University (Stockholms Högskola), Stockholm, the chemist Nils Löfgren synthetized the local anesthetic (LA) lidocaine, which was first named "xylocaine". Bengt Lundquist from the same Institute recognized its anesthetic properties. The previously used local anesthetic – procaine, from the amino esters group, did not match the needs of the surgeons. It was an unstable compound with a short time of action. In contrast to it, the newly developed drug, xylocaine (labeled in the beginning as LL30), had strong analgesic properties, longer duration of action, and was stable (1). The following years, from 1946 to 1949, Torsten Gordh, an anesthesiologist from the Risk Hospital in Stockholm, Sweden, studied the clinical properties of the compound LL30. Finaly, in 1949, the pharmacy "Astra" introduced lidocaine with the trade name "Xylocaine" (2% lidocaine with/ without epinephrine 1:100,000) on the market. It was the first local anesthetic from the amino amide class which properties promised to become the most popular local anesthetic widely used for all types of regional anesthesia (2).

Today, in addition to the existence of newer local anesthetics, lidocaine is still popular as a local anesthetic used for various types of blocks in regional anesthesia, as an antiarrhythmic agent and as a drug in the treatment of post-surgery pain, neuropathic pain and ventricular arrythmias.

The parenteral (intra venous - IV) use of lidocaine, as one of the compounds in the multimodal management of pain and multimodal anesthesia, opened a new era for the drug. According to the recent evidence (preclinical and clinical data), parenteral lidocaine with plasma concentration of 1-3mg/ml, provides better postoperative pain relief with an opioid sparing effect, decreases the acute pain, prevents the chronic postsurgical pain, and has antihyperalgesic effects (3).

The aim of this paper is to refresh the knowledge of lidocaine and to present the known and unknown effects of lidocaine.

For this purpose, valuable literature of more than 30 articles, metanalyses, Internet data, Medline and Cochrane database was consulted.

Pharmacology of Lidocaine

The main clinical property of lidocaine is its **strong anesthetic potential.** It is the first local anesthetic from the **amino amide** group, derived from xylidine as a tertiary amine.

The molecular structure of lidocaine is C14H22N2O, consisting of one aromatic ring on which hydrogens and amine group are added. It is a stable solution, found commercially as 1% and 2% solution, with or without epinephrine (1:100,000). It is lipophilic with high lipid-solubility and low pKa – 8, that makes it a slight base. These properties promote its rapid onset of action and moderate duration of action: from 170 to 190 minutes (4). In circulation, lidocaine has the affinity to bind proteins of 64% and provides 1% fat solubility. Lidocaine's onset of action is 3-5 minutes, with a half-life of 30–120 minutes and total toxic dose > 4.5 mg/kg (5). It is metabolized in the liver through N-dealkylation and hydroxylation by hepatic enzyme Cytochrome P450, to active and inactive metabolites (6).

The newer developed effects of lidocaine could not be explained by its standard sites of action on high-voltage cation ion channels, namely on sodium channels. Its analgesic effect results

from the open state of the sodium ion channels preventing depolarization.

The nociceptive effect of the IV applied lidocaine is due to the increased threshold of pain and stimulation of the inhibitory pathways of pain of the intraspinal realized acetylcholine. The next site of action is in the CNS where glycine-like hyperpolarization is produced and on NMDA receptors which are inhibited by inhibition of glutamatergic neurotransmission. Lidocaine anti-arrhythmic effects are manifested by affinity for its receptors playing a role as a sodium channel blocker – (phase 0 - the Na+ channel open/ active and phase 2-*inactivated*/ refractory). It decreases the permeability of the neuron membrane to sodium, which causes inhibition of depolarization resulting in blocked conduction (7).

Clinical Use of Lidocaine

Regional anesthesia

Lidocaine is the most common local anesthetic used for regional anesthesia. It is used for infiltration in infiltrative anesthesia; it is suitable in different concentrations for all types of blocks, including neuraxial blocks. It is prepared in gels or ointment for topical anesthesia, or sprays for airways anesthesia (8). The mode of application and the different concentration for local anesthesia are presented in Table 1.

Table 1. Different concentrations and modes of application of lidocaine used for regional anesthesia.

Mode of application for RA
• Concentrations of 0.05 to 0.1% → **s.c.** infiltration
• 0.25 to 0.5% → **intravenous** regional anesthesia
• 1 to 2% → regional **nerve blocks**, including neuraxial blc-s and in **intravenous** preparations for antiarrhythmic use
• 1 to 2% gel for **local** use (urine catheter)
• 4% solution for **topical** anesthesia (aye, mucous, spray)
• 5% **ointment** for skin, mucous of rectum
• 10% solution for **airway** anesthesia

Lidocaine's Effects on CNS

In 1999, Mitchell with his colleagues studied the cerebral protection of lidocaine during cardiac surgery. It was concluded that IV application of lidocaine during cardiac surgery had a protective cerebral role which was unrelated to any effects on depression or anxiety (9). Based on his findings and the studies on molecular bases of lidocaine, it was concluded that IV applied lidocaine had several effects on CNS. It produces inhibition on nicotinic and acetylcholine receptors, inhibition of presynaptic calcium channels in the dorsal root ganglion, inhibition of the opioid receptors, inhibition of neurite growth, inhibition of muscarinic cholinergic receptors, and prevention of substance P from binding to natural killer (NK) cell receptors (10).

Anti-inflammatory Effects of Lidocaine

The mechanisms on analgesia of the IV applied lidocaine were studied by Lauretti (2008) (11). In 2020, during the Covid-19 pandemic, lidocaine was approved to be a strong anti-inflammatory

agent which can be compared to steroids and NSAIDs (12). It was found that low concentration of lidocaine had an effect on PMNs, macrophages and monocytes. The anti-inflammatory function is a process in which neutrophils change from a resting state to an active state. Lidocaine plays a role of a membrane-ion transporter, which dysregulates cellular pH levels and depresses the cytokine release. It affects phagocytosis, migration, exocytosis and cellular metabolism (13). When used for multimodal anesthesia, where a bolus lidocaine of 1.5mg/kg was injected at the start with a maintenance dose of 3mg/kg/h until one hour after the end of surgery, the levels of pro-inflammatory markers (IL-1, IL-6, TNF-α and IFN-γ) in serum were significantly reduced (3).

Antibacterial Effects of Lidocaine

In the beginning of the 20th century, the first doubts about the antibacterial effects of local anesthetics appeared. The study of Murphy *et al.* (1954), approved and documented that 0.5% of tetracaine had antibacterial properties and was toxic to *Pseudomonas*. In the last decade, several studies about the antibacterial effects of lidocaine have been conducted and have shown that it inhibits the growth of different microorganisms (Gram-positive and Gram-negative bacteria, mycobacteria and fungi) (14, 15). In 2007, Begec Z. and his colleagues in an *in vitro* study found that pure and alkalinized lidocaine significantly inhibited the growth of *S. aureus, E. coli,* and *P. aeruginosa.* The authors did not approve of the benefits in alkalinization of lidocaine compared to pure lidocaine (16).

Effect of Lidocaine on Immune Function

In one *in vivo* experimental study from 1985, it was shown that chronic exposure to lidocaine had led to impairment of lymphocyte function and changes in the expression of the immune response (17). Later, Herroeder *et al*. showed that systemic lidocaine significantly attenuated the plasma levels of IL-6, IL-8 and IL-1ra (18). Yardeny *et al*. documented that perioperative lidocaine attenuates the production of both pro- and anti-inflammatory cytokines (19). The study of Angjushev D. *et al*. (2024) that evaluated the effects of local anesthetics on immunity during mastectomy, proved the benefits of perioperative lidocaine on immunity. It was found that preoperative infusion of 1/% lidocaine preserves the function of the NK cells, and significantly increases the level of TNFα, as well as provokes a minimal decrease of lymphocytes level (20).

Anticancer Effects of Lidocaine

In the literature, it has been shown that *in vivo* and *in vitro* use of lidocaine plays an important role in the suppression of tumorigeneses. It is found that IV injection of lidocaine in different concentration kills various types of cancer cells, increases the apoptosis, decreases tumor recurrence and distant metastasis (21,22). Because of these effects of lidocaine, in 2020 Zhou D. and his colleagues proposed lidocaine to be reposited as an anticancer drug (23).

The lidocaine anticancer spectrum is wide. Single administration and various doses of lidocaine have possibilities to suppress lung cancer (24, 25), breast cancer (26, 27, 28), gastric cancer (29, 30), liver cancer (31), glioma, melanoma, tongue cancer, etc. (32, 33, 34, 35, 36).

The possible mode of action of lidocaine on tumorigenesis belongs to the activation of nuclear factor NF-κB signaling pathway, proinflammatory gene induction, mitogen-activated protein kinases (MAPKs), enhanced immune function (increased NK cells cytotoxicity, predomination of Th1 cells over Th2), and inhibition of the epidermal growth factor receptor (EGFR) (37,38).

In vitro studies on cultivated tumor cells showed that lidocaine in different concentrations suppress the carcinoma cells proliferation, migration, growth and chemosensitivity (39), and *in vivo* induces cell apoptosis by modulating the lncRNA-MEG3/miR-421/BTG1 pathway (40).

Lidocaine as a Chemosensitizer

Several *in vitro* and *in vivo* studies have shown that the use of lidocaine during chemotherapy can sensitize some chemotherapeutics to many types of resistant cancer cells (10, 27,29) (Table 2).

Table 2. Effects of lidocaine on some chemotherapeutics.

Lidocaine effects:
1. Enhances the cytotoxicity of **cisplatin** in various cancer cells,
2. Can sensitize **5-FU**,
3. Sensitizes **Cytomycin C**,
4. Is used in **hyperthermia therapy,** etc.

Effects of Lidocaine on Acute Lung Injuries in Covid-19

During the Covid-19 pandemic, complications related to the development of acute respiratory distress syndrome (ARDS) were the most commonly seen. The anti-inflammatory effects of lidocaine were used for treatment of acute lung injury. Lidocaine was used in the form of nebulizer. It was shown that lidocaine anti-inflammatory effect led to decreasing PMN granulocyte accumulation in the lung (40). Nebulized lidocaine was established to be a novelty in the treatment of patients with COVID-19-related lung injuries. It was found that nebulization with lidocaine reduced the cytokine storm and showed better improvement of the lung injury connected with the COVID-19 (10).

IV Use of Lidocaine

According to the above-mentioned various effects of lidocaine, it can be concluded that it has a wide range of indications for usage. Table 3 illustrates medical branches where this local anesthetic can be used.

Table 3. IV application of lidocaine.

IV application of lidocaine
• **Resuscitation and cardiology** -Treatment of arrythmia
• **Neurology and neurosurgery** – Effects on CNS
• **Anesthesiology:**
◦ IV regional anaesthesia
◦ Multimodal anaesthesia
◦ Postoperative acute pain
◦ Treatment of nociceptive pain
• **Oncology**
◦ Palliative care
◦ Anticancer drug
• **Infective diseases-ARDS-Covid-19**

Conclusion

The aim of this review was to develop and to present the lesser-known effects of lidocaine. I hope that the readers will find some interesting novelties concerning lidocaine. Many investigations are still going on. I believe that new trials will bring many other benefits for the patients providing better and safer anesthesia for them.

Declaration of Interest

Hereby, I, Marija Sholjakova, MD, PhD, the Author of this topic, declare that I have no competing interest.

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INTRAFETAL INTERVENTIONAL PROCEDURES AND ANESTHETIC IMPLICATIONS

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Abstract

Intrafetal surgery is an operative procedure which is performed on a pregnant mother to treat her baby before it is born. Maternal-fetal surgery can occur either during the middle of pregnancy or at the end of the pregnancy. In all cases, anesthesiologists are involved to provide for the comfort and safety of pregnant mothers and their babies. As these defects and malformations have become more readily identified, the number of innovative therapies has also amplified. Rapid advances in imaging techniques and prenatal diagnosis have allowed for the progressive development of prenatal interventions and surgeries and today they have become an integral part of the management of high-risk pregnancies. In addition, the rapidly growing capability of digital optics and miniaturized instrumentation has now allowed fetoscopy procedures to become a reality.

There are 3 basic types of surgical interventions: 1. Minimally invasive midgestational procedures, 2. Midgestational open procedures, 3. Ex-utero intrapartum treatment (EXIT). These procedures require many manipulations and monitoring in both the mother and the unborn fetus.

The combination of underdeveloped organ function and usually life-threatening congenital malformation places the fetus at considerable risk. Fetal surgery also leads to enhanced surgical and anesthetic risk in the mother including hemorrhage, infection, airway difficulties and amniotic fluid embolism, so anesthetic management should focus on maintaining adequate uteroplacental blood flow, optimizing surgical conditions, and minimizing maternal and fetal risk.

Key Words: *Maternal-fetal surgery, fetoscopy, ultrasound guided procedures.*

Introduction

Maternal-fetal surgery also known as antenatal surgery, prenatal surgery, is a growing branch of intrafetal medicine that covers any of a broad range of surgical techniques that are used to treat congenital abnormalities in fetuses who are still in the pregnant uterus. Fetal surgery can occur either during the middle of pregnancy or at the end of the pregnancy. In all cases, anesthesiologists are involved to provide for the comfort and safety of pregnant mothers and their babies. As these defects and malformations have become more readily identified, the number of innovative

therapies has also amplified. The rapid advances in imaging techniques and prenatal diagnosis, have allowed for the progressive development of prenatal interventions and surgeries and today they have become an integral part of the management of high-risk pregnancies. In addition, the rapidly growing capability of digital optics and miniaturized instrumentation has now allowed fetoscopy procedures to become a reality (1-3).

History of Fetal Surgery

The first successful fetal interventional procedure performed was an intrauterine transfusion of red blood cells for erythroblastosis fetalis. This was done in 1963 by Sir William Liley who completed the procedure via the intra-peritoneal route.[2,3] In 1982 a landmark meeting occurred involving almost all clinicians who, at that time were actively involved in fetal treatment and surgery. They met in what was the first organized conference in the field of fetal surgery, and agreed to share information, establish a registry, and provide guidelines for this promising and rapidly growing discipline. Dr. Michael Harrison stated at the meeting that "All case material, regardless of outcome, should be reported to a fetal-treatment registry, so that the benefits and liabilities of fetal therapy can be established as soon as possible", and this statement remains as true today as it was almost 35 years ago (3).This document is a consensus statement on anesthesia for maternal–fetal interventions from a collaborative workgroup of the American Society of Anesthesiologist (ASA) Committees on Obstetric and Pediatric Anesthesia and the Board of Directors of the North American Fetal Therapy Network (NAFTNet). This document describes the perioperative anesthetic considerations for maternal–fetal interventions and details the role of the anesthesiologist in the multidisciplinary fetal therapy team (3,4).

Ethical Considerations in Fetal Surgery

The decision to intervene must pass three criteria:

1. Invasive therapy should have high probability of being lifesaving or of preventing serious and irreversible disease, injury or disability for a fetus and the child to be
2. Invasive therapy poses low mortality risk and low or manageable risk of serious disease, injury or disability to the fetus and the child to be;
3. The maternal mortality and morbidity risk is very low or manageable. The autonomy of the pregnant woman must be central to any decisions regarding intervention as she is assuming risk to self with a potential of no benefit to self (3-6).

Risk for Fetus and Mother

The combination of underdeveloped organ function and usually life-threatening congenital malformation places the fetus at considerable risk. Surgery and anesthesia lead to significant risks to the fetus and can result in fetal death and morbidity. Altered coagulation factors predispose the fetus to bleeding and cause difficulty in achieving surgical hemostasis during fetal surgery. This problem is compounded by the small blood volume of the fetus. Fetal surgery can result in premature labor and birth. Initially surgeries were only performed in cases of impending fetal death. With the advancements in anesthetic and surgical techniques, the risks have

decreased, and the indications broadened (5-12).

Fetal surgery also leads to enhanced surgical and anesthetic risk in the mother including hemorrhage, infection, airway difficulties and amniotic fluid embolism. Only ASA class I and II mothers with very sick fetuses are taken up for fetal surgery.

Fetal Surgery

There are 3 basic types of surgical interventions:

1. Ex utero intrapartum treatment (EXIT) (9-11)

These are also known as OOPS i.e, operation on placental support. These interventions are performed on vaginal delivery or caesarean section. Only a portion of the fetus is delivered and brief procedures such as endotracheal intubation or examination of neck mass done while the fetus is still connected to the placenta through the umbilical cord. Only brief procedures were possible as placental support rarely lasts for more than 10 minutes during routine births. Techniques are being evolved to allow placental support to continue for an hour or longer. It is possible to secure airway in cases ranging from cystic hygroma to complete high airway obstruction syndrome. The following procedures are being done as EXIT procedures:

Disease	Procedure
• Congenital Diaphragmatic at Hernia	Removal of tracheal balloon inserted 22–27 weeks with midgestational procedure.ECMO cannulation for severe pulmonary hypoplasia.
• Congenital high airway obstruction Syndrome(CHAOS)	Perform tracheostomy.
• Giant cervical neck mass	Resection of mass.
• Anticipated difficult intubation	Laryngoscopy, bronchoscopy, tracheostomy.

2. Midgestation open procedures *(8-12)*

Recognition of fetal defect in early pregnancy allows intervention in midgestation to prevent irreversible damage or development of secondary disease. Hysterotomy is required to access the fetus who is returned to the uterus after completion of surgery for the rest of the gestation. Fetal surgery is performed through a low transverse abdominal incision. Placental location is determined by ultrasonography, and a wide uterine incision is given by a specially designed absorbable stapler for performing bloodless hysterotomy. The fetal part is exteriorized for surgery and after completion of the surgery the fetus is placed back into the uterus which is closed.

The fetus continues to grow for the rest of the gestation with reversal of the disease process that prompted the fetal intervention. Example is repair of meningomyelocele at 22 weeks of gestation to prevent damage to central nervous system tissues due to prolonged exposure to amniotic fluid. The sequelae of bladder and bowel dysfunction and clubfeet may be prevented. The indications for open midgestation fetal surgery are the following:

Disease	Procedure
• Meningomyelocele	Surgical repair of meningomyelocele.
• Sacrococcygeal teratoma	Surgical resection of teratoma.
• Intrathoracic masses	Resection of mass.
• Congenital DiaphragmaticHernia	Temporary tracheal occlusion with intrathoracic liver.
• Congenital Cystic Adenoid Malformation	Lobectomy, pneumonectomy.

3. Minimally invasive midgestation procedures (8-13)

Because the uterus is a fluid filled organ, small endoscopes allow excellent visualization of fetal and placental structures as long as uterine distention is maintained with irrigating fluid. These are basically of 2 types:

1.Fetendo(fetoscopy) procedures - Aberrant placental vessels providing imbalance of blood flow to twins can be identified and ligated in this way to prevent fetal death due to twin-twin transfusion syndrome. Other surgeries possible with this technique are radiofrequency ablation or coagulation of non-viable twin's umbilical cord in twin reversed arterial perfusion and division of amniotic bands in amniotic band syndrome. Using fetoscopy, these aberrant vessels and bands can be identified and coagulated. Fetal procedures, such as fetal cystoscopy with laser ablation of posterior urethral valves, are also now technically possible and are being undertaken.

2. FIGS-IT - This is a term used for fetal image guided surgery for intervention or therapy and describes the method of manipulating the fetus without either an incision in the uterus or an endoscopic view inside the uterus. The manipulation is done entirely under real-time cross-sectional view provided by the sonogram. This is the same sonogram as is used for diagnostic purposes, but in this case is used to guide instruments.

Like Fetendo, it can be done either through the mother's skin or, in some cases, with a small opening in the mother's abdomen. It can often be done under regional anesthesia like an epidural or a spinal, or even under local anesthesia. This is the least invasive of the fetal access techniques and, thus, causes the least problem for mother in terms of hospitalization and discomfort (6,7,13).

Structure of Fetal Therapy Centers

There is substantial variation in the organizational setup of fetal therapy centers worldwide. Mother care is typically coordinated by a multidisciplinary team that includes maternal–fetal medicine (MFM) specialists, pediatric surgeons, neonatologists, anesthesiologists, radiologists, perioperative nurses, social workers and geneticists. The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics have made recommendations on the general components of an fetal therapy centers, emphasizing the importance of maternal autonomy, explicit informed consent, multidisciplinary approach, availability of support services, oversight of centers and collection of outcomes data (6,12).

Suggested Components of Fetal Therapy Centers

Component	Function
1. Prenatal imaging (ultrasonography, fetal MRI, fetal echocardiography). 2. Maternal–fetal medicine/pediatric surgery, including perinatal nursing. 3. Nurse coordinator.4.Obstetric anesthesia. 4. Genetics. 5. Neonatology, including nursing. 6. Pediatric anesthesia. 7. Pediatric cardiology. 8. Adult medicine and critical care. 9. Social worker and spiritual support. 10. Palliative care - Palliative postdelivery care, perinatal hospice services. 11. Language interpretation and cultural diversity specialist services. 12. Medical ethicist. 13. Institutional review board. 14. Database and IT support services.	1. Accurate diagnosis of fetal anomalies. 2. Prenatal consultation, intervention, and post-delivery management. 3. Care coordination, resource and education. 4. Maternal management during fetal interventions. 5. Diagnosis and counseling for genetic disease. 6. Prenatal consultation, peripartum, and postdelivery care. 7. Fetal/neonatal management during fetal interventions. 8. Prenatal diagnosis, postdelivery care, fetal monitoring during complex procedures. 9. Consultation as needed. 10. Coordination of social services, patient advocacy and perinatal loss support. 11. Palliative postdelivery care, perinatal hospice services. 12. Consultation, consent, and follow-up services. 13. Consultation and oversight as needed. 14. Oversight of experimental and research related interventions. 15. Reporting, data collection and sharing, research.

Preoperative Evaluation

Preoperative evaluation includes multidisciplinary team meeting with mother and her family to discuss risks, benefits, anticipated outcomes and alternatives for both fetus and the mother. The anesthesiologist is a critical member of the multidisciplinary team that evaluates the mother's suitability for undergoing a procedure (4,12). The standard medical, surgical, obstetric and anesthetic history must be solicited, and a targeted physical examination should be performed focusing on the airway, cardiopulmonary system and spine. The anesthesiologist should explicitly discuss the risks of the planned anesthetic, understanding that the mother assumes the surgical and anesthetic risks for the benefit of the fetus. If members of the multidisciplinary team identify preexisting maternal comorbidities that significantly increase the maternal risk of perioperative morbidity or mortality, a multidisciplinary discussion should occur to review the maternal risks and potential fetal benefits, and the mother should be given the opportunity to decline the planned procedure.

Standard adult fasting guidelines are applicable (12,18). Maternal preoperative laboratory testing is guided by history and physical examination. While a type and screen are adequate for

minimally invasive maternal–fetal interventions, a type and crossmatch should be ordered for open maternal–fetal surgeries and EXIT procedures. In addition, 0-negative, leukocyte- reduced, irradiated, cytomegalovirus-negative blood crossmatched to the patient should be readily available for the fetus (4,11,18).

A comprehensive maternal–fetal evaluation should include a review of all fetal imaging studies in a multidisciplinary meeting to evaluate the extent of anatomic and physiologic derangement. Often, serial fetal imaging studies are performed to monitor the growth of pulmonary lesions, progression of heart failure, development of fetal hydrops, worsening of mediastinal shift, airway compression, as well as fetal genetic studies are included in preoperative evaluation. Pertinent information for the anesthesiologist includes gestational age, fetal cardiac function, estimated fetal weight for drug dosing and placental location, which determines patient's positioning and the need to exteriorize the uterus (6,7,12,21).

The multidisciplinary team, including neonatology, should also discuss the plan for the fetus in the event of an intraoperative maternal arrest and/ or the need for fetal resuscitation.

Fetal Physiology and Drug Transfer

Cor

More than half of the fetal blood volume resides in the placenta and is approximately 110–160mL/kg, from the start of the second trimester to term. Fetal cardiac output is mainly a function of fetal heart rate (FHR). This is because fetal myocardium is less compliant than adult myocardium and less responsive to fluctuations in preload. Right ventricular and left ventricular output are not equivalent in the fetus, so cardiac output is described in terms of the combined cardiac output (CCO) of both ventricles. A normal fetus has a CCO of 425–550 mL/kg/min. During surgical procedures resulting in significant fetal blood loss, the degree of hypovolemia and transfusion end point requires vigilant monitoring of both FHR and intraoperative fetal cardiac function using echocardiography (4,18).

Lung

Fetal lungs are fluid filled, and the pulmonary epithelium secretes approximately 100mL/kg/d of fluid that exits the fetal trachea to be either swallowed or introduced into the amniotic fluid (12,18).

Liver

Although immature, the fetal liver synthesizes coagulation factors. These coagulation factors do not cross the placenta and are in lower concentration and less effective in forming clots compared to adults. The mother coagulation f-ors does not cross the placenta. Fetal liver synthesizes coagulation f-ors from the 5th gestation week and fetal blood coagulates from the 11th week. The coagulation f-ors are measurable at 19-23th g. week, but the fetus from 19-23th g. week has 10-30% of adult coagulation f-ors, and from 30-38th g. week has 10-50% of adults. The fetus also has hyporeactive thrombocytes.

Although fetal hepatic enzymes are less functional than in adults, most medications in the umbilical vein undergo a significant amount of fetal hepatic metabolism (first-pass metabolism)

before circulating to the fetal brain or heart. Although these fetal metabolic enzymes are less functional than those of adults (12,20).

Drug Transfer

Molecules smaller than approximately 1000 Daltons are primarily exchanged between the maternal and fetal circulation by placental diffusion. The degree and rate of transfer are determined by transplacental concentration gradients, molecular weight, protein binding, ionization and lipid solubility. All drugs cross the placental barrier to some degree, but a few are significantly restricted.

Examples of medications with severely limited maternal–fetal transfer include nondepolarizing neuromuscular blockers, succinylcholine, glycopyrrolate, unfractionated heparin, low-molecular-weight heparins and insulin. Volatile anesthetics, opioids, benzodiazepines and atropine readily cross the placenta (15,16,18).

Fetal Analgesia

Pain is a subjective phenomenon that is difficult to assess. Direct fetal interventions, including the passage of a needle into the fetus, result in a hormonal stress response that is decreased with fetal opioid administration. Pituitary–adrenal, sympathoadrenal, and nociceptive components of the stress response are present by 19 weeks' gestation allowing a fetus to reflexively withdraw from a noxious stimulus without input from the cerebral cortex (i.m. needle). Thalamocortical connections to the somatosensory cortex allowing the perception of pain are developed after 25th g. week (25 – 30 weeks' gestation). By 30 weeks' gestation, EEGs demonstrate patterns of wakefulness and sleep, by 34 weeks' gestation, EEG electrical activity is present 80% of the time, with wake/ sleep patterns similar to adults. Opioid analgesics can reach the fetal circulation by: maternal administration, direct fetal intramuscular administration (fentanyl-20 μgr/kg), intravenous umbilical cord administration (fentanyl - 15μgr/kg) (15-17,22-24). Fetal movement can decreased by: intramuscular(rocuronium -2.5mg/kg) or umbilical administration of a muscle relaxant (1.0mg/kg) and atropine 15-20 μgr/kg.27,28 The umbilical cord and placenta have no known pain receptors, so procedures that only involve these tissues (e.g., intrauterine transfusion [IUT] or laser ablation for twin-to-twin transfusion syndrome [TTTS]) do not require fetal administration of analgesics. These procedures, maternal opioid administration (e.g., remifentanil) and subsequent placental transfer can assist with fetal immobility, but this is not always required (30). For open maternal–fetal procedures, the use of maternal general anesthesia allows the transfer of anesthetics from the mother to the fetus, but direct fetal administration of opioid is still required to blunt the fetal stress response to invasive procedures reliably (6,7,13,25).

Anesthetic Techniques

The anesthetic technique for any maternal–fetal intervention depends on the planned surgical approach, degree of invasiveness, maternal comorbidities and patient/ surgeon preference. The anesthesia team must have a thorough understanding of maternal and fetal physiology, as well as the planned maternal–fetal intervention. For open maternal–fetal and EXIT procedures, expertise in obstetric and pediatric anesthesia is required.

Anesthesia for Minimally Invasive Maternal–Fetal Interventions (16-29 g. weeks)

The most minimally invasive maternal–fetal interventions are performed with local anesthetic infiltration, with or without maternal sedation. Preoperatively, consider the maternal administration of aspiration prophylaxis medications, including nonparticulate antacids, H2 receptor antagonists, and/ or metoclopramide, restriction of i.v. fluid (pulmonary edema from irrigation fluids). Standard ASA monitors should be used. Neuraxial techniques or general anesthesia may be necessary depending on the number and size of port sites, anticipated patient's position, surgeon preference and maternal comorbidities, such as aspiration risk, severe anxiety and inability to tolerate the supine position with uterine displacement for the length of the procedure. Although preoperative tocolytics (indomethacin p.o., Mg sulfate) may be administered, profound intraoperative uterine relaxation is not necessary for minimally invasive procedures, and maternal administration of sedatives and analgesics only provides limited fetal analgesia via transplacental transfer. Prophylactic antibiotics are also recommended (19,28).

For maternal–fetal interventions on non-innervated tissues such as the umbilical cord (intrauterine transfusion, percutaneous umbilical blood sampling) and placenta (laser photocoagulation for twin-to-twin Sy), no additional fetal analgesia is necessary.

For more invasive maternal–fetal interventions, such as percutaneous balloon valvuloplasty or fetoscopy endoluminal tracheal occlusion, fetal analgesia is provided using an intramuscular or intra-umbilical venous administration of a fetal mixture containing opioid and muscle relaxant, often accompanied with atropine to minimize the risk of fetal bradycardia. Fetal monitoring, during minimally invasive maternal–fetal interventions, typically involves fetus heart rate monitoring using Doppler ultrasonography at the beginning and the end of the maternal–fetal intervention (12,18).

Anesthesia for Open Maternal–Fetal Interventions (operation on placental circulation 23-26 g. weeks)

Open maternal–fetal surgeries are typically performed under maternal general anesthesia (inhalation agents - sevoflurane provide dose-dependent uterine relaxation necessary for optimum fetal surgical exposure plus nitroglycerin). Preoperatively, a high lumbar (L1–3) epidural catheter is inserted for postoperative analgesia. Secondary to concerns of intraoperative hemodynamic instability, the epidural catheter is frequently not initiated until maternal wound closure, but with enough time remaining to ensure adequate analgesia during emergence and extubating. Preoperatively, consider the maternal administration of medications for tocolysis (indomethacin and Mg sulfate, decrease premature uterine contractions) and aspiration prophylaxis. For venous thromboembolism prophylaxis, mechanical or pharmacologic methods, including low-dose unfractionated heparin or low-molecular-weight heparin, should be administered according to published guidelines, based on maternal comorbidities, current fetal status, concern for reoperation or urgent delivery, and timing of planned catheter removal (20,28). Intraoperative fluid administration is frequently restricted to <2L to minimize concerns for postoperative maternal pulmonary edema (19). Minimal postoperative coughing avoid uterine dehiscence.

After maternal laparotomy and uterine exposure, the placental borders are mapped with a sterile ultrasound probe. After ensuring adequate uterine relaxation, a hysterotomy is performed. Subsequently, amniotic infusion with warm lactated Ringer's solution (with antibiotics) is infused into the uterine cavity to maintain uterine volume, to maintain fetal temperature and to avoid compression of umbilical cord. Following optimal fetal positioning, a fetal intramuscular dose of opioid and nondepolarizing muscle relaxant is administered intramuscular or intra-umbilical for fetal analgesia and immobilization. Atropine may also be administered to minimize the chance of fetal bradycardia. Fetal monitoring is provided by pulse oximetry, continuous or intermittent echocardiography, fetal scalp electrodes and umbilical blood sampling (13,23).

Anesthesia for EXIT (ex utero intrapartum treatment) Procedures

The EXIT procedure enables securing the fetal airway and performing other life-saving fetal interventions, while the fetus remains on placental circulatory support. EXIT procedures are performed at or near-term gestation, the fetus is delivered at the end of the operation (under general or spinal-epidural anesthesia).

1. EXIT procedure secures the airway (ET, LMA, tracheostoma) in fetuses with oropharyngeal masses, laryngeal atresia, neck masses, or severe micrognathia causing airway obstruction, congenital high airway obstruction syndrome.
2. EXIT fewer common indications include resection of intrathoracic masses, causing mediastinal compression and debulking of sacrococcygeal teratomas, bronchogenic cyst, congenital pulmonal airway obstruction.

The anesthetic management of a mother undergoing an EXIT procedure is similar to that of open maternal–fetal surgery with some key differences. While EXIT procedures are typically performed under maternal general anesthesia, they have also been successfully accomplished using maternal neuraxial anesthesia with the administration of a nitroglycerin, infusion for uterine tocolysis and remifentanil infusion for fetal immobilization and analgesia (22,24). The fetus is delivered at the end of the procedure, and uterine relaxation is only needed intraoperatively, so magnesium sulfate is not required to prevent postoperative uterine contractions. The guiding principles of an EXIT procedure include (1) achieving adequate uterine relaxation to maintain uteroplacental circulation, (2) maintaining uteroplacental blood flow and maternal hemodynamics, (3) preserving uterine volume by partial delivery of the fetus and amnioinfusion, (4) minimizing fetal cardiac dysfunction, and (5) reversal of uterine relaxation after umbilical cord clamping (26-28).

Fetal Resuscitation

The fetus depends on uteroplacental support, and during fetal surgeries, preserving the uteroplacental circulation by maintaining maternal hemodynamics, achieving adequate uterine relaxation, preserving appropriate intrauterine fluid volume and avoiding uterine contractions, are critical. Fetal bradycardia is a reliable indicator of fetal compromise that must be addressed immediately. The common causes of fetal bradycardia include mechanical compression or kinking of the umbilical cord, uterine contractions, placental separation, maternal hypotension, umbilical artery vasospasm, anemia or hypoxemia. Less common causes include fetal hypovolemia,

hypothermia and anemia (27,28). All efforts to avoid maternal hypothermia should be used. The presence of placental circulation makes the fetal temperature highly dependent on maternal temperature, and maternal hypothermia will result in fetal hypothermia, which is associated with fetal bradycardia (27,28). If fetal bradycardia occurs, the anesthesiologist should increase maternal inspired oxygen, administer vasoactive drugs and intravenous fluids to ensure appropriate maternal blood pressure and heart rate, administer additional tocolytic agents or increase the concentration of volatile anesthetic agents in the presence of uterine contractions, and rule out aortocaval compression as a cause of maternal hypotension.

The surgeons should rule out mechanical compression of the umbilical cord by repositioning the fetus and increase the amniotic fluid volume. Placental abruption must also be ruled out. If these initial measures are unsuccessful, fetal resuscitation medications (e.g., epinephrine, atropine) should be administered to the fetus via the intramuscular route. Fetal resuscitation may also include the administration of crystalloid or blood products and the performance of chest compressions (27,28).

Conclusion

A wide range of maternal–fetal interventions are being performed across fetal therapy centers worldwide, and the anesthetic techniques have evolved over the years. Maternal safety is paramount, and the risks to the mother must be balanced against benefits to the fetus. The anesthesiologist plays a critical role and should be involved at all levels in these multidisciplinary maternal–fetal interventions. Anesthetic management should focus on maintaining adequate uteroplacental blood flow, optimizing surgical conditions, and minimizing maternal and fetal risk.

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"BUILDING COLLABORATIVE ENVIRONMENT FOR WORKPLACE SUCCESS."

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Abstract

The foundation of any successful institution is teamwork. Improved performance, a more engaged staff, and elevated levels of trust are observed in collaborative workplaces. Establishing a collaborative environment among medical experts is crucial in the medical sector to ensure organizational success and effective patient care. The dynamics of teamwork in healthcare environments are challenging, with a special emphasis on interactions among leaders and employees. This evaluation assesses and improves collaboration dynamics among healthcare professionals by introducing the DISC (Desired Outcome, Outputs, Process and Enablers) assessment framework. This framework classifies individuals into distinct personality types: Dominant, Outstanding, Supportive and Cautious.

Inspired by number of personality typologies, such as the well-known 4 Bird Personality Test with its dove, owl, peacock and eagle archetypes, the DISC evaluation adds further archetypes to its repertory of characters. The afore-mentioned supplementary personas offer refined perspectives on personal inclinations and modes of communication in healthcare groups. To get a better idea of how the birds cooperate, you can mix and match the afore-mentioned categories. Although, the data that comes out of it should be used as a reference to assist us in making improvements to our life in light of the conclusions.

Healthcare leaders can customize tactics to foster productive collaboration by utilizing the unique qualities of each personality type and the traits that go along with them. The DISC evaluation is investigated in the application approach to promoting a collaborative culture among healthcare teams through case studies and useful insights. At the end, this strategy leads to better patients' care outcomes, staff satisfaction and organizational success.

Key Words: *DISC bird personality test, collaborative environment, workplace success.*

Introduction

In the dynamic realm of healthcare, where patients' outcomes hinge upon the seamless collaboration of multidisciplinary teams, the significance of effective communication and teamwork cannot be overstated. Moreover, what communication means, is the imparting or exchanging of information by speaking, writing or using some other medium. Beyond the conventional metrics of success, such as clinical outcomes and financial performance, the quality of interactions among healthcare professionals profoundly impacts the overall patients' experience and organizational resilience. Recognizing the pivotal role of collaboration dynamics in shaping healthcare

delivery, this article delves into the intricacies of communication styles and their implications for fostering a collaborative environment in healthcare settings. However, the importance of communication extends far beyond its impact on patients' care alone - it serves as the linchpin for workplace collaboration, employee engagement and organizational success(1,2).

Communication Styles and Perception

Effective communication transcends mere transmission of information, it encompasses the intricate interplay between intention and perception. While individuals may have clear intentions behind their communication, how their messages are perceived by others can vary significantly.

Perception, in this context, refers to the way others interpret and make sense of our communication, often influenced by factors such as personal experiences, cultural backgrounds, and preconceived notions (3).

Understanding the gap between intention and perception is essential for navigating communication challenges and fostering effective collaboration within healthcare teams. Communication failure is the first cause for medication errors, delays in treatment and wrong-site surgeries, and second cause for operative and postoperative events and fatal falls.

For instance: A healthcare leader may intend to provide constructive feedback to a team member to drive performance improvement. However, if the recipient perceives the feedback as criticism or a personal attack, the intended message may be lost, leading to miscommunication and potential discord within the team (2,3).

Similarly, a team member may express concerns about a proposed treatment plan during a multidisciplinary meeting, intending to ensure patient's safety and well-being. However, if colleagues perceive the feedback as resistance or defiance, it may hinder open dialogue and collaboration, impeding the decision-making process (3).

By acknowledging the role of perception in communication, healthcare professionals can strive to bridge the gap between intention and interpretation, fostering a culture of transparency, empathy and mutual understanding. Through active listening, clarifying intentions and seeking feedback, teams can mitigate misunderstandings, enhance communication effectiveness, and cultivate a supportive work environment conducive to collaboration and success.

By incorporating the concepts of perception and intention into the discussion of communication styles, we deepen our understanding of the complexities inherent in healthcare communication and highlight strategies for promoting effective collaboration (4).

Communication and Collaboration in Healthcare

Communication lies at the heart of healthcare delivery, serving as the conduit through which information flows, decisions are made and care is coordinated. In the context of collaborative healthcare environments, effective communication extends beyond mere exchange of information to encompass active listening, empathy and mutual respect among team members. However, the inherent complexities of healthcare, characterized by diverse roles, hierarchical structures

and time constraints, often pose significant challenges to seamless collaboration. Factors such as communication breakdowns, hierarchical barriers and conflicting priorities, can hinder the cohesive functioning of healthcare teams, compromising patient safety and care quality (1,2,4).

Introduction to DISC Evaluation

Enter the DISC (Dominance (D), Influence (I), Steadiness (S) and Conscientiousness (C)) evaluation framework, a systematic approach to assessing and optimizing collaboration dynamics among healthcare professionals. Rooted in the principles of organizational psychology and behavioral science, the DISC framework offers a nuanced understanding of individual communication styles and their implications for team dynamics. By categorizing individuals into distinct personality types - Dominant, Influence, Steadiness and Conscientiousness - the DISC evaluation provides valuable insights into interpersonal interactions, decision-making processes and leadership styles within healthcare teams (5,6).

Application of DISC Evaluation in Healthcare

Armed with insights from the DISC evaluation, healthcare leaders can devise tailored strategies to enhance collaboration, optimize team performance and improve patients' outcomes. By leveraging the unique strengths and communication styles of each personality type, healthcare teams can overcome barriers to effective communication and foster a culture of trust, respect, and innovation. Whether navigating complex clinical scenarios, resolving conflicts or driving quality improvement initiatives, the DISC framework serves as a guiding compass for promoting synergy and collective success in healthcare environments (6,7).

Comparison with Bird Personality Test

Drawing inspiration from established personality typologies like the Bird Personality Test, the DISC evaluation expands upon traditional archetypes to offer a more nuanced understanding of communication preferences in healthcare contexts. While the Bird Personality Test provides a foundational framework based on dove, owl, parrot and eagle archetypes, the DISC evaluation introduces supplementary personas tailored to the intricacies of healthcare settings. By incorporating diverse perspectives and refining existing typologies, the DISC framework enriches our understanding of communication dynamics and interpersonal relationships within healthcare teams (5,7).

Integration of DISC Assessment Test

DISC assessment test helps us:

- Understanding our behavior and communication preference,
- Measures behavior – a person's manner of doing things,
- It uses observable language – based on behaviors,
- NO right – NO wrong – NO best style (It use neutral language).

This test categorizes individuals into four primary personality types: Dominance (D), Influence (I), Steadiness (S) and Conscientiousness (C), each with distinct communication preferences and behavioral tendencies. All styles are positive and contribute in meaningful ways. Each style possesses unique strength and capabilities. We have the capacity to adapt to different situations and there is no need to change the core essence of who we are. All people exhibit all four-DISC styles in varying degrees of intensity.

Aligning the DISC assessment with the characteristics of the bird personas identified in the DISC evaluation provides a comprehensive framework for understanding communication dynamics in healthcare teams.

For example: Individuals exhibiting traits of the "Dominance" personality type in the DISC assessment may align with the "Eagle" persona in the DISC evaluation, characterized by assertiveness, direct communication and a focus on results. Eagle motto is "Be brief, be bright and be gone!"

Similarly, individuals with traits of the "Influence" personality type in the DISC assessment may resonate with the "Parrot" persona in the DISC evaluation, known for their sociability, enthusiasm and preference for verbal communication. Parrot motto is "Anything is possible!"

Those displaying traits of the "Steadiness" personality type in the DISC assessment may correspond to the "Dove" persona in the DISC evaluation, characterized by their supportive nature, preference for harmony and emphasis on relationships. The dove's motto is "Be the glue that holds people & projects together!"

Lastly, individuals demonstrating traits of the "Conscientiousness" personality type in the DISC assessment may align with the "Owl" persona in the DISC evaluation, known for their analytical thinking, attention to details and preference for structured communication. Owl motto is "Get it right with precision, data and details!"

By integrating the DISC assessment test with the DISC evaluation, healthcare leaders gain deeper insights into the diverse communication styles present within their teams. This holistic approach facilitates tailored communication strategies, promotes understanding among team members, and fosters a collaborative culture that enhances patients' care outcomes.

With this integration, we can further enrich our understanding of communication styles within healthcare teams and provide a more comprehensive framework for promoting collaboration and effective teamwork (7-10).

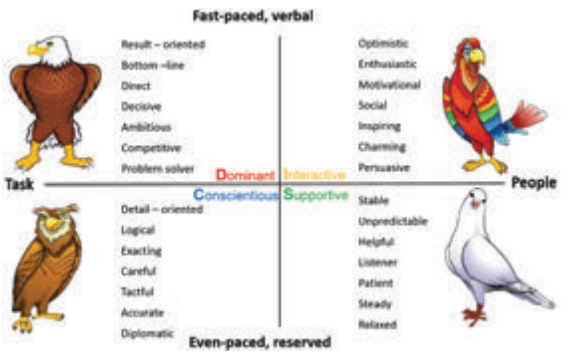

Figure 1. DISC test styles.

Case Studies and Insights

Through real-world case studies and empirical research, the transformative impact of the DISC evaluation on healthcare collaboration comes to light. From academic medical centers to community clinics, organizations across the healthcare spectrum have witnessed tangible benefits from implementing DISC-inspired strategies. By fostering open dialogue, cultivating psychological safety and promoting inclusive decision-making, healthcare teams have achieved remarkable improvements in care coordination, staff engagement and patients' satisfaction. These success stories underscore the potential of the DISC framework to drive meaningful change and build collaborative environment for workplace success and elevate the standard of care in healthcare delivery. Coworkers who effectively manage their own emotions (self-awareness) and reactions to the emotions of others (self-regulation) demonstrate better clinical outcome, greater professional satisfaction, increased empathy, improved teamwork within health care organization. BIny Harvard PhD thesis of emotional intelligence is found out that EI is responsible for 58% of professional success, regardless of job category (8,9).

Conclusion

In conclusion, the journey towards a collaborative healthcare workplace begins with a deep understanding of communication dynamics and their implications for teamwork and patients' care. By embracing the principles of the DISC evaluation and leveraging the diversity of communication styles within healthcare teams, organizations can cultivate an environment where collaboration thrives, innovation flourishes and patients' outcomes excel. As we navigate the evolving landscape of healthcare delivery, let us harness the power of effective communication to forge a path towards excellence, compassion and resilience in patients' care.

The golden rule for effective communication is "Treat others as you want to be treated." The home rule is "Treat others as they need to be treated.", because, we are more likely to get our needs met when those around us get their needs met.

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ECHOCARDIOGRAPHIC INSIGHTS OF WEANING FAILURE: PREDICTION & PERSPECTIVES

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Abstract

It has been reported that around 20-30% of mechanically ventilated patients will develop weaning failure. Since the causes of weaning failure could be diverse, a structured ABCDE approach was developed in order to deal successfully with such patients. Cardiac dysfunction as a reason for weaning failure will be discussed in this article, as well as the role of point of care echocardiography in detection and treatment guidance. Regarding the process of switching patients from positive pressure ventilation to spontaneous breathing, few cardiopulmonary interactions occur with potential of failing especially in patients with cardiac and pulmonary comorbidities. It is well known that in every patient with cardiac dysfunction the level of SvO2 is expected to be lower than 50%. Systolic disfunction is less frequent cause of weaning failure and could be diagnosed by simple measurement of MAPSE or LV FAC. On the contrary, diastolic dysfunction is the leading cause for weaning failure from cardiac origin precipitated by the elevating of preload and afterload by the spontaneous respiration. Diastolic disfunction could be easily assessed by measuring the E/A ratio using transmitral PW Doppler and measuring e' using septal tissue doppler. Calculation of E/e' ratio produces a value of Left Atrial Pressure (LAP) which could be converted in Pulmonary Capillary Wedge Pressure (PCWP) by using the equitation of Nageh. Measuring a high E wave, low e' wave and a higher E/e' ratio were strongly associated to a diastolic disfunction in a patient that was difficult to wean. Performing echocardiography before and during a spontaneous breathing trial should be a mainstay for ruling out the weaning failure risk because of cardiac dysfunction. Higher values for E/e' showing high left ventricular filling pressures in patients who are difficult to wean suggest that diastolic dysfunction lies in the essence of weaning failure.

Key Words: *Diastolic disfunction , Point of Care Echocardiography, Weaning Failure.*

Introduction

Weaning failure has been defined as an experiencing spontaneous breathing trial failure or a need of reintubation within 48 hours of an extubation a previously mechanically ventilated patient (1). Regardless the cause weaning failure has been associated with significant morbidity and mortality related to long lasting positive pressure mechanical ventilation (2). Weaning failure etiology could be diverse and in most of the cases multifactorial including different pathophysiological pathways that disable the patient to be weaned off successfully.

Since termination of positive pressure ventilation and transition to spontaneous breathing initiates complex physiologic cardio-pulmonary interactions while reaching homeostasis, this could be a source of multiple cardiac disturbances in patients with already known or not yet established diagnosis of underlying cardiac disease. Termination of mechanical ventilation leads to a greater right ventricular preload while negative intrathoracic pressures at the end of inspiration generate greater left ventricular afterload. Both, elevated preload and afterload with the increased sympathetic activity and work of breathing lead to significantly greater myocardial oxygen consumption due to the need of increased contractility as a response to the myocardial stretch. Increased preload and afterload in combination with increased work of breathing could lead to marked elevation of pulmonary artery occlusion pressure clinically manifesting as a Weaning Induced Pulmonary Oedema (WiPO). All physiological happenings which are demanded by the switch of positive pressure ventilation to spontaneous breathing are compared to an exercise stress test for the cardiovascular system by Pinsky MR. et al. (3). Despite many pathophysiological events that could be involved in the development of weaning failure, so far, the central role plays the elevation of the preload and the afterload initiated by the negative intrathoracic pressure which could have deleterious effects over the previously diseased heart which myocardium is not ready to meet the body needs.

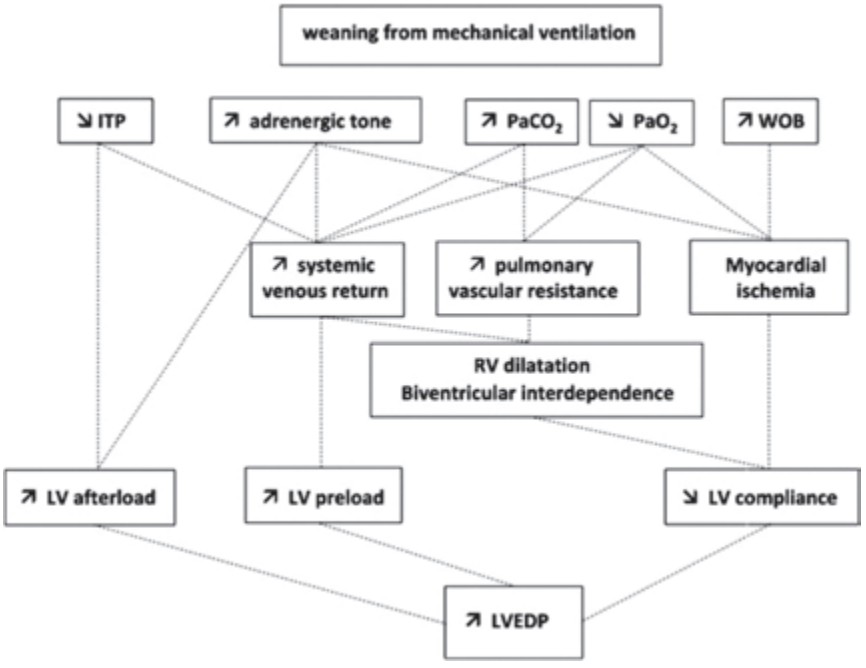

Figure 1. Pathophysiology of weaning failure.

Regarding the cause of weaning failure, many studies highlight the importance of cardiac competence and existing cardiac diseases as a main reason why some patients are difficult to wean, and others are not. Therefore, according to Boles JM et al. cardiovascular dysfunction is a leading cause for weaning failure (1), while in 42% of all patients that failed to be weaned properly, heart failure was found to be the underlying cause (4). Evidence for WiPO was found in 59% of the patients in the study of Liu J. et al. where cardiac comorbidities and COPD were identified as an independent risk factor (5). Despite comorbidities, Liu J et al. has identified that the presence of negative passive leg raising test was associated to development of WiPO (8) which means that positive hydration balance in critically ill patients contributes to developing weaning failure.

Establishing a WiPO diagnosis demands right heart catheterization, in order Pulmonary Artery Occlusion Pressure to be assessed and measured, and values above 18mmHg are considered as a cut off value in terms of confirming the diagnosis (6). Nowadays, WiPO has been diagnosed non-invasively using transthoracic echocardiography, cardiac biomarkers and measuring extravascular lung water. Therefore, critical care echocardiography and lung ultrasound are the mainstay in diagnosing the cause and mechanism of weaning failure. According to Teboul JL., assessment of LV diastolic function is far more important than LV systolic function when talking about the cardiac origin of weaning failure (7) appointing the importance of preserved left ventricular compliance as a key to successful transition from positive pressure ventilation to a spontaneous breathing. Assessment of LV diastolic function could be easily done in 4 chamber view of the heart with measuring the transmitral Pulse Wave Doppler velocity, where we can distinguish two waves: E (early diastole) and A (atrial kick). The first, E wave is important when assessing diastolic function in combination with E' or e' which are measured using Tissue Doppler, measuring these variables at the level of the mitral ring at lateral and septal position respectively.

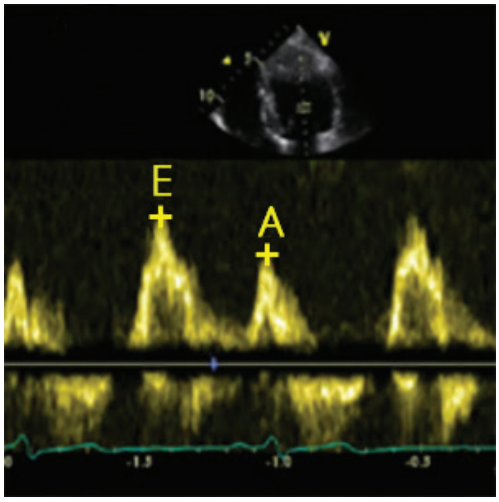

Figure 2. Assessment of transmitral flow and measuring E (early diastole) & A (atrial kick).

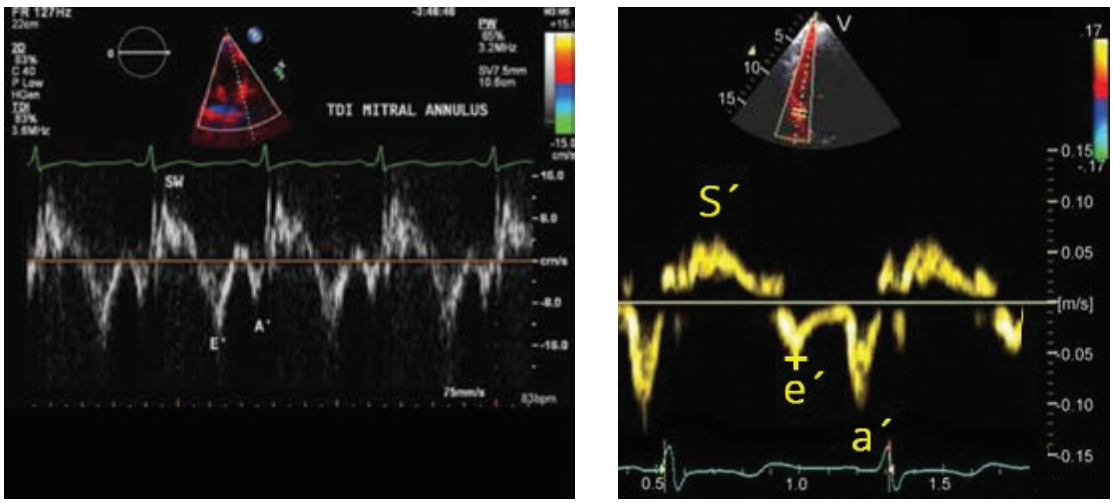

Figure 3 and 4. Tissue Doppler trace of lateral E' and septal e'.

According to the literature, measuring the E/E' and E/e' indexes is useful in assessment of LV filling pressures. E/E' is considered as normal when the values measured are below 8 which is confirming PAOP lesser than 18mmHg (8). Therefore, higher values for E/E' and E/e' indexes suggest higher LV filling pressures and LV diastolic dysfunction. Patients exhibiting a higher E/E' before the beginning of the weaning, or with incremental trend during the spontaneous breathing trial, will develop weaning failure (9,10). In the metanalysis of Almeida CA it was confirmed that higher baseline levels of E/E' before weaning starts, as well as developing higher E/E' indexes during the weaning process, were strongly associated with weaning failure (11). Since values of E/E' and E/e' represent the left ventricular filling pressures in terms of interpretation of the results of the above mentioned metanalysis increased left ventricular filling pressures suggest existing a non-compliant ventricle which stiffness could be a limitation for successful weaning. Increasing the velocity of E' during weaning process has shown association with successful weaning, while the lack of improvement of E' was associated with weaning failure (12). Hence, serial transthoracic echocardiographic exams should be performed in order to follow trending of the E' as a surrogate of left ventricular relaxation capability in terms of cardiac performance during weaning. Measurement of E' and E/E' in a time framework obviously could assess patient's readiness for weaning, as well as to predict development of its failure. De-novo wall motion abnormalities, as well as increasing of the already existing or de-novo developed mitral regurgitation, were found in patients where cardiac ischemia was present, and were identified as the underlying cause for weaning failure (13). Serial echocardiographic assessment of cardiac function was recommended in terms of screening and early diagnosis of weaning failure. The baseline examination should be done prior the start of the spontaneous breathing test, and the second examination should be performed in 15-30 minutes after starting the spontaneous breathing test (14) having in mind that cardiac failure as a reason for weaning failure will be met early on or immediately after starting spontaneous breathing test. One study has compared the modes of weaning and the frequency of weaning failure where particular modes were used, and they concluded that PSV+PEEP was superior mode of weaning versus PSV+ZEEP and T-peace in terms of weaning failure incidence. PSV+ZEEP is a better mode than T-peace, while T-peace was found to be the most associated ventilation mode with weaning failure by cardiac origin (4).

Weaning failure was more strongly associated with diastolic dysfunction rather than LV systolic function (15). Therefore, weaning failure was met in patients with higher E/e' indexes, higher E wave and lower e' wave which suggest myocardial stiffness. Elevating the values for E/e' but not E/A, was associated with weaning failure (11) which means that high left ventricular filling pressures as a result of myocardial stiffness play a crucial role in unsuccessful weaning. The importance of the diastolic function in successful weaning was once again elaborated in a study where dobutamine stress test was performed in patients difficult to wean and has revealed elevating the E/E' in those patients who failed to wean but did not change in patients where weaning was successful (16). Isolated diastolic dysfunction was more frequent in patients with weaning failure in comparison to ones with systolic dysfunction. Again, greater E/e' index as well as lowering the e' were identified to be associated with weaning failure as a sign of diastolic incompetence of the left ventricle (17).

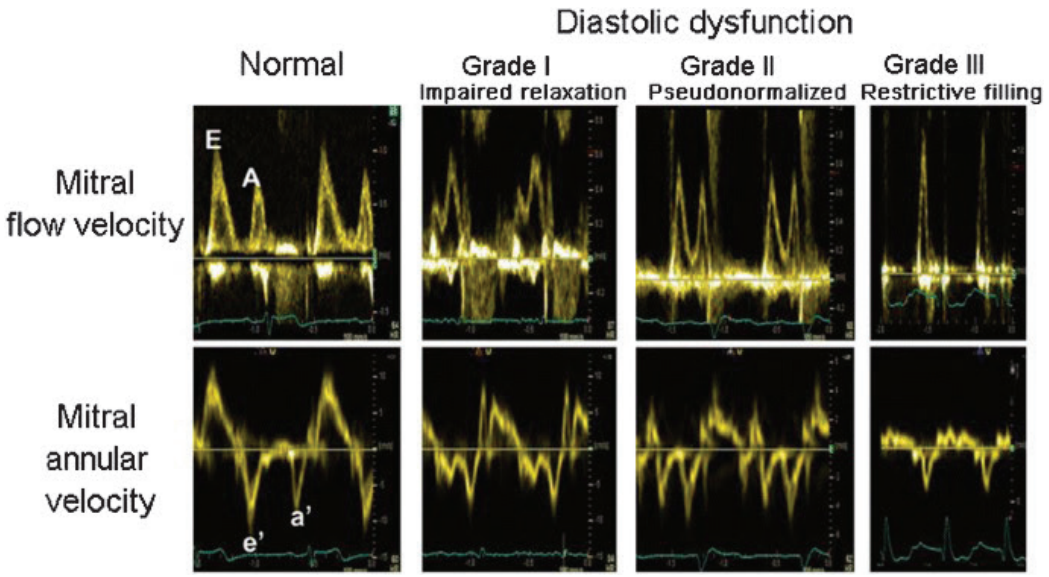

Figure 5. Doppler tracing in different stages of diastolic disfunction.

According to the all above-mentioned statements, performing a Point of Care Echocardiographic examination should be done before starting weaning due to risk detection and stratification which appoints the predictable power of estimated E/E', E/e' and E/A, but also during the spontaneous breathing trial where patients with silent diastolic disfunction will develop greater values for E/E' and E/e' due to lowering of E' and e' which will reveal myocardial stiffness and incompetence of the left ventricle to be as compliant as needed. Performing an echocardiographic examination after unsuccessful weaning will definitely help in confirming the diagnosis if there is underlying cause of cardiac origin.

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PSYCHOLOGICAL AND SOCIAL INFLUENCE OF IDIOPATHIC SCOLIOSIS ON ADOLESCENTS AND THEIR CAREGIVERS

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Abstract

Introduction: Adolescent idiopathic scoliosis (AIS) is a lateral curvature of the spine greater than 10° in children aged 10-18 years. The deformity may progress severely during adolescent development and if the curve is greater than 45°, an operative treatment should be considered. This condition is accompanied by cosmetic deformity and dissatisfaction of adolescents with their own body image, which results in changes in their mental health and lifestyle. In addition, family functioning and the emergence of parental anxiety and depression may be affected after a child is diagnosed with a chronic health condition.

Objective: Recognition of mental health disorders in the patients and their parents in order to take appropriate measures that would improve the outcome of AIS treatment.

Method: Research was performed, using available databases, including PubMed and Google Scholar, to capture relevant research published covering AIS.

Results: Adolescents with scoliosis may show a less positive outlook on life, suffer from lower self-esteem, and have difficulty relating to peers. However, there is conflicting evidence whether the different stages of treatment, such as observation, bracing or surgery, affect the long-term psychological effect of scoliosis. Parents' depression and anxiety were closely related to their children's depression and anxiety. The parents face challenges such as acquiring adequate knowledge about scoliosis, participating in decisions about the type of treatment and managing their child undergoing invasive spine surgery.

Conclusion: Psychosocial support is a key component in promoting better outcomes in adolescents as they cope with the challenges associated with idiopathic scoliosis. Providing parents with adequate information and resources on how to support their child can alleviate some of the emotional burden they experience.

Key Words: *adolescent idiopathic scoliosis, mental health, parents, quality of life.*

Introduction

The purpose of this lecture is to systematically review the experiences of adolescents diagnosed with adolescent idiopathic scoliosis and the experiences of their parents in order to understand their needs and concerns, related to health care, as well as to assist health professionals in sup-

porting patients and their parents.

Definition

Scoliosis is a complex three-dimensional deformity of the spine, characterized by a lateral deviation of at least 10 degrees, with rotation of the vertebrae, and it is usually associated with a reduction of the normal kyphosis curvature of the spine (hypokyphosis) (1,2).

It can be divided in congenital, neuromuscular and idiopathic. Idiopathic scoliosis is classified as:

- Infantile (0-3 years),
- Juvenile (3-10 years).
- Adolescent (10-19 years) (AIS). (1)

Adolescent idiopathic scoliosis is the most common type of idiopathic scoliosis and occurs in 85% of the cases, predominantly in female children in a 3:1 ratio compared to male children. During growth, this ratio increases to 9:1.

The causes of adolescent idiopathic scoliosis are unknown. Current data suggest a multifactorial pathogenesis. There is often evidence of a positive family history. Such data indicate that there is a genetic predisposition. Other factors that can affect the occurrence of AIS are metabolic, hormonal and biomechanical disorders (3, 4, 5).

The **diagnosis** is established by X-ray imaging in the posterior-anterior position (Figure 1).

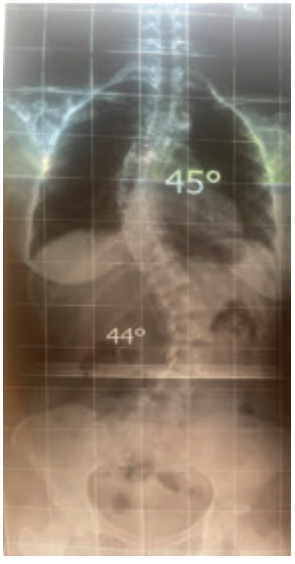

Figure 1.

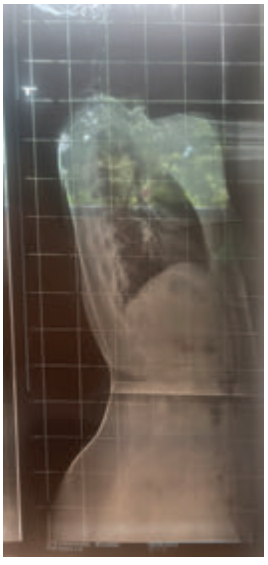

Figure 2.

To measure the degree of the curve, the Cobb method is used. The Cobb angle is known as the gold standard when it comes to diagnosing and evaluating scoliosis. It is determined by drawing lines from the upper and lower parts of the most inclined vertebrae of the curve, and the resulting angle is expressed in degrees. Standardized lateral radiography is performed to evaluate

any sagittal abnormality (Figure 2). A bending X-ray is performed to assess the flexibility of the curve and spine (Figures 3,4).

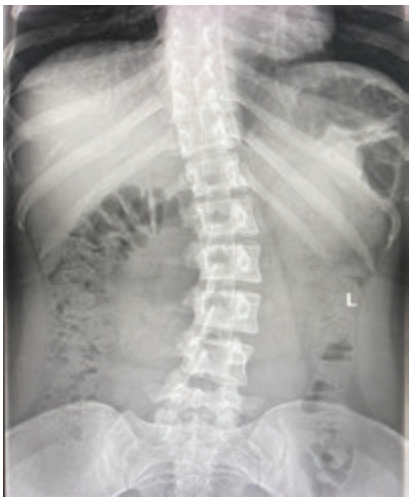

Figure 3.

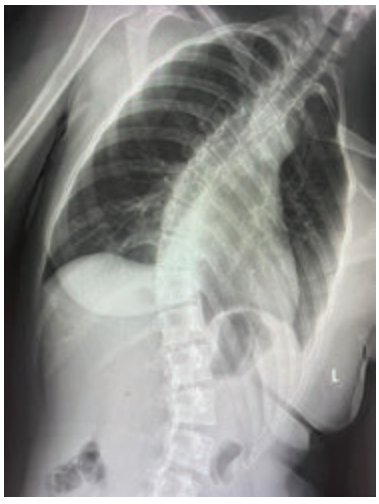

Figure 4.

The main options for the **treatment** of scoliosis are:

Observation and physical therapy (physiotherapeutic scoliosis-specific exercises (PSSE) - curves less than 25 degrees,

Orthosis (bracing) - curves between 25 and40 degrees,

Operative treatment - curves greater than 45 (40) degrees (5.6).

The choice of the best treatment is based on the maturity of the patient (age, menarcheal status), location and magnitude of the curve, severity and risk of curve progression (6). The goals of conservative treatment, from observation to bracing and physiotherapeutic scoliosis-specific exercises (PSSE), have been accordingly adapted in order to control curve progression, to avoid surgery, and to prevent or treat respiratory dysfunction (7,8). Conservative treatment can give results only if it is started immediately after the diagnosis if the diagnosed scoliosis manifests itself with a curve less than 25-35 degrees and if the patient is in the growth phase. If the growth is complete, the application of the corset does not give results (9).

Adolescent idiopathic scoliosis (AIS) involves a high possibility of progression, primarily in girls during the rapid growth spurt in puberty (9). If the curvature continues to progress more than 40 degrees despite the application of appropriate exercises and orthosis, surgery is required (10). When untreated, idiopathic scoliosis can lead to severe trunk deformities, which can limit the general quality of life and wellbeing of adolescents with idiopathic scoliosis (11). However, regardless of the treatment prescribed, in the current literature there is a critical threshold between 30° and 50° associated with a high risk of long-term curve progression (12). Curves greater than 50 degrees in thoracic region and greater than 30 degrees in lumbar region progress at a rate of 0.5 to 1 degree per year into adulthood. Curves greater than 60 degrees can lead to pulmonary functional deficit. Therefore, once the disease is recognized, effective treatment should be instituted to address the deformity and prevention of its long-term clinical problems (5,13,14).

Impact of AIS on Mental Health

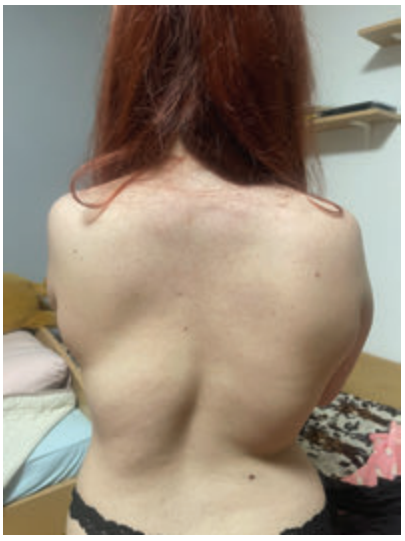

Figure 5.

The first change that most of the patients notice is body deformity. This may be a perception of asymmetry in the shoulders, waist, chest or ribs (Figure 5).

Breast asymmetry may be the first thing female patients notice. Pure body image can negatively affect patients' mental health, resulting in anxiety and depression (15). Basic reasons that lead to changes in mental health are the following (experience of the patients with AIS) (19):

Fear of the unknown.

Large number of adolescents who have been diagnosed with scoliosis are hearing about it for the first time, which causes great fear about the way they will continue to live and their future. "When I was first diagnosed, I had never heard of scoliosis so a lot of my anxiety came from the fear of the unknown, I didn't know what my future would look like, and it was terrifying. Nowadays, it's much better and with social media and the Internet being more accessible, it's easy to see that many people live full lives with scoliosis."

Anxiety of curve progression

AIS is usually diagnosed in early adolescence (10-12 years), usually during a regular school systematic review. During growth, the curve may progress despite therapeutic measures taken, such as exercise and bracing. "I was diagnosed at 14 and I had my surgery at 24. In those 10 years, I struggled a lot with the anxiety that my scoliosis was progressing or would progress in the future. In my early 20s, the anxiety got so bad, that it consumed me".

Anxiety around other people

Fear that someone present may notice the deformity of the adolescent's back or make an unpleasant comment. That's why adolescents tried their best to cover themselves up. "When I was a teenager and my early 20s, I had huge anxiety around other people as I was paranoid that someone would notice my back or say something about it, so I tried my best to cover myself up".

Pre-and post-surgery anxiety

Fear of the extent and invasiveness of the surgical intervention, risk of neural damage. Postoperatively, there is fear of the uncertainty of the postoperative outcome, i.e. whether the spine will fuse - fear of any activities. "I don't know how I got through this period, but I felt like I wasn't in my own body, like it wasn't happening to me. The only way I coped was to read other people's success stories and convince myself I would be ok. But during this time, I felt like my life was on hold, I felt like I couldn't make plans for the future, and I could hardly concentrate on anything". Post surgery anxiety: "I took so many pictures of my back over the first 12 months comparing them, as I was so convinced that my spine had moved, I also measured my height constantly".

Anxiety about the future

Fear of whether they will feel back pain in the future, whether it will worsen, whether a repeat operation will be necessary, concern for the disc under the fusion site. "I worry about my back pain – will it get worse etc., and I also worry about my lower back discs and if I'll need further surgery." (19).

Standardized questionnaires such as the Bad Sobernheim Stress Questionnaire (BSSQ) and the Scoliosis Research Society 22 Questionnaire (SRS-22) (16), as well as the Behavioral Assessment System for Children, Second Edition (BASC-2) were used to assess mental health among adolescents with AIS (17).

The BASC-2 has been administered to more than 1 million children in the United States. It can detect clinical and subclinical levels of psychosocial problems in five domains: school problems, internalizing problems, inattention/ hyperactivity, emotional symptom index and personal adjustment. These questionnaires determined that adolescents with scoliosis might show a less positive outlook on life, suffer from lower self-esteem, and have difficulty connecting with peers. Anxiety is the most common concern of teenagers, with similar intensity as in pediatric cancer and heart transplant patients (16,17,18).

There is conflicting evidence as to whether different stages of treatment, such as observation, wearing a brace or surgical treatment, affect the long-term psychological effect of scoliosis. It was found that 32% of patients with AIS showed significant psychological distress, regardless of the type of treatment (17).

If the patient with AIS is waiting for surgical treatment due to a pronounced deformity of the spine greater than 40 degrees and constant back pain, clinical symptoms and often due to the cosmetic effect of AIS itself, the approach by health professionals and the surgeon must be very

careful because of the pronounced vulnerability of these patients. From previously performed analysis, four key themes have been generated (19).

"Proceeding with caution," describes the adaptation of adolescents to the physical impact of their AIS (not being able to engage in a sport they previously practiced in the future due to strain on the spine). This was demonstrated by an adolescent who recalled attending a school trip where she could not participate to the same level as her peers: "they were doing emm, kind of like bungee jumping and I just chose not to do it because I went rock climbing with them before that and I was in bits after, so I just didn't want to risk it … it looked fun though." (Female, 16).

"Am I different?" captures adolescents' perceptions of their different appearance and visibility of their condition. *Appearance Changes* focuses on adolescents' perceptions of their condition and how it has affected their appearance. "When I was getting out of the shower one day I just kinda noticed in the mirror like, it was kinda odd like, a bump at the lower back and my shoulder blade was kind of gone out a bit […] I had no idea what it was, I thought maybe it could be a tumor or something." (Male, 17). *Hidden Condition* captures how adolescents manage the visibility of their condition. Many adolescents believed their scoliosis was not very noticeable; "I don't think they (peers) notice it, being honest, I never talk to them about it. I think it's just me because I see it every day." (Female, 14). They acknowledged that their scoliosis would be more visible in certain situations such as swimming, wearing tighter or more revealing clothing, or while getting changed for P.E. at school.

"Emotional Journey" captures the *rollercoaster* of emotions from shock at diagnosis to the terrifying realization of the severity of their condition. "I was definitely, my head was spinning a bit, I was thinking about everything that could happen and, just because I wasn't really expecting it to look like that at all, especially seeing the S [curvature on the X-ray]." (Female, 16). While experiencing a rollercoaster of emotions throughout the presurgical period, adolescents could gain some reassurance through realizing they were not alone, so these emotional journeys capture the second subtheme *Not the Only One*. "When you're there you kind of feel like there's other people and there's always someone worse than you and you feel… it's going to be okay like I'm not the only one." (Female, 13). Seeing the results of surgery provided reassurance: "I was actually talking to one girl and I think she got [surgery] when she was like seventeen and it makes you more relaxed when you talk to people, like knowing that you're actually going to be fine after surgery." (Female, 16).

Finally, the concerns and expectations of adolescents about their future surgery are covered by the theme **"No pain, no gain"**, whereby they want to accept the operative treatment and finally leave the surgery behind. "Once I get the surgery done, I feel like I'll be able to get back to normal." (Female, 14) (19).

Parents and close family caregivers may also experience anxiety and depression after their children are diagnosed with a chronic condition. Parents must take on new responsibilities or give up past activities due to the stress of their children's deformities and changes in their mental health (20-23).

The mental health and quality of life of the parents was examined in the same way as in their children using standardized nine-item Patient Health Questionnaire (PHQ-9) and a seven-item Generalized Anxiety Disorder scale (GAD-7). Depression and anxiety in parents are closely related. More than half of the parents diagnosed with possible major depressive disorder (pMDD)

also had pGAD. Depression and anxiety almost always go together because depression tends to be past-oriented, while anxiety is future-oriented (16,20). Parents' depression and anxiety are closely related to their child's depression and anxiety. One of the main causes leading to pMDD in parents is a Cobb angle of the major curve ≥50° in their children, as well as the career/ stress system. Low level of parental education appears to be an independent risk factor for parental pMDD. Low household's income is a risk factor for parental pGAD (16,20).

Common mental disorders (CMDs) such as depression and anxiety can have implications for long-term health outcomes associated with increased fatigue, impaired long-term disease activity and physical disability (16).

In the preoperative period, anxiety and depression in parents are represented in a higher percentage compared to their children. Parents face challenges such as acquiring adequate knowledge about scoliosis to participate in health care decisions and to cope with their child undergoing invasive spine surgery. During this period, their psychological wellbeing can be seriously disturbed and negatively affects the general state of health. Considering parents' experiences and support needs during this anxiety-provoking period is an important step in providing family-centered care and promoting better outcomes for adolescents experiencing AIS (22,23,24).

The level of parental anxiety decreases significantly from the preoperative to the postoperative phase, but it still remains high (21,22,23). Parents view deformity differently from the patient, as they overestimate their child's stress level and have greater concerns and expectations regarding scoliosis surgery. Therefore, it is very important for healthcare professionals treating scoliosis to recognize and address parental CMDs when parents accompany a patient with AIS to see a physician (16,22,24).

Patient's Satisfaction and Quality of Life after Surgery

The primary Cobb angle ranged between 45 and 85, before surgery was significantly reduced. Shoulder imbalance was reported in all patients per operatively, that was absent in all except one patient that had slight elevation of the right shoulder after surgery. All had pelvic tilt before surgery that was absent postoperatively except for two patients who had slight tilt with significant improvement after surgery. Only 1 [5.0%] had postoperative complications (hypovolemic shock).

Patient's satisfaction and quality of life is measured by using the Scoliosis Research Society -22r (SRS-22r, the most recent version) questionnaire after posterior spinal instrumented fusion of AIS. According to these questionaries, patient's satisfaction was measured in five domains: pain, function, self-image, mental health and satisfaction. In all five domains a good outcome was achieved with surgery. Majority of the patients were satisfied with the outcome of the surgery (Figures 5, 6, 7).

Surgical treatment of AIS had the highest probability to achieve better Cobb angle correction with good function and lower complication rate (Figure 8) (25,26).

Surgical treatment of AIS had the highest probability to achieve better Cobb angle correction with good function and lower complication rate (Figure 8) (25,26).

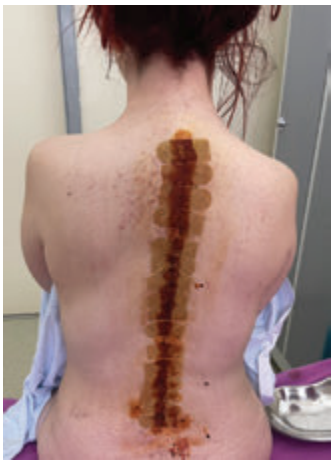

Figure 6.

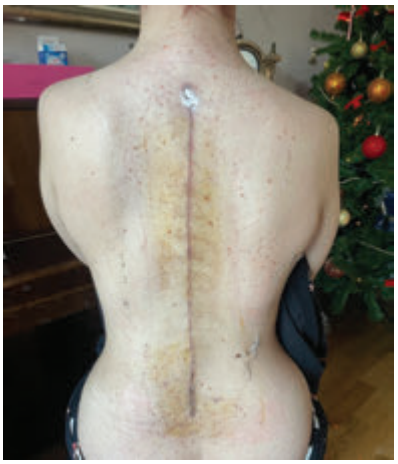

Figure 7.

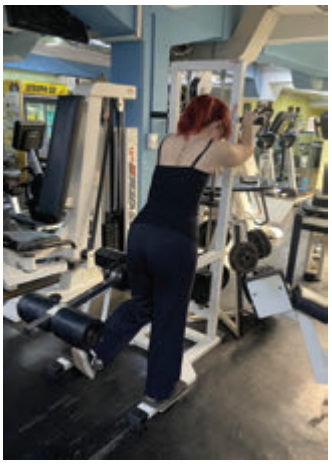

Figure 8.

How to deal with scoliosis anxiety?

Adolescents

- Talk to others in the same boat,
- Exercise to keep strong,
- Accepting scoliosis,
- Supporting others with scoliosis,
- Therapy – especially CBT (Cognitive Behavioral Therapy) can help.

Parents

- Providing parents with adequate information about scoliosis and its treatment, so that they can best support their child;
- Addressing concerns about surgical complications, post-operative pain and how to best support your child before and after surgery;
- Top of Form
- Sharing your own experiences;
- Supporting other families with the same issue.

Abbreviations:

- AIS – Adolescent Idiopathic Scoliosis,
- PSSE - physiotherapeutic scoliosis-specific exercises,
- BSSQ – Bad Sobernheim Stress Questionnaire,
- SRS-22 - Scoliosis Research Society 22 Questionnaire,
- BASC-2 - Behavioral Assessment System for Children, Second Edition,

- PHQ-9 – nine-item Patient Health Questionnaire,
- GAD-7 - seven-item Generalized Anxiety Disorder scale,
- pMDD – possible Major Depressive Disorder,
- CMDs - Common Mental Disorders.

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PEDIATRIC TRACHEOTOMY IN AIRWAY MANAGEMENT- ANESTHESIOLOGY POINT OF VIEW- NARRATIVE REVIEW

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Abstract

There is a wide range of basic and advanced techniques and ways of securing pediatric airways nowadays: from invasive to noninvasive, intubating and non-intubation techniques. The growing number of airway devices on the market is a sign that no device is perfect nor one size fits all. Surgical tracheostomy is a life-saving procedure performed for emergent or expectant airway compromise due to upper airway obstruction or to support the need for prolonged ventilation. Although it is generally thought of as safe, morbidity in the pediatric population is higher than in adults due to smaller operating field, immaturity of tissues, anatomical specificities of the child's neck or presence of craniofacial dysmorphism. In some cases, tracheostomy is also a permanent solution for airway management. According to the literature, indications for tracheostomy in pediatric patients have changed a bit. Pediatric candidates for tracheotomy are few and often burdened by their primary diseases, requiring interdisciplinary planning, timing and preparing for the procedure.

Key Words: *airway management, pediatric anesthesia, surgical tracheotomy*.

** Parts of this text were published in: Curić Radivojević R., Otmačić I., Vukušić I., Šimić I., Prstačić R., Prgomet D. Place for Pediatric Tracheostomy, Anesthesiology Point of View - Our Experience. 1st International Congress of Anesthesiology and Intensive Care – Proceeding. 13 – 15. October 2023. Budva (Montenegro): 222-225.*

Introduction

There is a wide range of basic and advanced techniques and ways of securing pediatric airways nowadays: from invasive to noninvasive, intubating and non-intubation techniques. The growing number of airway devices on the market is a sign that no device is perfect nor one size fits all. Surgical tracheostomy is a life-saving procedure performed for emergent or expectant airway compromise due to upper airway obstruction or to support the need for prolonged ventilation. Although it is generally thought of as safe, morbidity in the pediatric population is higher than in adults due to smaller operating field, immaturity of tissues, anatomical specificities of the child's neck or presence of craniofacial dysmorphism (1-3). In some cases, tracheostomy is also a permanent solution for airway management. According to the literature, indications for tracheostomy in pediatric patients have changed a bit (3-6). Since the introduction of the procedure, it was primarily used for emergency airway management because of the upper airway obstruction primarily by infection origin (e.g. diphtheria or croup, polio). Because of effective vaccination protocols and the widespread use of antibiotics, infectious diseases have become less and less of a concern, and the invention of modern intensive care and therapies in the last

70 years. Instead, tracheotomy is now performed at a younger age because of congenital anomalies of the respiratory tract, prolonged mechanical ventilation and intubation, and airway toilet. Main reasons for prolonged mechanical ventilation in infants nowadays are bronchopulmonary dysplasia in preterm infants and central hypoventilation. Main reasons for airway obstruction are the following: craniofacial abnormalities, congenital or acquired subglottic stenosis, severe tracheomalacia and bilateral vocal cord paralysis (2). In most cases, this procedure is done electively in already intubated patients. But the non-intubated patients with airway compromise pose a significant challenge for the anesthesiologist (2).

At the authors institution (7), a retrospective chart review was performed on pediatric patients who had a tracheostomy during the 5-years study period (between 2018 and July 2023) at University Hospital Centre Zagreb (UHC), Croatia. 50 surgical tracheostomies have been done during that period, in pediatric patients (<18 years old). Majority of indications for tracheostomy were for cardiopulmonary (n= 25; 49%) and neurological disease (n= 13, 25.5%), followed by congenital or acquired airway obstruction (n=8; 15.7%), craniofacial anomalies (n=4, 7.8%) and only 1 case of traumatic injury (2%). All the patients were ASA 3 or more, with more than 2 comorbidities. Some patients simultaneously had more congenital defects: e.g., cardiopulmonary and airway obstruction or craniofacial and neurological disease. Two thirds of the pediatric tracheostomies were performed for children under one year of age, and one-fifth for children under one month of age. 14 (28%) were premature and 10 (20%) had a low birth weight. The age at tracheostomy was younger in patients who had a tracheostomy for airway obstruction, cardiopulmonary or craniofacial anomalies when compared to patients with neurologic impairment or traumatic injury. Ten (20%) out of 50 patients had an emergency tracheotomy. Main reasons for that were impeding upper airway obstruction: 3 of 10 patients could not be intubated, and they were ventilated with 2 hands face mask technique, one was managed by using of supraglottic airway during the tracheostomy. The rest were intubated in the operating room, using a video-laryngoscope. Over the last 5 years, there were no tracheostomy-related deaths (7).

Preoperative Considerations

Assessment and Optimization

Timing of tracheotomy in pediatrics on prolonged mechanical ventilation is still a debate and the practice is different between the centers (5). Obtaining informed consent can sometimes be challenging. Preparing the parents, caregivers in a calm and trustful place, with a simple understandable language, and the time to ask questions is helpful.

Preoperative assessment should be focused on evaluation of the airway and comorbidities. In already intubated patients, information about ease of intubation and indication, course of neonatal intensive care should be reviewed, type and settings of ventilation, cardiopulmonary status, vasopressors ongoing, anticoagulation therapy etc. In non-intubated patients with craniofacial abnormalities, evaluation of the airway is of paramount importance, to formulate an appropriate anesthetic plan and backup plans for airway management with the difficult airway chart in place, including rigid bronchoscope and experienced team in place.

Premedication with sedative agents are contraindicated in non-intubated patients. However, antisialagogues are recommended (2).

Intraoperative Considerations

Elective tracheotomies must be carefully planned in working hours with the experienced team of ENT surgeon (in Croatia) or pediatric surgeon, scrubbed nurses, anesthesiologist and technician familiar with the procedure and caring for the pediatric cases. Surgical equipment must be prepared in the OR before the patient comes, and the whole team members should be present.

Positioning

Traditional positioning for tracheotomy is extended neck with the log roll below the shoulders and the round pillow under the head for stabilization. This is not a problem in adult patients without neck pathology. However, in pediatric patients especially in preterm ones and neonatal patients with short neck, and PVC tube in place, one must weigh the risks of reintubation with the railroaded tube against kinking and obstruction of the tube during the procedure. The authors suggest that the trained person, wearing surgical gloves, holds the tube and the neck extended during the procedure, securing the tube from misplacement and kinking, and that way is ready to remove the tube when the time comes to exchange it with the tracheal cannula (TC). Some centers prefer tape slings over the chin to maintain extension and soft tissue over the trachea (2).

The type of anesthesia depends on the situation, e.g., plan of induction, giving neuromuscular blocking agent or preserving spontaneous ventilation, but preoxygenation and apneic oxygenation is recommended in all cases.

Surgical technique is not a matter of this article and will not be discussed here. However, stay sutures are useful and recommended by the authors, in the smallest patients in case of emergencies in the early postoperative period, before stoma formation.

Tracheostomy Tube Size

Choosing a correct tracheal cannula (TC) is of paramount importance in neonates, since the standard pediatric cannulas will be too long for neonates, with undesirable bronchial placement of the TC. Same size ID TCs, but neonatal are shorter for up to 9mm than pediatric ones and will fit in most of the cases. However, despite mandatory capnography verification of the correct placement, auscultation, fiberoptic verification of the tip above the carina in an unextended neck (neutral position) is recommended by the authors, especially in preterms, or in case of anomalies of the thorax.

Intraoperative complications include airway fire, development of subcutaneous emphysema, pneumothorax, pneumomediastinum, bleeding, recurrent laryngeal nerve injury and slip of the TC into soft tissue outside the airway. Tube position can be quickly checked with a flexible bronchoscope (2.5 OD). For further information about the TC read: Pediatric Tracheostomy Tubes: Recent Developments and Our Current Practice (8).

Postoperative Care

Pediatric airway management does not end in the operating room. The patient is transferred to the intensive care unit. Careful suctioning of the tube is important to prevent clogging because any obstruction can impede oxygenation and ventilation. Stoma care and education about it to parents or caregivers is very important. Meticulous care to secure the TC in place is needed to prevent dislodgement. Backup TC and endotracheal tube need to be at the bedside, if any problems arise.

Tracheostomy Multidisciplinary Team

The importance of a multidisciplinary approach in children with tracheostomies, at every stage, cannot be overstated, from pre-operative discussions to long-term care and eventual decannulation. Patient's safety and tolerance are central to these considerations. Aside from issues of safety, stoma care and ongoing management of airway pathology, many of these children have other physical, medical, developmental, communicational and psychological problems that must be addressed in parallel. Additionally, the long-term impact on their families and other careers should not be overlooked (8).

Greene ZM at all (9) conducted research on education, training, clinical support and confidence of speech-language therapists. Their results showed that most of the speech-language therapists were accessing professional development and receiving expert support and felt confident managing patients with a tracheostomy. However, less than half of them felt up to date about the subject and only 35% felt that they work in an optimal team for tracheostomy management. Authors concluded that speech-language therapists are eager to access further professional development and training.

Furthermore, Hall at all (10) conducted qualitative research with the aim to explore the experience of caring for children with tracheostomies from the perspectives of parents and healthcare professional caregivers. Their findings suggested that there is a need to facilitate further standardization support available for parent caregivers. Potential solutions to be explored could include the development of a pediatric tracheostomy service specification, increasing use of pediatric tracheostomy specialist nurse roles, and addressing the emotional and psychological support needs of caregivers.

Handouts with information and education in case of leaving home with the tube afterwards must be provided. Home kit with spare cannulas, leaflet with information about the TC size, type, date of stoma placement, size of aspirating catheter is recommended, such as the one in the National tracheostomy safety project website: https://tracheostomy.org.uk/storage/files/NTSP_YELLOW_Paeds_Algorithm_Combo_2.pdf) (11).

Tracheotomy and Speech Therapy

Children with tracheostomy have difficulty producing voice due to the changes in airflow that occur when a tracheostomy tube is placed. Because of the lack of sufficient airflow and limited voicing, children with tracheostomy may have speech delays, articulation disorders, phonolog-

ical disorders, as well as difficulty with breathing and speech coordination (12). However, if enough airflow is generated around the tracheostomy tube, those children may have the ability to speak. In a study from Jiang and Morrison (13), a group of children without neurological disorders had normal speech and language development in 60.9% of cases. According to the same authors, achieving earlier decannulation improved the chances of normal speech and language development. Occlusion of the tracheostomy tube is the most effective way to produce voicing with a tracheostomy tube. Occluding the tracheostomy tube can occur with digital occlusion, a speaking valve or capping. Benefits of a speaking valve besides voice include restoring positive airway pressure, improved swallowing, improving secretion management, reducing the risk of aspiration etc. A speaking valve is placed at the end of the tracheostomy tube. It can usually fit any size of tracheostomy tube. Once the valve is placed, air flows in through the tracheostomy tube, and exhaled air flows around the tracheostomy tube, through the vocal folds and out the upper airway for speech (12). Only a trained clinician can determine if it is appropriate and place the valve.

One-way speaking valves have been successfully used to restore speech in adult patients after tracheostomy tube placement. One-way speaking valves can also be used in children after tracheostomy tube placement. Other authors (14) tried to summarize the evidence on the use of one-way tracheostomy tube speaking valves in children and found that most of the literature focused on tolerance of speaking valves but does not provide sufficient evidence regarding the impact of a speaking valve on verbal communication in children. Authors highlight the need for pragmatic and interventional research that can better inform clinical practice in the future.

However, children with tracheostomy who are beginning to use a speaking valve can have difficulties with adjustment to the change in airflow. That is why a wear schedule with increasing time with the valve on and education are important. At the beginning wearing a speaking valve can be frightening for a child because they need to learn how to breathe through the vocal folds and out the upper airway and use their upper airway for speech (12). One way to improve speech in children with tracheostomy is speech therapy. Speech therapists provide a comprehensive assessment of the child's strengths and weaknesses and can work with the family on implementing speaking valves and potentially improving voice, speech and swallowing (12). Some activities like "Songs for Kids with Trachs" can be a fun and distracting way to help improve tolerance. Research has shown that music can have a positive effect on speech development and may reduce anxiety for those on mechanical ventilation (12). Considering the above, speech therapists play an important role in the development of speech when it comes to children with tracheostomy. Therefore, it is important to know if they have enough chances to learn and develop their skills and if they get enough institutional support about that specific subject.

Decannulation

Decannulation must be considered if the indication/ problem and the child's situation has been resolved. However, a staged/ protocolized approach is recommended to avoid unnecessary emergencies. Recently, a group of authors from the German speaking area, Boschen at all (15), proposed an algorithm with diagnostic and therapeutic procedures for a safe and successful decannulation process. In the initial clinical assessment, the following points should be considered:

Outpatient

Assessment of the respiratory status:

- Absence of episodes of hypoxemia or hypoventilation,
- No history of recurrent or severe respiratory infections,
- Sufficient technique to clear airway secretions,
- Respiratory stability during TC changes (as reported by the caregivers),
- A decannulation plan should be in line with other therapeutic objectives (e.g., major surgery, palliative care, complex neurologic or progressive disease),
- No relevant swallowing difficulties.

A. **Functional assessment of the upper airway** to exclude relevant obstruction of the upper airway (using one way speaking valve to TC, speech therapy, swallowing difficulties).

Inpatient

A. **Assessment of ventilation during sleep** (polysomnography with transcutaneous pCO2, recommended).

B. **Endoscopic assessment of the airways**

Flexible laryngo-tracheo-bronchoscopy is recommended before decannulation to assess upper and lower airways. OSAS and significant adenoid/ tonsillar hypertrophy, the suprastomal airway and the bed of TC have to be assessed with preserved spontaneous breathing under light sedation. During the procedure, the TC is temporarily removed and stoma occluded to estimate spontaneous breathing and airway without TC.

As the equipment is not widely distributed in all hospitals, patients should be sent to tertiary centers with the available equipment and personnel.

Modifications of TC (using downsizing or capping of TC after endoscopy done) (15).

Decannulation

For the final decannulation procedure, all children need to be hospitalized. The TC is removed, and the tracheostomy is covered using an airtight seal. Once a stable condition has been confirmed, the patient is discharged home with the permanent taped stoma. The caregiver needs to be equipped with a small TC tube to allow rescue intubation of the shrinking tracheostomy in the outpatient setting. Regular outpatient follow-up visits (approximately every 4 weeks) are scheduled to monitor the patient, to assess shrinking of the tracheostomy and to plan final surgical closure (15).

Conclusion

Although seldom performed, tracheostomy is the procedure of choice in a selected group of pediatric patients. The risks and benefits of the procedure must be weighted-up for each patient.

Attention to details during the procedure and preparation is of utmost importance. Pediatric airway management doesn't end in the operating room, especially as far as the tracheotomy is concerned. Interdisciplinary care, stoma nurses and speech therapists are crucial for patient's and caregivers' education and patient's safety. In proper indications and with adequate preparations, the procedure is safe and effective in managing the airway of pediatric patients. Decannulation has to be considered and performed, if all the proposed diagnostic and therapeutic steps are previously done. In some cases, it is a permanent solution.

Acknowledgment and Author

This article presents the authors' opinion from the clinical practice and does not necessarily present the latest evidence based practice. Since the rarity of the procedure in pediatric cases, randomized control trials are not likely to be done for the majority of stated issues, but we think that they have to be stated out and can contribute to patient safety.

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SHOULD MUSCLE RELAXANT BE USED FOR TRACHEAL INTUBATION IN PEDIATRIC PATIENTS?

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Abstract

Muscle relaxants (MR) nowadays represent the standard for general anesthesia. Succinylcholine (ScH) is the only depolarizing neuromuscular blocking agent considered the gold standard for airway management. Administering rocuronium at a dose ranging from 0.90-1.20mg/kg in anesthetized children induces neuromuscular blockade (NMB) nearly as rapidly and profoundly as ScH at doses of 1-1.5mg/kg. The use of NMBDs is associated with a higher success rate of intubation, facilitating controlled and assisted mechanical ventilation, reducing the required amount of anesthetic agents. Additionally, NMBDs can improve the quality of intubation, reduce airway-associated complications and the incidence of critical respiratory events. To minimize the risk of residual NMB occurrence, monitoring the depth of neuromuscular blockade should be implemented as a minimum monitoring. Tracheal intubation without neuromuscular blocking drugs is alternative technique, but it carries risks, such as hypotension, bradycardia, sinus arrest, asystole and airway damage. Intubation can be difficult or fail, especially in the absence of muscular paralysis (26.9%). A recent meta-analysis, that included 1,651 ASA I-II participants, demonstrated that during light-to-moderate depth of anesthesia, the use of NMBDs can improve the quality of intubation conditions (excellent: 76%, $p<0.001$; acceptable: 68%, $p<0.001$) and it was associated with better hemodynamic stability, a smaller reduction in blood pressure and heart rate, as well as a lower incidence of arrhythmias during induction of anesthesia. With the use of NMBDs, during intubation itself, there were fewer failed first-pass attempts (1.6%vs7.5%; $p<0.0001$), fewer closing/ closed vocal cords (3.7%vs11.1%; $p<0.0001$), and fewer unacceptable conditions (7.0%vs20.1%; $p<0.0001$). NMBDs reduce the amount of anesthetic needed, leading to fewer side effects and faster recovery of consciousness. Avoidance of NMBDs never improves the quality of intubation and is associated with a higher incidence of failed first intubation attempts (30-37%) and respiratory adverse events (30-33%). Adapting practice by carefully selecting NMBDs, monitoring NMB and properly using reversal agents, represent essential measures to prevent complications.

Should Muscle Relaxant be Used for Tracheal Intubation in Pediatric Patients?

Muscle relaxants (MR) nowadays represent the standard for general anesthesia. Over the years, they have found a suitable place both with adults and children. Based on earlier understandings, some practitioners were apprehensive about using muscle relaxants in younger children, but with this knowledge, we can safely engage in it. In frequent clinical practice with children, there are main clinical questions related to non-depolarizing neuromuscular blocking drugs (NMBDs): Are NMBDs necessary to facilitate tracheal intubations in pediatric patients? Does the intensity of NM blockade influence a patient's outcome? What are the strategies for the diagnosis and treatment of residual paralysis?

The technological advances aimed at improving ventilation in pediatric anesthesia have been hindered by several factors. These include limitations in the choice of airway devices and the use of ventilators that are not specifically adapted to the respiratory physiology of young children (1). Current evidence-based lung ventilation strategies promoted in adult anesthesia may be useful in children (2). A significant advancement has been achieved through the Anesthesia Practice In Children Observational Trial (APRICOT), a large multicentric European observational study conducted across 33 countries and involving 261 institutions. The study reported a high incidence of critical respiratory events in different age groups. During this observation, young age, medical history, presence of airway hypersensitivity and medical condition (ASA physical status) were identified as independent risk factors for these events (3)

Succinylcholine (ScH) is the only depolarizing neuromuscular blocking agent in clinical use and is considered the gold standard for airway management due to its advantages: onset in less than 1 minute, approximately 5 minutes duration, and no need for reversal. Elimination depends on hydrolysis by butyrylcholinesterase (also known as plasma cholinesterase or pseudocholinesterase). The indications for ScH use are very clear: rapid sequence inductions, difficult airways, trauma and treatment of laryngospasm. Contraindications, therefore conditions in which ScH should not be used, include the risk of malignant hyperthermia, burns, spinal cord injuries, hyperkalemia or myopathic conditions (4,5). Rocuronium at a dose greater than 0.9mg/kg presents a viable alternative to succinylcholine. Administering rocuronium at a dose ranging from 0.90 to 1.20mg/kg in anesthetized children, induces neuromuscular blockade (NMB) nearly as rapidly and profoundly as ScH at doses of 1-1.5mg/kg. However, this comes with the trade-off of prolonged recovery. Lower doses administered during light or moderate anesthesia provide adequate conditions with minimal potential for adverse effects, even for short procedures. Additionally, in conditions involving sevoflurane anesthesia, small amounts of rocuronium (0.15-0.30mg/kg) are suitable for improving intubation. This occurs through potentiation of the muscular-blocking effect during sevoflurane administration and reversal of this potentiation upon withdrawal of sevoflurane (6). The use of NMBDs is associated with a higher success rate of intubation, facilitating controlled and assisted mechanical ventilation, and also reducing the amount of anesthetic agents required. Additionally, NMBDs can improve the quality of intubation and reduce airway-associated complications, as well as the incidence of critical respiratory events, especially when airway instrumentation is performed at inadequate levels of anesthesia. In the long-term, they contribute to the improvement of surgical conditions and facilitate the development of various surgical techniques, including laparoscopy (7–9).

The physiological factors of pediatric patients differ from those of adults in certain pharmacokinetic and pharmacodynamic characteristics. Effective use of NMBDs in pediatric practice requires understanding of fundamental differences in responses. The immaturity of the neuromuscular junction manifests in inadequate formation and number of acetylcholine receptors, as well as in the synthesis of acetylcholine. The relatively high cardiac output in infants and children results in faster circulation times, facilitating rapid transfer of NMBDs to and from their sites of action. The relatively high volume of extracellular fluid in infants and children corresponds to an increased volume of distribution of NMBDs and influences dose requirements. After infancy, maturational changes in sensitivity are complete, and the response of a child becomes similar to that of an adult. However, because maturational changes in certain of these characteristics counterbalance, dosing requirements do not differ markedly with age. In general, onset is more rapid in pediatric patients. Dose-response studies suggest that infants require at least 3mg/kg and children - 2mg/kg of succinylcholine to reliably achieve conditions suitable for intubation. The duration of action of these doses is about the same or somewhat less than that of the standard 1mg/kg intubating dose in adults (6–8 min). If an intravenous (i.v.) line is not available, succinylcholine may be administered via intramuscular (i.m.) injection. In this case, doses of 5mg/kg for infants and 4mg/kg for children are required to produce 85–100% twitch depression. Maximum block is achieved in 3–4 minutes and lasts for about 15–20 minutes (10,11). What is it that discouraged practitioners from using NMBDs decades ago? The initial motivation was to avoid ScH, especially after halothane induction, or to avoid relatively long-acting muscle relaxants for short surgical procedures, due to possible anaphylactic reactions (12).

One of the numerous challenges during the perioperative period in children is managing difficult airways. Airway difficulties are common in young children, who are more prone to hypoxemia (13) because of a decrease in their functional residual capacity.

Hypoxemia during apnea develops earlier and progresses faster in children than in adults. Preoxygenation significantly delays the onset of dangerous desaturation in all age groups, although the rapid denitrogenating process in very young children, due to their large ratio of minute ventilation to functional residual capacity, means that extended preoxygenation offers little additional benefit over shorter periods. Given the challenge of achieving adequate preoxygenation in certain age groups of children compared to adults, it becomes essential to tailor further airway management to each patient accordingly (14). Muscle fatigue is quickly established due to lower levels of type 1 slow-twitch muscle fibers (15). The age of the child significantly influences the approach, with infants and neonates requiring different considerations compared to older preteenager children. Anesthetic techniques and airway management also vary accordingly. The choice of muscle relaxants and their antagonists, along with the availability of neuromuscular monitoring, enhance the management of NMB. Consequently, they reduce the incidence of residual paralysis and complications associated with relaxant use in the postoperative period (16).

However, this approach exposes patients to the risks of residual neuromuscular blockade (RNMB), which include postoperative pulmonary diseases and respiratory complications such as pulmonary atelectasis, decreased oxygen saturation, upper airway obstruction, regurgitation, silent aspiration, pneumonia and patient discomfort. Additionally, it may lead to reintubation and prolonged hospital stays. Clinical signs of recovery (such as squeezing the hand or lifting the head) are not sufficiently sensitive compared to accelerometry and require active patient's involvement, which can be challenging and influenced by the patient's age (17). Residual neuromuscular blockade (RNMB) remains unacceptably high in operating rooms (48.2%) and post-anesthesia care units (PACU) (26.9%). To minimize the risk of RNMB occurrence, moni-

toring the depth of neuromuscular blockade should be implemented as a minimum monitoring requirement for safe anesthesia. Train-of-four (TOF) should recover to greater than 0.9 before tracheal extubating (18).

Incidentally, the decision between qualitative or quantitative electromyography (EMG) monitoring is crucial. However, neither of these methods has been well-studied in neonates and infants. Train-of-four (TOF) monitoring in neonates, infants and children may pose challenges, as it could be difficult or impossible to perform. Factors such as the positioning of the arms, which may be tucked at their sides, and unreliable monitoring, particularly in smaller patients, can hinder the process. In such cases, clinicians often rely on clinical signs to assess readiness for extubating, including tidal volume, negative inspiratory force, grimace, crying, pulling legs or arms, purposeful movements, as well as assessment of skeletal muscle strength. It's assumed that TOF monitoring is generally feasible if the patient's body weight exceeds 10kg. However, achieving complete recovery by the end of surgery is mandatory for safe anesthesiology practice (19).

Currently, there are two drugs designated for neuromuscular blockade reversal: neostigmine and sugammadex. Before sugammadex arrived on the scene, neostigmine was routinely used. However, the main limitation of neostigmine is its capability to reverse only shallow blockade (TOF 1-2), and it acts on both amino-steroids (such as rocuronium and vecuronium) and benzylisoquinolines (such as atracurium and cis-atracurium). Additionally, neostigmine's effect has a slow onset and a ceiling effect. Administering neostigmine in patients with deep blockade (TOF 1) can lead to paradoxical deepening of the blockade (PDB). Furthermore, its inability to immediately reverse rocuronium blockade may increase the risks of postoperative RNB. Neostigmine administration is associated with various negative effects, including bradycardia, hypersalivation and bronchoconstriction. Therefore, it is recommended to use neostigmine with anticholinergics to mitigate these effects (16).

On the other hand, there is sugammadex, the first non-competitive antagonist for the RNMB. It is a modified γ-cyclodextrin and features a unique mechanism different from that of acetylcholinesterase inhibitors. Sugammadex rapidly encapsulates rocuronium or vecuronium (amino-steroids) through one-to-one molecular binding. This mechanism provides fast and predictable reversal effects of NMB and efficiently decreases the incidence of residual block (20–22). Sugammadex has been used extensively in surgical practice in adult patients in recent years (23). Simultaneously, this novel agent has been frequently used in pediatric anesthesia, particularly among anesthesiologists with fewer years of practice (24). In June 2021, the FDA expanded the indication to include the use of sugammadex in pediatric patients over 2 years of age. A recent study by Lang et al. evaluated a total of 18 randomized controlled trials (RCTs) involving over 1,000 pediatric patients. The results indicated that the administration of sugammadex in children was associated with a shorter duration from the administration of reversal agents to achieving a TOF ratio greater than 0.9 and a shorter interval from RNMB to extubation, compared to acetylcholinesterase inhibitors or placebo. These findings confirm and strengthen the results of previous meta-analyses. Sugammadex dosing according to the manufacturer's recommendation varies based on the TOF count:

- If there are 2 twitches, the recommended dose is 2mg/kg.
- If there are 1 to 2 post-tetanic twitches, the recommended dose is 4mg/kg.
- If there are no twitches (indicating fully reversed deep neuromuscular blockade), use the largest recommended dose of 16mg/kg (17).

Studies on intubation without NMBDs have focused on intubating conditions, hemodynamic responses, changes in intraocular and intracranial pressure or cerebral blood flow velocity. However, it remains unclear why clinicians have adopted these techniques when NMBDs have become cleaner, shorter-acting, more easily reversible, or possess characteristics that make reversal unnecessary (12).

Taking all that into consideration, it's worth knowing that there are also alternative techniques, but not without risk. Cases of hypotension, bradycardia, sinus arrest, asystole and airway damage, have been reported when relaxant-free methods have been used (25). Pediatric patients with difficult tracheal intubation are at risk of complications, such as laryngeal morbidity, esophageal intubations and cardiac arrest (2%), particularly in those aged 24 months or younger. Intubation can be difficult or fail, especially in the absence of muscular paralysis (up to 26.9%). Failure rates and adverse events can reach up to 33% when NMBDs are omitted (15). Tracheal intubation has been carried out at light-to-moderate planes of anesthesia, during which airway reflexes can be enhanced. With coughing or movement during laryngoscopy, glottic exposure can be difficult and can be complicated by vocal cord closure, resulting in partial or complete loss of the patient's airway. A necessary prerequisite for this technique is mandatory adequate CNS depression (3). In a recent meta-analysis summarizing the results of 22 trials, which included 1,651 ASA I-II participants in 62 dose groups, it was demonstrated that during light-to-moderate depth of anesthesia, the use of NMBDs can improve the quality of intubation conditions (excellent: 76%, $p<0.001$; acceptable: 68%, $p<0.001$) and was associated with better hemodynamic stability, a smaller reduction in blood pressure and heart rate, as well as a lower incidence of arrhythmias during induction of anesthesia. With the use of NMBDs, during intubation itself, there were fewer failed first-pass attempts (1.6% vs 7.5%; $p<0.0001$), fewer closing/ closed vocal cords (3.7% vs 11.1%; $p<0.0001$), and fewer unacceptable conditions (7.0% vs 20.1%; $p<0.0001$). Overall, as part of the induction sequence, NMBDs reduce the amount of anesthetic needed, leading to fewer side effects associated with anesthesia and faster recovery of consciousness (26). Avoidance of NMBDs never improves the quality of intubation and is associated with a higher incidence of failed first intubation attempts (30-37%) and respiratory adverse events (30-33%). As a result, even in 64% of cases, intubation failed when NMBDs were not administered (27,28). Both sevoflurane and propofol can profoundly depress pharyngeal and laryngeal reflexes and muscular movement at deeper planes of anesthesia. Therefore, it's not surprising that the time to return of spontaneous respiration can be prolonged and may exceed that of short-acting NMBDs (26,29).

The anesthesia plan should always be tailored to the individual patient. Since the guidelines from the European Society of Anesthesiology and Intensive Care were published in February 2023, regarding perioperative management of neuromuscular blockade, they undoubtedly helped each clinician in individualizing the anesthesia plan. Below is a summary of recommendations (R):

R1: We recommend using a muscle relaxant to facilitate tracheal intubation (1A: high quality of evidence, strong recommendation).

R2: We recommend the use of muscle relaxants to reduce pharyngeal and/or laryngeal injury following endotracheal intubation (1C: low quality of evidence, strong recommendation).

R3: We recommend the use of a fast-acting muscle relaxant for RSII such as succinylcholine 1mg/kg or rocuronium 0.9 to 1.2mg/kg (1B: moderate quality of evidence, strong recommendation).

R4: We recommend deepening neuromuscular blockade if surgical conditions need to be improved (1B: moderate quality evidence, strong recommendation).

R5: There is insufficient evidence to recommend deep neuromuscular blockade in general to reduce postoperative pain or decrease the incidence of peri-operative complications (2C: low-quality evidence, weak recommendation).

R6: We recommend the use of ulnar nerve stimulation and quantitative NMM at the adductor pollicis muscle to exclude residual paralysis (1B: moderate-quality evidence, strong recommendation).

R7: We recommend using sugammadex to antagonize deep, moderate and shallow neuromuscular blockade induced by amino-steroidal agents (rocuronium, vecuronium) (deep: post-tetanic count >1 and TOF count 0, moderate: TOF-count 1 to 3, shallow: TOF-count 4 and TOF-ratio < 0.4) (1A: high-quality evidence, strong recommendation).

R8: We recommend advanced spontaneous recovery (i.e. TOF-ratio >0.2) before starting neostigmine-based reversal and to continue quantitative monitoring of neuromuscular blockade until a TOF-ratio of more than 0.9 has been attained (1C: low-quality evidence, strong recommendation)(16).

Based on the knowledge presented, the use of NMBDs is a common practice in modern anesthesia, aimed at minimizing harmful effects and enhancing usefulness for patients. Adapting practice by carefully selecting NMBDs, monitoring NMB, and properly using reversal agents represent essential measures to prevent complications.

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PEDIATRIC TRANSFUSION: WHAT IS NEW?

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Abstract

Most of the blood components in our country rely on volunteer blood donors, so they need to be wisely used. When we make a decision about transfusions in pediatric population, we must consider the potential risks and benefits of blood products before transfusion. There are many medical conditions that require transfusion, including acute blood loss, iatrogenic blood loss, hemoglobinopathy, hematologic and nonhematologic malignancies, as well as stem cell transplant. Due to limited amount of evidence–based literature, a significant number of pediatric transfusion practices, particularly for non-red blood cell products, are based on guidelines from adult population. However, there are important differences that are unique for children, especially for preterm newborns and infants.

In recent years, clinical trials focused on pediatric transfusion are more frequent. Generally, restrictive red blood cells transfusion thresholds (< 70g/L) are considered safe for stabile, critically ill patients (**1B**). Recent studies of platelet transfusion thresholds in preterm neonates have shown that restrictive prophylactic thresholds as low as 25x109/L are safe and have lower risk for bleeding than liberal thresholds greater than 50x109/L. Major bleeding, such as intraventricular hemorrhage, in the early neonatal period seems not to depend on the severity of thrombocytopenia. Prolonged prothrombin time, thrombin time and/ or activated partial time in absence of bleeding, is not an indication for neonatal fresh frozen plasma (FFP) transfusion. In massive transfusion, protocol of fixed ratio of red blood cells, plasma and platelets (1:1:1) is used and this ratio should be based on volume (ml) rather than units.

Studies showed that 74% of the patients transfused with red cell component and 42% of FFP transfusion might be avoidable. Rational use of blood products is essential.

In decision-making about transfusion, clinicians should not rely only on Hgb level, but they need to consider patient's co-morbidity, symptoms and signs (acuity of anemia, hemodynamic stability, and presence and nature of underlying conditions). What we must change in our clinical practice is to avoid FFP transfusion in non-bleeding neonate for only to correct what seem "abnormal" values of blood tests.

Key Words: *pediatric transfusion, red blood cells, plasma, platelets, guidelines.*

Introduction

Transfusion therapy for a variety of medical conditions represents a valuable model of treatment. Most of the blood components in our country, as in many countries around the world,

rely on volunteer blood donors, so they need to be wisely used.

A trial conducted in United Kingdom about use of red cells in neonates and children (The UK National Comparative Audit of the Use of Red Cells in Neonates and Children 2010) (1), showed that 74% of transfused patients received a single red cell component during their admission, suggesting that many transfusions might be avoidable. Another trial about fresh frozen plasma (FFP), also in UK (The 2009 National Comparative Audit of the use of FFP)(2) confirmed that, contrary to published guidelines, 42% of FFP transfusions were given 'prophylactically' in no bleeding infants, on the basis of prolonged values of clotting tests. That is a lot of wasted blood products from which someone else could benefit.

Pediatric transfusion practices are highly variable due to the limited evidence-based literature. Pediatric transfusion is a complex area covering a wide range of ages, from intrauterine life till adolescence, so it is very challenging to develop and implement standardized guidelines in vulnerable patients' population.

Red Blood Cells Transfusions

When we are deciding whether to transfuse or not, we need to consider the potential risk and benefits of transfusion. A red blood cells (RBC) transfusion provides an immediate increase in oxygen carrying capacity in a setting of severe symptomatic anemia in order to improve tissue oxygenation (3). Also, potential benefit of transfusion in very preterm neonates include a lower cardiac output to maintain the same level of oxygenation (Fredrickson et al, 2011). These benefits need to be weighed against possible adverse outcomes.

The Serious Hazards of Transfusion (SHOT) initiative collects and analyses information on adverse events and reactions in blood transfusion from all healthcare organizations that are involved in the transfusion of blood and blood components in the United Kingdom. SHOT initiative has reported a higher rate of adverse events in children, including identification errors (confusion of maternal and neonatal samples, problems with multiple births), especially in the first year of life. Other adverse events include:

- *Acute hemolytic reactions*, usually due to the mistransfusion of ABO-incompatible RBCs. In order to prevent this kind of reaction, we need to double check the patient's and sample identification.
- *Delayed hemolytic reactions*, presented as jaundice and/ or an unexpected fall in hemoglobin, 2 to 10 days following transfusion. During the days following a blood transfusion the patient produces antibodies.
- *Febrile reactions* due to the presence of cytokines from leukocytes of the donor RBC package. These reactions can be reduced with leukoreduction.
- *Allergic and anaphylactic reactions*, from mild rash and itching to fatal anaphylaxis.
- *Transfusion-related acute lung injury (TRALI)* has a high incidence of mortality and should be suspected if patient presents with hypotension, fever, dyspnea and pulmonary edema, within six hours of a transfusion (Table 1).
- *Transfusion-associated circulatory overload (TACO)* usually presented in children with impaired cardiac function, during or within six hours of a transfusion, as dyspnea, ortho-

pnea, tachycardia and a wide pulse pressure, often with hypertension (Table 1).

- *Metabolic side effects* – hypocalcemia and hypoglycemia due to the infused citrate from the preservative solution and hyperkalemia due to the transfusion of large volumes or rapid transfusion of irradiated blood. Mannitol and adenine, components of preservative solutions, can cause osmotic diuresis or nephrotoxicity especially in neonates who receive large volumes of blood, due to their accumulation (4).
- *Transfusion-associated graft-versus-host disease (TA-GVHD)* – is caused by donor's lymphocytes transfused into a patient whose immune system does not have the capacity to destroy them. TA-GVHD is fatal in 90% and can be prevented using irradiated products. Patients who should receive irradiated products that are with risk for TA-GVHD include: preterm newborns, low-birth-weight infants; children with primary immunodeficiencies; patients on immunosuppressive therapy and organ transplant recipients.
- *Infections* – there is low incidence of transfusion-transmitted infections because all donated blood is extensively screened for viruses (HIV, HAV, HBV, HCV, CMV, Parvovirus B19) and bacteria (5).

Table 1. Differences between TRALI and TACO.

	TRALI	**TACO**
Transfused volume of blood	Small volume	Large volume
Hypertension	Uncommon	
Fever		No
Brain natriuretic peptide	Normal	↑
Diuretic therapy	No respond	Respond

British Committee for Standards in Hematology (BCSH) published guideline in 2016 about transfusion in very preterm neonates (<32 weeks gestational age). In Table 2 suggested red cell transfusion thresholds are given for **very preterm neonates**. These recommendations have been developed from randomized controlled studies of very low birth weight (VLBW) babies (gestational ages mostly <31 weeks gestation) (6). **Infants with chronic lung disease**, which is defined as oxygen dependency beyond 28 days of age, is recommended to be transfused as suggested in Table 2, according to their clinical status, since there is no specific evidence relating to transfusion in this group of pediatric patients.

Table 2. Suggested transfusion thresholds for very preterm neonates.

Postnatal age	**Suggested transfusion threshold Hgb (g/L)**		
	Ventilated	On oxygen/NIPPV*	Off oxygen
First 24h	< 120	< 120	< 100
First week (1-7d)	< 120	< 100	< 100
Second week (8-14d)	< 100	< 95	< 75 – 85
≥Third week (15d onwards)	< 100	< 85	< 75 – 85

*NIPPV – non-invasive positive pressure ventilation

NOTE: Suggested transfusion thresholds in Table 2 do NOT apply for moderate to late preterm (≥32 weeks gestational age at birth) or term neonates.

In recent years, multicenter clinical trials involving **preterm infants** showed that restrictive transfusion thresholds reduced transfusions without increasing mortality or serious morbidity(7-11). One of the largest trials was the ETTNO trial (Effects of liberal versus restrictive Transfusion Thresholds on survival and Neurocognitive Outcomes) conducted in 36 level III/IV neonatal intensive care units in Europe. This randomized clinical trial includes 1,013 infants with birth weights of 400g to 999g at less than 72 hours after birth. Neurodevelopmental outcomes (cognitive deficit, cerebral palsy, or severe visual or hearing impairment) were similar between restrictive and liberal transfusion groups. Also, there were no statistically significant difference between groups in the occurrence of necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity and growth (10).

In 2021, Pang Wang et al., published meta-analysis that included five trials (3,325 neonates) showing that patients assigned to restrictive versus liberal transfusion protocols had similar mortality rates (14% in both groups) (12). Also, there were no differences in both groups, in the rates of bronchopulmonary dysplasia, sepsis, necrotizing enterocolitis, retinopathy of prematurity, intraventricular hemorrhage and in-hospital stay. Two trials that included 1,739 patients were assessing neurodevelopmental outcomes at 18 to 24 months and rates of neurodevelopmental impairment were similar in both groups (39 versus 36 %).

In Table 3 are summarized suggested hemoglobin and hematocrit thresholds for RBC transfusion appropriate for term and preterm neonates cared for in the NICU, based on postnatal age and clinical status.

Table 3. Suggested transfusion thresholds for preterm and term neonates.

Postnatal age	Gestational age	Hemoglobin (hematocrit) thresholds for transfusion	
		Neonates with clinical instability	Neonates without clinical instability
0-7 days	Any	11 g/dL (32%)	10 g/dL (29%)
8-14 days	<35 weeks	10 g/dL (29%)	8 g/dL (24%)
	≥35 weeks	7 g/dL (21%)	7 g/dL (21%)
≥15 days	<35 weeks	8 g/dL (24%)	7 g/dL (21%)
	≥35 weeks	7 g/dL (21%)	7 g/dL (21%)

NOTE: These thresholds do NOT apply to neonates with acute severe or ongoing blood loss, cyanotic congenital heart disease, severe alloimmune hemolytic disease, severe persistent pulmonary hypertension of the newborn (PPHN), or those on extracorporeal circuit membrane oxygenation (ECMO).

Clinical instability is defined if at least one of the following is present:

- Need for invasive mechanical ventilation;
- Need for non-invasive positive pressure ventilation with FiO2 > 0.4;
- Acute sepsis or necrotizing enterocolitis with hemodynamic instability requiring pressor

support;

- Circulatory failure requiring inotropic/ vasopressor support;
- >6 documented apneas requiring moderate intervention per 24 hours;
- Also, in this group are included neonates that need to undergo major surgery and within 48h after the surgery.

In the setting of significant acute blood loss in neonates, we do not rely on Hgb/Hct levels. We make the decision to transfuse based on the estimated blood loss. Transfusion is generally warranted if blood loss is estimated to be >10% of the neonate's total blood volume or if there are signs related to anemia persistent (e.g., persistent acidosis, tachycardia) after adequate volume replacement with crystalloid.

In 2017, Jill M Cholette published a randomized trial involving 162 infants with congenital heart disease who needed to undergo surgical repair or palliation. Patients were randomly assigned to postoperative restrictive transfusion strategy (RBC transfusion for hemoglobin level less than 7g/dL for biventricular repairs or less than 9g/dL for palliative procedures) or liberal transfusion strategy (RBC transfusion for hemoglobin level less than 9.5g/dL for biventricular repairs or less than 12g/dL for palliative procedures regardless of clinical indication) (13). In the restrictive transfusion group, there were less postoperative RBC transfusion than in the liberal transfusion group (48% versus 80%). There were no statistically significant differences in in-hospital mortality (7% versus 6%), need for extracorporeal membrane oxygenation support (3% versus 4 %), or in-hospital stay (MD 13 days in both groups).

There are several randomized clinical studies showing that restrictive transfusion strategy (Hgb threshold of 9g/dL for cyanotic and 7g/dL for noncyanotic disease) may reduce transfusion-related risks without increasing other adverse outcomes (i.e. lactic acidosis, multiorgan dysfunction syndrome, prolonged intensive care length of stay or death) (13–17).

For neonates with severe persistent pulmonary hypertension (PPHN), the threshold used to trigger red blood cell transfusion is hemoglobin level <15g/dL (hematocrit <40%). This target is higher than the target used in other neonatal populations (e.g., preterm neonates) because these neonates are at high risk of developing tissue hypoxemia due to the effects of right-to-left shunting and cardiac function impairment. In order to reduce the risk of developing tissue hypoxemia, there is need for increasing the oxygen carrying capacity. Also, these neonates undergo frequent phlebotomy, and as result of this they have considerable iatrogenic blood loss.

Data from clinical observations of children with chronic hemolytic anemia (sickle cell anemia) suggest that a hematocrit of 20% (Hgb of approximately 6.7g/dL) can generally be tolerated without adverse events (18). In 1999, the Transfusion Requirements in Critical Care (TRICC) trial (19) showed that nonbleeding critically ill adult patients that received red blood cell transfusion on hemoglobin level less than 7g/dL seemed to have lower mortalities and morbidities than those who received RBC transfusion on hemoglobin level less than 10g/dL. After that publication, in 2007, the Transfusion Requirements in the Pediatric Intensive Care Unit (TRIPICU) (20) study included 637 hemodynamically stable critically ill children admitted to the pediatric intensive care unit (PICU) randomized either to restrictive transfusion strategy (7g/dl) (320 patients) or to liberal transfusion strategy (9.5g/dl) (317 patients). They evaluated severity and progression of multiorgan dysfunction syndrome, 28-days mortality, sepsis, infection, transfu-

sion reactions and length of stay, and they did not find statistically significant differences in both groups. The patients in the TRIPICU liberal group did not have increased mortality or cardiopulmonary complications, opposite to adults in the liberal group of the TRICC trial.

The published guidelines about red blood cell transfusion in infants and children are based on observational data, a few clinical trials, and derivate form data of studies in adult patients (21, 22). In 2018, the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI) (22, 23) published recommendations about red blood cell transfusion, not only in generally critically ill children, but they also subdivided them in categories according to the presence and nature of underlying clinical condition. In general population of critically ill children who are hemodynamically stabile, they recommended minimum and maximum hemoglobin transfusion threshold of 5g/dL and 7g/dl, respectively (23). They also recommend posttransfusion level of hemoglobin of 7 to 9.5g/dL rather to targeting to normal levels of Hgb according to the age. In the setting of acute brain injury, TAXI recommended hemoglobin transfusion threshold from 7 to 10g/dL (24), 7 to 8g/dL for hematopoietic stem cell transplant and for oncology patients who need to undergo chemotherapy where marrow suppression is expected (25).

Preoperatively, children with anemia should be evaluated, and managed the cause of anemia. In emergency setting, American Society of Anesthesiologists recommends hemoglobin level <8g/dL as perioperative red blood cell transfusion trigger. This trigger is NOT recommended for infants and children <35kg (26), and also for children with certain comorbidities that require higher Hgb levels to safely undergo general anesthesia. Children whose intraoperative blood loss is estimated to be more than 15% of their total blood volume should be transfused with red blood cells regardless of the hemoglobin level (27). Surgeries that are associated with high risk of intraoperative blood loss are cardiac surgeries, orthopedic surgeries (particularly scoliosis), neurosurgery (craniosynostosis repair) and some surgical procedures in oncological patients.

Children who need support from extracorporeal circuit membrane oxygenation (ECMO) should receive red blood cell transfusion if hemoglobin level is <13g/dL (28). Anemia in children with chronic kidney diseases should be treated with iron supplementation and/ or erythropoietin rather than RBC transfusions.

OTHER Recommendations about RBC Transfusions

According to guidelines in United Kingdom, for large volume transfusion in neonates and infants, it is recommended to transfuse red cells before the end of Day 5 following donation (Grade 1C). This recommendation is used internationally. But, according to India Evidence-based Clinical Practice Guidelines about use of blood products in newborns published in 2020, the use of only "fresh (<7 days old) packed red blood cells" for transfusion in neonates and infants is NOT recommended. Neonatal units should follow the existing standard practice of blood bank (oldest first) (Grade 1A) (29). They made this recommendation based on Cochrane review comparing transfusion of fresher versus older red blood cells for different conditions (30). This Cochrane review included 16 randomized clinical trials, from which 5 trials enrolled neonates. There were no differences in in-hospital deaths, in-hospital infections, and post-transfusion serum level of potassium in both groups (fresh vs old RBC transfusion). Using fresh RBC did not decrease the risk of necrotizing enterocolitis. In the group of neonates transfused with "fresh" RBC had fewer exposers to different donors, but the numbers of transfusions per patients were similar in both groups.

According to India Evidence-based Clinical Practice Guidelines: "Irradiation of packed red blood cells and other cellular blood components for use in neonates is strongly recommended", especially in large volume transfusions (>20ml/kg) (Grade 1C) (29). In Europe and America irradiation of blood components in order to prevent TA-GVHD, is recommended in the following situations (Grade 3B) (31,32):

- intrauterine transfusion of RBC and platelets;
- transfusion of RBC (including exchange transfusion [ET]) and platelets after intrauterine transfusion;
- transfusion of RBC and platelets in very low birth weight newborns (≤1,500g) and/ or with a gestational age ≤30 weeks;
- neonates with congenital or acquired immunodeficiency;
- recipients of hematopoietic stem cells.

In patients with risk of developing TA-GVHD, red blood cell, platelet and granulocyte concentrates should be irradiated, but there is no need for fresh frozen plasma, cryoprecipitate or fractionated plasma products to be irradiated (Grade 1B). Blood components are irradiated with dose between 25 and 50Gy. Red blood cell units should be irradiated within 14 days after collection and may be stored for 14 days. It is recommended red blood cells to be transfused within 24h of irradiation, due to the risk of hyperkalemia (Grade 1A). If irradiated RBC can't be given within 24h after irradiation, they must be washed with physiological saline in order to remove any excess of potassium. Once washed, the RBC must be transfused as soon as possible and, in any case, not later than 24 hours after preparation.

Platelet Transfusion

Platelet transfusions are given in order to prevent or decreasee bleeding due to the quantitative or qualitative dysfunction of platelets.

There are limited clinical trials related to platelet transfusions in pediatric population, so there is no evidence-based recommendations at this time. Today's recommendations are based on experts' opinions, clinical observation and on a few clinical trials. Recommended triggers for prophylactic platelet transfusions in pediatric population differs from those in adult population because pediatric patients have higher risk of bleeding, and also higher bleeding compared to adults (33).

In Table 4 are summarized suggested thresholds of platelet count for platelet transfusion in neonates according to the recommendations by British Society of Hematology published in 2016 (34).

Table 4. Suggested thresholds of platelet count for platelet transfusion in neonates.

Platelet count (× 109/l)	Indication for platelet transfusion
<25	Neonates with no bleeding (**Grade 2C**), including neonates with NAIT

Platelet count (× 109/l)	Indication for platelet transfusion
<50	Neonates with bleeding, current coagulopathy, before surgery
<100	Neonates with major bleeding or requiring major surgery (e.g. neurosurgery), ECMO

NAIT – neonatal alloimmune thrombocytopenia; ECMO – extracorporeal circuit membrane oxygenation.

What concern us the most in early vulnerable neonatal period, especially in preterm neonates, is the high risk of intraventricular hemorrhage. Recent studies indicate poor correlation between platelet count and risk of bleeding in children (33,35). A review about transfusions in neonatal patients was published in 2021, by Patrizia E Zerra and Cassandra Josephson. This review showed that the mechanism of bleeding in intraventricular hemorrhage in preterm neonates does not depend on the platelet count and is not related to hypoproliferative thrombocytopenia (35).

Neonatal alloimmune thrombocytopenia (NAIT) is diagnosed when healthy neonate presents with severe thrombocytopenia and purpura. It is due to intrauterine passing through the placenta of maternal antibodies to antigens on fetal platelets causing thrombocytopenia with high risk (10%) of intracerebral hemorrhage. Antibodies to HPA-1a (80-90%), HPA-5b or HPA-3a can cause NAIT. It is recommended to consider intravenous immunoglobulin in case of platelet refractoriness in NAIT, if platelets are negative for HPA-1a/5b or antigen-matched platelets are unavailable (Grade 1C) (34). Platelet refractoriness, which is defined as corrected count increment (CCI) less than 7.5x109/μl measured 10 – 60 minutes after finished platelet transfusion, can be due not only to immune cause (NAIT), but also to non – immune cause (massive bleeding, fever, sepsis, splenomegaly, disseminated intravascular coagulopathy (DIC), liver dysfunction, thrombotic thrombocytopenic purpura (TTP), immunosuppressive therapy).

In Table 5 are summarized suggested thresholds of platelet count for platelet transfusion in older children according to the recommendations from British Society of Hematology published in 2016 (34), from Association for the Advancement of Blood and Biotherapies (AABB) published in 2015 (36) and from the American Society of Clinical Oncology (ASCO) published in 2018 (37).

Table 5. Suggested thresholds of platelet count for platelet transfusion in older children.

Platelet count (× 109/l)	Indication for platelet transfusion
<10	Children with no bleeding, prophylactically
<20	• Minor invasive procedure (bone marrow biopsy) • Sepsis • Laboratory evidence of DIC in the absence of bleeding • Anticoagulant therapy • Risk of bleeding due to a local tumor infiltration • Insertion of a non-tunneled central venous line
<40	Prior to lumbar puncture*

Platelet count (× 109/l)	Indication for platelet transfusion
<50	• Moderate hemorrhage (e.g. gastrointestinal bleeding) • Minor surgery (except at critical sites) • Tunneled central venous line insertion
<75-100	• Major hemorrhage or significant post-operative bleeding (e.g. post cardiac surgery) including bleeding due to DIC • Surgery at critical sites: neurologic or ophthalmic surgery
<100	ECMO

DIC - disseminated intravascular coagulopathy; ECMO - extracorporeal circuit membrane oxygenation.

*This transfusion trigger varies in different clinical trials from 10 to 50x109/L depending on the clinical situation (<50x109/L is recommended transfusion trigger for platelet transfusion in clinically unstable children, non-acute lymphoblastic leukemia (ALL) patients or new diagnosed ALL patient with blasts in cerebrospinal fluid).

Fresh Frozen Plasma and Cryoprecipitate Transfusion

Coagulation parameters in pediatric population vary and are age related. Vitamin K dependent clotting factors are 40-50% lower than those in adult population, so it is expected activated partial thromboplastin time (aPTT) along with prothrombin time (PT) to be longer, especially in preterm infants. Also, factor VIII and von Willebrand factor (vWF) levels are elevated in the first six months of life. D-dimers level is normally elevated especially in the first six months and until puberty. Although coagulation parameters in pediatric population seams abnormal, hemostatic function may be normal, because pro-coagulant and anti-coagulant factors are in balance.

In 2015, Oliver Laurent Karam and al. published an international multicenter prospective study, including 101 pediatric intensive care units from 21 countries in six weeks period (13 192 clinically ill pediatric patients) (38). This study showed insignificant difference in pretransfusion and posttransfusion values of INR (1.5 vs 1.4) and aPTT (48 vs 41 sec). Pediatric patients with severe coagulopathy (INR >2.5 or aPTT >60 sec) had significant improvement from plasma transfusions.

Fresh frozen plasma is indicated to be given in (34,39):

- Patients who need to undergo invasive procedure with a risk of significant bleeding and who have an abnormal coagulation profile (PT/INR >1.5 x mid-range of age-related normal value and/or APTT >1.5) and in patients with bleeding associated with DIC (Grade 2C);
- Inherited factor deficiencies when specific factor concentrates are not available (Grade 1B);
- Reversal of warfarin in an emergency situation, only if PCC is unavailable (Grade 1B);
- Patients with liver disease or vitamin K deficiency, with bleeding, or prior to an urgent invasive procedure or surgery (Grade 1B);
- To replace clotting factors as part of a massive transfusion protocol.

Fresh frozen plasma is NOT recommended to be given (34,39):

- "Prophylactically" in non-bleeding patients, in order to "correct" minor abnormalities of PT or aPTT (Grade 1C);
- As volume replacement or for prevention of intraventricular hemorrhage (Grade 1B).

Data from United States of America showed that 3% of all pediatric patients and 12 - 13% of all intensive care patients had received plasma transfusion during their administration (40,41). Clinical practice in United Kingdom and Canada differs from published recommendations. Data from adult and pediatric studies showed that 65% of fresh frozen plasma transfusions in critically ill patients were not given according to the published guidelines and 34% of plasma transfusions were ordered for non-bleeding patients without planned invasive procedure (42, 43). Considering transfusion-related adverse events and increased incidence of organ dysfunction, hypercoagulability, nosocomial infections and mortality associated with plasma transfusions, previously mentioned findings should worry us.

Fresh frozen plasma contains fibrinogen, though cryoprecipitate has higher concentration of fibrinogen (10 – 15ml of cryoprecipitate is equivalent to 200 – 250ml FFP, regarding to fibrinogen concentration). Cryoprecipitate is NOT recommended to be given "prophylactically" in non-bleeding patients with decreased fibrinogen (Grade 2C). Cryoprecipitate is recommended to be given in patients with:

- Fibrinogen level <1g/L (congenital or acquired hypofibrinogenemia) before surgery at risk of significant bleeding when fibrinogen concentrate is not available (Grade 2C);
- vW disease, with bleeding, prior invasive procedure or surgery, when DDAVP is ineffective or contraindicated (<2 years of age) (Grade 2C).

Viscoelastic assays (thromboelastography or rotational thromboelastometry) are recommended as tools for assessment of hemostatic potential and individual therapeutic guide transfusion and antifibrinolytic therapy (44).

Transfusion Volumes and Rates

Red Blood Cells

Transfusion volume of red blood cells in neonates and infants is 10 – 20ml/kg administrated at 5ml/kg/h. The duration of RBC transfusion should not be longer than four hours. The maximum rate should be 150ml/h. Transfusion volumes of 15ml/kg are generally recommended for non-bleeding neonates (Grade 2C). Transfusion volume >20ml/kg in non-bleeding pediatric patient is NOT recommended due to the risk of transfusion associated circulatory overload (TACO).

Platelets

Platelets are usually given in doses of 10 – 20ml/kg with rate of 10 – 20ml/kg/h. Children weighted >15kg can receive 1 apheresis unit (300ml). A faster rate (within 30 minutes) is associated with transfusion reactions. Doses of 5 – 10ml/kg of platelet transfusion are expected to increase the platelet count by 50 – 100x109/L in non-refractory patients. Post transfusion platelet count

should be performed 10 – 60 minutes after transfusion. Platelet refractoriness is defined as poor post-transfusion platelet count increment (CCI <7.5x109/μL) after ≥2 consecutive platelet transfusions.

Corrected count increment:

$$CCI = \frac{(posttransfusion\ count - pretransfusion\ count) \times body\ surface\ area\ (m2)}{number\ of\ platelets\ transfused}$$

NOTE: number of platelets in one unit differs depending on the type of platelet unit (apheresis platelet unit = 3x1011/300 mL and whole blood-derived platelet unit = 5.5x1010/50 mL).

Fresh frozen plasma

Fresh frozen plasma in all children is given in doses of 10 – 20ml/kg and this dose is expected to increase the clotting factors by 15 – 20% in absence of consumption. Dose should be administrated at rate of 10 – 20ml/kg/h. As in RBC transfusion, FFP transfusion volume >20ml/kg in non-bleeding pediatric patients is NOT recommended due to the risk of transfusion associated circulatory overload (TACO).

Cryoprecipitate

Cryoprecipitate is given in doses of 5 – 10ml/kg in all children at a rate of 10 – 20ml/kg/h.

NOTE: Cryoprecipitate unit from whole blood (package of ~ 36ml) should be given in doses of 10ml/kg and cryoprecipitate apheresis unit (package of ~ 60ml) should be given in doses of 5ml/kg.

Massive Transfusion Protocol

Massive blood loss in pediatric patients can be due to trauma, but more commonly is expected in surgical settings. Massive blood loss in pediatric population is defined as blood loss of one total blood volume in 24 hours, or 40ml/kg in 3 hours or 2 – 3ml/kg/h. In Table 6 are presented total blood volumes in different pediatric age.

Table 6. Total blood volume in pediatric population.

Age	Blood volume
Preterm neonate	100ml/kg
Term neonate – 3 months	80 – 90ml/kg
Infant	70 – 80ml/kg
>2 years	70ml/kg

In 2015, Lucas P Neff and al. published a retrospective observational study including 1,100 children who suffered combat injuries. This study showed that patients who received more than 40ml/kg of total blood products in the first 24 hours, had higher risk of in-hospital death than

those that received less then 40ml/kg (15% vs 6% respectively) (45).

Massive blood protocol consists of balanced transfusion of red blood cells, plasma and platelets in order to prevent developing dilutional coagulopathy that can worsen bleeding (46–48). Blood products (RBC: FFP: platelets) are recommended to be given in 1:1:1 ratio. This ratio should be based on volume (ml) rather than units. Therapeutic aims with this protocol are: Hgb 80g/l, fibrinogen >1.5 g/l, PT ratio <1.5, platelet count >75 × 109/l.

The Royal College of Pediatrics and Child Health since 2012, based on the CRASH-2 study in adults (2010), recommended using tranexamic acid in children presenting with major traumatic injuries (Grade 2C) (initial dose of 15mg/kg in 10 minutes intravenous within 3h of trauma, followed by 2mg/kg/h for 8h or until the bleeding stops). Also, tranexamic acid should be considered in all children undergoing surgery where there is a risk of significant bleeding (Grade 1B) (34).

Conclusion

We know clinicians commonly use only hemoglobin thresholds to decide when to transfuse. But as clinicians we should not rely only to Hgb level for decision-making. We need to consider patient's co-morbidity, symptoms and signs (acuity of anemia, hemodynamic stability and presence and nature of underlying conditions). What we must change in our clinical practice is to avoid FFP transfusion in non-bleeding neonates for only to correct what seem "abnormal" values of blood tests. We need to think about the big picture. The numbers are here to help us, but sometimes they can only confuse us.

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PREOPERATIVE PREPARATION OF CARDIAC PATIENT FOR NON-CARDIAC OPERATION

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Abstract

Preoperative cardiovascular management is an essential component of overall perioperative cardiovascular care. It involves preoperative detection and management of cardiovascular disease and prediction of both short- and long-term cardiovascular risk. It affects anesthetic perioperative management and surgical decision-making. This requires individualized management. Careful preoperative preparation at least a week before surgery, rational decision for the necessary tests and examinations, good cooperation with the cardiologist and surgeon, and careful planning of early postoperative treatment are key for better outcome after surgery and reduced postoperative complications.

Introduction

Traditionally, the care of patients undergoing major surgery has been tailored to the index operation, and the disease being treated by this procedure. There is evidence that the postoperative complications relate primarily to the interaction between the inflammatory response to the tissue injury of surgery and a patient's physiological reserve, modulated by the type and the quality of surgery[1]. The response to surgery becomes the primary "disease process" and the consequent organ dysfunction, the condition to which care should be focused[2].

The aim of perioperative medicine is to deliver the best possible pre-, intra- and post-operative care to meet the needs of patients undergoing major surgery[3].

Around 250 million major surgical procedures are performed worldwide each year1.

Cardiovascular complications account for the majority of the causes of postoperative morbidity and mortality with an incidence from 0.5 to 30%[4].

The incidence of perioperative cardiac death is estimated at 0.5-1.5%, and of major cardiovascular complications (non-fatal cardiac arrest, non-fatal myocardial infarction, heart failure, clinically relevant arrhythmias and stroke) of 2-3.5%. The risk is even higher in patients with underlying cardiovascular disease, in patients older than 70 years and undergoing major vascular surgery[5].

The optimal preoperative optimization of patients' condition, carefully planned surgical procedure, anesthetic perioperative management and postoperative rehabilitation, are crucial for the optimal outcome of surgical treatment.

The immediate aims of preoperative cardiac management are:

1. Identification of patients with potentially life-threatening cardiac disease that require preoperative assessment and treatment by cardiologist,
2. Identification of the most appropriate testing and avoidance of unnecessary testing,
3. Identification and implementation of the most appropriate medical and interventional cardiovascular treatment strategies[6].

Depending on the type of surgery and patients' characteristics, surgery could be performed in general or regional anesthesia. Nevertheless, whatever kind of anesthesia is going to be performed, the preoperative assessment is the same. Special attention needs to be paid to the medication that the patient is taking regularly. Regional anesthesia has been shown in numerous studies to decrease the perioperative neuroendocrine stress response and therefore to reduce the number of thrombotic complications[7].

Preoperative Assessment

Depending on how much time for clinical evaluation before surgery we have, we decide for further changes in perioperative management. The 2014 ACC/AHA Perioperative Guidelines proposed a stepwise approach to perioperative cardiac assessment[8].

Stepwise Approach

1. Assessment of the surgical urgency.
2. Assessment of the presence or absence of acute coronary events or unstable cardiac condition.
3. Classification of surgical procedures according to the risk of complications from the cardiovascular system.
4. Assessment of the patient's functional capacity.
5. Determination of clinical risk factors for postoperative cardiac complications.

The preoperative assessment begins with a determination of surgical urgency, followed by an assessment of the presence or absence of a preoperative acute coronary event, and concludes with perioperative risk calculation for major adverse cardiac events (MACE).

If the patient is at low risk for MACE, then no further testing is needed, and the patient may proceed to surgery without any further evaluation.

Different tools and calculators are available to predict perioperative cardiac mortality. Every surgery has a different risk of morbidity and mortality, with the highest being that of vascular and emergency surgeries.

The Lee Revised Cardiac Risk Index (RCRI) is a simple tool that has been validated to assess the perioperative risk of major cardiac events. The presence of kidney and heart failure, insulin-dependent diabetes, ischemic heart disease (IHD), history of transient ischemic attack or cerebrovascular accident and type of surgery, are included in RCRI. Intrathoracic, intra-abdominal, or suprainguinal vascular surgeries represent the highest risk.

The ACS National Surgical Quality Improvement Program (NSQIP) surgical risk calculator uses procedural codes to predict procedure-specific risk with large number of outcomes. It takes into account whether the procedure is emergent or not, and 21 patient-specific variables. It then calculates the risk of MACE along with 8 other outcomes[9].

If the patient is at high risk for MACE, then the functional capacity of the patient is determined objectively. The patients' functional capacity is easy to assess by their daily activities. Low exercise tolerance is associated with poor perioperative outcomes. The main purpose of perioperative assessment of functional capacity is to predict the individual's ability to increase oxygen delivery in the perioperative period.

Duke Activity status index (DASI) and Specific Activity Scale are used to determine functional status of the patients. They are a structural questionnaire that grades exercise ability based on a series of questions related to exercise equivalences ranging from the ability to wash and dress without breathlessness to strenuous activity such as swimming and playing tennis[10].

Functional status is easier to determine by asking simple questions about their activity and translating the answer into MET. One MET is defined as the resting or basal oxygen consumption of a 40-years-old, 70kg man. Watching TV represents MET 1, stair climbing at a slow pace represents MET 4, and jogging or swimming 7 MET. Based on MET, functional capacity is classified as poor (<3 METs), moderate (4-6 METs), good (7-10 METs) and excellent (>10 METs). Patients having a functional capacity of less than 4 METs are at increased risk of perioperative complications. Patients who have a good or excellent functional capacity of greater than 4 METs, do not need further testing and should proceed to the surgery. Also, patients scheduled for low-risk procedures do not require any testing at all. Special considerations should be made for patients who have either poor functional capacity, or patients in whom functional capacity is unknown. If further testing would lead to a perioperative change in management and will have an impact on decision-making regarding patient care, pharmacologic stress testing is recommended before the non-cardiac surgery. Depending on the result of the stress test, patients proceed to coronary revascularization and then proceed for the surgery on optimal therapy[11].

Surgical Risk

Based on an expected combined incidence of cardiac death and non-fatal myocardial infarction within 30 days of surgery, surgical procedures can be divided into low, intermediate and high risk with estimated 30-days cardiac events rates of 1%, 1%-5% and >5% (Table 1).

Table 1. Cardiac risk stratification.

Low risk < 1%	Intermediate risk 1-5%	High risk> 5%
Breast	Intraperitoneal	Aortic- open
Dental	Intrathoracic	Peripheral vascular[2]
Endocrine	Vascular[3]	Duodenum
Eye	Head and neck surgery	Pancreas
Gynecology[1]	Neurosurgical	Liver resection
Reconstructive	Orthopedic[2]	
Orthopedic[1]	Lung, kidney, liver transplantation	
Urologic[1]	Urologic[2]	
TEA or KAS a. carotid		

[1]minor surgery, [2]major surgery, [3]peripheral arterial angioplasty/ carotid, endovascular aneurysm

Patients undergoing vascular surgery carry the highest risk of suffering a perioperative cardiac event. Risk stratification provides a useful tool to identify the need for preoperative cardiac evaluation, drug treatment and assessment of risk for cardiac events. Abdominal aortic aneurysm repair or major lower extremity arterial revascularization are classified as high-risk procedures, while endovascular procedures, carotid endarterectomy and peripheral angioplasty are classified as intermediate-risk procedures.

Invasive and Non-invasive Testing Before Non-cardiac Surgery

Resting ECG, echocardiography, myocardial imaging technique and cardiac stress tests have very low (0-33%) positive predictive values for perioperative cardiac events[12].

A 12-lead ECG gives important prognostic information in patients with IHD related to short- and long-term morbidity and mortality. It also provides a baseline that can be compared postoperatively if any change in the clinical status of the patient occurs. Preoperative resting echocardiography is recommended in patients with severe valvular heart disease, and in patients undergoing high-risk surgery for the evaluation of left ventricular function.

Stress tests will primarily detect flow-limiting lesions, but not non-flow-limiting plaques. However, the latter often consist of vulnerable plaques and they are frequently a source of perioperative myocardial infarction[13].

In patients with poor functional capacity, scheduled for elevated risk noncardiac surgery, it is reasonable to evaluate with either dobutamine stress echocardiogram or pharmacologic stress myocardial perfusion imaging, only if it changes further management. Routine screening is not recommended in patients going for low-risk non-cardiac surgery.

The indications for preoperative coronary angiography are identical to those in the non-operative setting. Before performing a preoperative coronary angiography it should be clear that the patient is a potential candidate for subsequent preoperative coronary revascularization[6].

The recommendation for preoperative coronary angiography is acute ST-elevation myocardial infarction (STEMI), non-STEMI, unstable angina and angina unresponsive to medical treatment.

The measurement of laboratory markers of myocardial injury (troponin) is recommended in high-risk patients if such measurements of injury will lead to intervention. Evaluation of markers of cardiac injury is recommended in patients at high risk for MACE who may benefit from such an intervention, and routine measurement is not recommended without patient's selection[14].

Preoperative Coronary Revascularization and Antiplatelet Therapy

There is no evidence supporting that either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) decreases intraoperative or postoperative cardiac events as part of perioperative management for non-cardiac surgery. The indication for CABG and PCI is the same as for nonsurgical patients; that is patients with acute coronary syndrome. For the patients scheduled for time-sensitive noncardiac surgery, balloon angioplasty or bare-mental stent (BMS) placement is preferred for management15. For patients on dual anti-platelet therapy (DAPT) for whom non-cardiac surgery is planned, the urgency of the surgery and the risk of bleeding along with the risk of ischemic events and stent thrombosis, should be considered. Elective non-cardiac surgery, in patients in whom DAPT must be discontinued prior to surgery, should not be performed within 30 days after BMS implantation or 3 months after DES. Non-cardiac surgeries should be delayed for 14 days after balloon angioplasty.

The highest risk of stent thrombosis is in the first 4 to 6 weeks after stent implantation. In case DAPT has to be discontinued for urgent or emergent surgery, such a decision should be individualized, weighing the risks and benefits11.

Discontinuation of aspirin may be responsible for 15% of all recurrent acute coronary syndromes in patients with documented stable coronary artery disease. Aspirin taken for secondary cardiac prevention should, in general, not be discontinued. Aspirin should be discontinued preoperatively if the expected risk of bleeding and its possible sequelae are similar or even higher than the known cardiovascular risk or acute discontinuation of aspirin.

Perioperative Medical Therapy

A variety of medications are usually prescribed to patients with cardiac disease. These medications could interfere with our perioperative management. Anesthesiologists should be aware of the medications that are taken by the patients regularly.

β-blockers

The 2014 ACC/AHA guideline provides recommendations for perioperative β-blockade based on multiple research articles16. Patients who are on β-blockers should be continued on them if they are well tolerated. Changes can be made before, during, or after surgery depending on clinical condition. Modification or even discontinuation may be necessary in patients with hypotension, bradycardia or hemodynamic instability due to bleeding. Initiation of β-blocker therapy

less than 1 day before surgery has minimal effect and can even be harmful. Abrupt withdrawal of β-blocker therapy in the perioperative period has shown to be harmful[17,18].

The dose of β-blocker should be titrated to the heart rate of 60-80 beats/min and arterial blood pressure >100mmHg.

Statin

In addition to their lipid-lowering effect, statins have pleiotropic effects which by various mechanisms improve endothelial morphology and function and stabilize coronary plaques[19]. A few non-randomized studies, reviews, meta-analyses and randomized controlled trials, have documented perioperative cardio-protection by statin[6].

There is also evidence that preoperative discontinuation of chronic statin therapy is associated with adverse perioperative outcomes. Perioperative statin therapy for non-cardiac surgery should be continued in patients taking them. If the patients who are going for vascular surgery are not on statin therapy, they should start it. If statin therapy is discontinued for whatever reason, it should be restarted as soon as possible.

Calcium channel blockers and α-2 agonists

There is limited data on the efficacy of calcium channel blockers in perioperative therapy for patients undergoing noncardiac surgery. Most of the benefits shown are attributed to diltiazem. Verapamil and diltiazem can worsen and even precipitate heart failure in patients with decreased left ventricle ejection fraction. If the patients are on calcium channel blockers, they should not discontinue, but lower the dose in case of hypotension.

α-2 agonist clonidine does not reduce perioperative cardiac events, but even increases the rate of nonfatal cardiac arrest and clinically significant hypotension[11].

Angiotensin II inhibitors

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) exert beneficial effects on cardiovascular and other organ function20.

If the patients are on ACE inhibitor or ARRBs for treatment of left ventricle dysfunction, the medication should not be discontinued, but if they are used to treat hypertension, transient discontinuation should be considered.

Postoperative Care

Postoperative complications occur within the first 48 hours after non-cardiac surgery, and it is important that the patients are under tight control at that time. Although postoperative pain management is one of the most important aspects of postoperative management, as pain is one of the factors that can contribute to myocardial infarction, analgetic could on the other hand even camouflage the chest pain due to the myocardial ischemia. It is recommended to use regional techniques for postoperative pain management like epidural analgesia, as it was proven that patients undergoing abdominal surgery reduce the incidence of perioperative myocardial infarction[20,21].

It is also recommended to obtain a 12-lead ECG in patients with symptoms and signs of myocardial ischemia, myocardial infarction or arrhythmia. Measurement of troponin is also recommended in these settings. Postoperative screening with troponin levels or ECG in asymptomatic patients at high perioperative risk of myocardial infarction has no benefits[22].

Regional Anesthesia for Cardiac Patients

The potential and well-known advantage of regional anesthesia over general anesthesia should be an asset in cardiac patients if surgery can be performed under the regional block. Disadvantages of regional anesthesia include hypotension from the uncontrolled sympathetic blockade, and the need for volume loading can result in ischemia[23].

The second concern relates to anticoagulation and antiplatelet therapy which is very common in cardiac patients. Regional anesthesia can be safely performed in patients receiving anticoagulant or antiplatelet therapy, provided that the patient management is based on the appropriate timing of needle placement and catheter removal relative to the timing of the anticoagulant drug administrated.

Various studies are now available supporting the use of regional anesthesia in patients at coronary risk. There are even beneficial effects of thoracic epidural anesthesia in patients with compromised cardiac function[24].

Epidural analgesia is desirable especially in the postoperative period in patients with IHD because tachycardia and hypertension due to pain increase oxygen consumption in the heart muscle and can cause ischemia of the heart.

Conclusion

Cardiac patients for non-cardiac surgeries still pose a challenge to an anesthesiologist. Careful preoperative preparation at least a week before surgery, rational decision for the necessary tests and examinations, good cooperation with the cardiologist and surgeon, and careful planning of early postoperative treatment, are key to a good outcome after surgery and reduce postoperative complications.

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ENHANCED RECOVERY AFTER SURGERY PROTOCOL IN CARDIAC SURGERY: REVIEW

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Abstract

Purpose of Review: Enhanced Recovery After surgery (ERAS) evidence-based protocols are multimodal and multi-professional approaches to reduce physiological and psychological stress, promoting postoperative recuperation, and reducing the likelihood of postoperative complications and the length of hospital stay. Returning patients to normal functional status as quickly as possible is the goal of ERAS. The ERAS protocol was initially created for patients undergoing colorectal surgery, but it has now been developed for almost all surgical subspecialties. Over the past few years, interest in using ERAS in cardiac surgery has increased. In this article, consensus recommendations for the best postoperative care of patients having undergone cardiac surgery will be presented. For each protocol element, a study of meta-analyses, sizable non-randomized investigations, randomized clinical trials and reviews was carried out. For each topic, a consensus recommendation was formed based on the evaluation of the evidence.

Summary: The implementation of cardiac ERAS involves more than just setting up a protocol. To maximize the speed and thoroughness of rehabilitation, ERAS calls for a gradual transformation in culture, overcoming the obstacles to starting and maintaining real organizational change, and switching to a patient-centered system of care critical team building, instruction, planning, and procedures required to create and maintain a successful ERAS cardiac program.

Key Words: *Cardiac surgery, Complications, ERAS, Enhanced recovery, Perioperative care.*

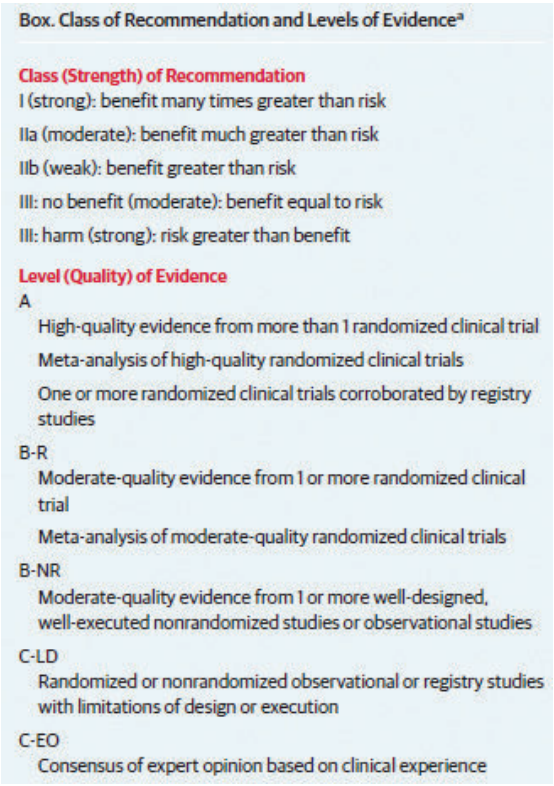
Introduction

Enhanced recovery after cardiac surgery (ERAS) is a multi-disciplinary approach to improve patient's outcomes, promote better recovery and reduce complications in patients undergoing cardiac surgery. The aim of ERAS protocol is to optimize pre-operative preparation, reduce surgical trauma and minimize postoperative stress. The protocol has been shown to improve patient's outcomes, including lower rates of complications, shorter hospital stays, and faster return to normal activities. It is important to note that ERAS is a multimodal and transdisciplinary care, and requires close collaboration between surgeons, anesthesiologists, nurses and other healthcare professionals to ensure successful implementation (1).

The fact that cardiac patients' age is increasing, have more comorbidities, as well as cardiorespiratory system problems, necessitated a cautious approach to the concepts of early recovery. Evidence based protocols have been implemented across multiple surgical specialties. ERAS was

first defined for colon surgery in 1997, and the first developments in cardiac surgery practice are in 2016-2017. The international ERAS Cardiac Society was formed in 2017 and subsequently published guidelines for what should be included in an ERAS cardiac program (1).

In this article, consensus recommendations for the best postoperative care of patients having undergone cardiac surgery will be presented. For each protocol element, a study of meta-analyses, sizable non-randomized investigations, randomized clinical trials, and reviews was carried out. For each topic, a consensus recommendation was formed based on the evaluation.



Box. Class of Recommendation and Levels of Evidence[a]

Class (Strength) of Recommendation

I (strong): benefit many times greater than risk

IIa (moderate): benefit much greater than risk

IIb (weak): benefit greater than risk

III: no benefit (moderate): benefit equal to risk

III: harm (strong): risk greater than benefit

Level (Quality) of Evidence

A

High-quality evidence from more than 1 randomized clinical trial

Meta-analysis of high-quality randomized clinical trials

One or more randomized clinical trials corroborated by registry studies

B-R

Moderate-quality evidence from 1 or more randomized clinical trial

Meta-analysis of moderate-quality randomized clinical trials

B-NR

Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies or observational studies

C-LD

Randomized or nonrandomized observational or registry studies with limitations of design or execution

C-EO

Consensus of expert opinion based on clinical experience

Figure 1. Class of Recommendation and Levels of Evidence (2).

Aim of this Review

This review seeks to provide an evidence-based review of bundled best practice interventions and therapies throughout the perioperative management of cardiac surgery patients. It is highly important for each cardiac surgery center to establish evidence-based protocols and patient-centered system of care to optimize speed and completeness of recovery. The need for an organized, methodical implementation process is essential for a successful program.

Methods

This review was mainly developed following the 2019 "Recommendations from the ERAS Society for Standards for the Development of Enhanced Recovery After Surgery Guidelines" (ERAS Standards) (3). Moreover, a comprehensive literature review was performed using PubMed and

Google Scholar search engine. We used the key words "enhanced recovery after surgery", "ERAS protocol cardiac surgery", "perioperative care in cardiac surgery", "cardiac surgery guidelines", "evidence-based practices following cardiac surgery". The most relevant and recent literature and current clinical guidelines were examined and summarized.

ERAS Elements

The protocol elements are divided into preoperative, intraoperative and postoperative strategies (Figure 2).

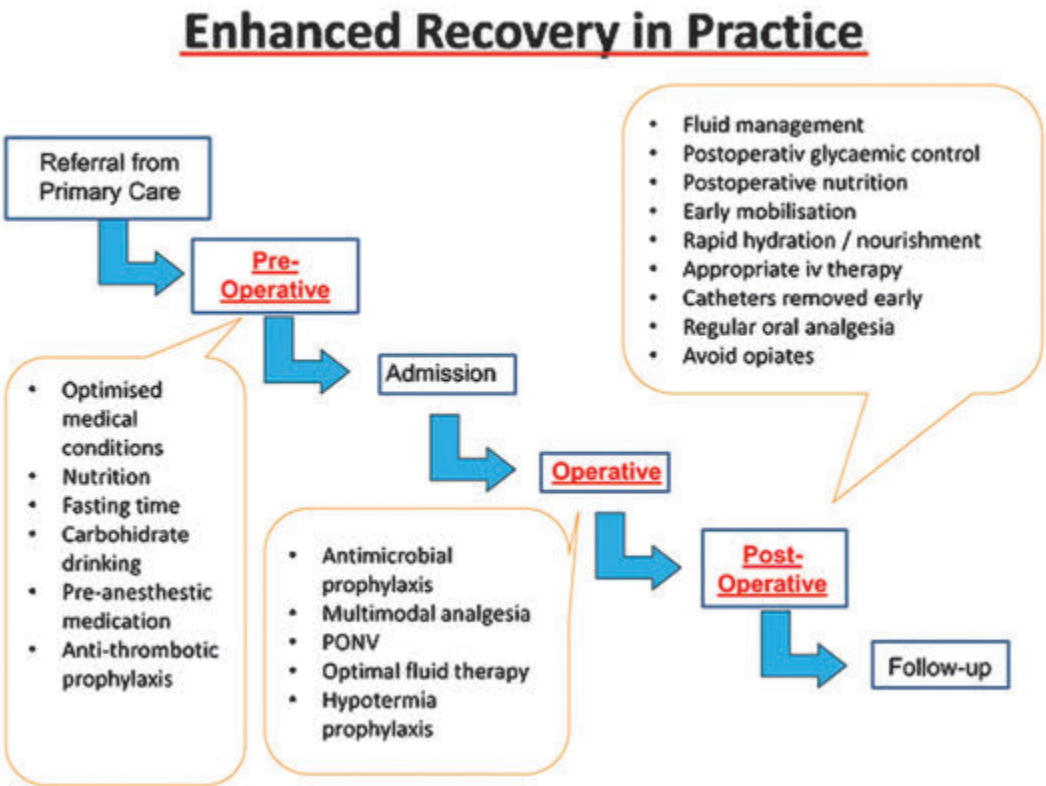


Figure 2. Enhanced recovery in practice.

Preoperative strategies

Preoperative Measurement of Hemoglobin A1c for Risk Stratification

Preoperative risk assessment is important to identify areas for optimization and determine a patient's suitability for surgery. Optimal preoperative glycemic control, defined by a hemoglobin A1c, which reflects glucose control in the previous 3 months, less than 6.5%, is associated with decreasing postoperative complications, including deep sternal wound infections, ischemic events and renal failure. Additionally, patients who present for cardiac operations with HbA1c greater than 7% have an increased risk of postoperative infections and in some studies increased hospital length of stay. Based on moderate-quality evidence, preoperative measurement of HbA1c and optimal glycemic control is recommended (Class IIa, Level C-LD) (3,4,5).

Preoperative Measurement of Albumin for Risk Stratification

Hypoalbuminemia (serum albumin <4.0g/L) is an independent predictor of worse outcomes after cardiac surgery, including greater likelihood of acute kidney injury, infection, increased length time on a ventilator, longer length of stay and higher hospital costs (independent of body mass index). In a large cohort study, an increased urine albumin-to-creatinine ratio was an independent factor associated with an overall increased incidence of mortality, acute kidney injury and longer hospital stay. Based on moderate quality of evidence, it can be useful to assess preoperative albumin before cardiac surgery (Class IIa, Level C-LD) (3,6,7,8).

Preoperative Correction of Nutritional Deficiency

Optimizing preoperative nutrition has the potential to improve a wide range of patients' outcomes – less surgical site infections, improved wound healing, shorter intensive care unit stay and reduced mechanical ventilation times, less hospital readmission and lower mortality. Preoperative malnutrition is associated with an increased proinflammatory, immuno-suppressive response to surgical stress. In patients undergoing cardiac surgery who have serum albumin level less than 3.0g/L, cachectic patients, nutritional supplementation within 7 to 10 days may improve outcomes. Based on current evidence, correction of nutritional deficiency is recommended when feasible (Class IIa, Level C-LD) (3,8,9).

Consumption of Clear Liquids Before General Anesthesia

Data published in international anesthesia guidelines have established a consensus on solid food fasting times of 6 to 8 hours prior to elective surgery and clear liquid fasting times of 2 to 4 hours prior to elective surgery. During the induction and maintenance of anesthesia there is risk of pulmonary aspiration. Patients including nonelective status, delayed gastric emptying, low cardiac output and the frequent use of transesophageal echocardiography (TEE), are at risk of aspiration. A small study in patients undergoing cardiac surgery demonstrated that an oral carbohydrate drink consumed 2 hours preoperatively was safe, and no incidents of aspiration occurred. Based on current data, clear liquids may be continued up to 2 to 4 hours before general anesthesia (Class IIb, Level C-LD) (3,8,10).

Preoperative Carbohydrate Loading

A carbohydrate drink (24gr complex carbohydrate beverage or a 12ounce clear beverage) 2 hours preoperatively improves postoperative glucose control, enhances return of gut function, and reduces insulin resistance and tissue glycosylation. Given the current supportive data, carbohydrate loading is given a weak recommendation at this point (Class IIb, Level C-LD) (3,8,11,12).

Patient Engagement Tools

Patients' education and counseling before cardiac surgery can be completed through printed material, application-based approaches and most effectively, in person. These efforts include explanations of procedures and goals that may enhance recovery and early discharge, and help in reducing perioperative fatigue, fear and discomfort. Data are emerging that software applications can promote compliance, capture patient-reported outcome measures, and engage patients. These platforms have the potential to decrease anxiety, reduce variation in care, increase patients' knowledge and improve health outcomes. It is recommended these efforts to be undertaken (Class IIa, Level C-LD) (3,8,13,14).

Prehabilitation

Elderly patients usually have reduced physiological reserve, while cardiac surgery is associated with significant stress on all body systems. Previous investigations have identified that up to 50% of older adults can be deemed as frail, defined as a cumulative decline in multiple physiological systems resulting in vulnerability to stressor events. These patients typically experience prolonged hospital length of stay, higher rates of postoperative morbidity, mortality and increased care costs. This is further compounded by malnutrition, which is evident in 20% of the patients presenting for cardiac surgery. A prolonged preoperative waiting period has been associated with stress and fear of death for the patients and their relatives. A cardiac prehabilitation program should include nutritional optimization, exercise training, education, social support and anxiety reduction. This strategy demonstrated the benefits of 3 to 4 weeks of prehabilitation. Multicomponent prehabilitation to optimize patients prior to nonurgent cardiac surgery may be considered (Class IIa, Level B-NR) (3,8,15,16).

Smoking and Hazardous Alcohol Consumption

Tobacco smoking and hazardous alcohol consumption present opportunities for preoperative interventions as risk factors for postoperative complications. They are associated with wounds, bleeding, respiratory, metabolic and infectious complications. Alcohol abstinence and smoking cessation for 1 month are related to advanced postoperative effects after surgery. This may be considered in cardiac surgery patients in nonurgent settings (Class I, Level C-LD) (3,8,17,18).

Intraoperative strategies

Surgical Site Infection Reduction

To help reduce surgical site infections, cardiac surgery programs should include a specific care bundle that includes depilation protocols, topical intranasal therapies, appropriate timing and stewardship of perioperative prophylactic antibiotics, combined with smoking cessation, adequate glycemic control, and promotion of normothermia in the post-operative period. Meta analysis with moderate quality has concluded that care bundles of three to five evidence-based interventions can lessen surgical site infections. Evidence supports topical intranasal therapies with mupirocin to eradicate staphylococcal colonization and reduce such infections. From 18% to 30% of all patients undergoing surgery, are carriers of Staphylococcus aureus, and they have three times higher risk of S. aureus surgical site infections and bacteremia. Topical therapy is recommended to be applied universally. Level IA data exists suggesting that weight-based cephalosporins should be administered fewer than 60 minutes before the skin incision and continued for 48 hours post-operatively. When the surgical procedure is longer than four hours, antibiotics require redosing. Meta-analysis of skin preparation and depilation protocols suggests that clipping is desired for shaving. Clipping using electric powered clippers should occur as much as close to the A preoperative bathe with chlorhexidine has been best validated to lessen bacterial counts withinside the wound and isn't always related to extensive stages of efficacy. Postoperative measures which include sterile dressing elimination within 48 hours and each day incision washing with chlorhexidine are doubtlessly beneficial. This bundle of recommendations is with level of evidence (class I, level B-R) (3,8,19,20,21,22).

Hyperthermia

Moderate-quality prospective studies have demonstrated that hyperthermia (core temperature >37.9°C) when rewarming on cardiopulmonary bypass (CPB), is associated with infection, cognitive deficits and renal dysfunction. Any postoperative hyperthermia within 24 hours after coronary artery bypass grafting has been associated with cognitive dysfunction at 4 to 6 weeks. Rewarming on CPB to normothermia ought to be combined with continuous surface warming. Hyperthermia should be avoided (class III, level B-R) (3,8,23).

Rigid Sternal Fixation

Most cardiac surgeons use wire cerclage for sternotomy closure because of lower cost of wires and low rate of sternal wound complications. This achieves compression and approximation, however, does not eliminate side-by-side movement and rigid fixation. In 2 multicenter randomized clinical trials, sternotomy closure with rigid plate fixation resulted in fewer sternal complications, significantly better sternal healing and no additional cost compared to wire cerclage at 6 months after surgery. Rigid sternal fixation can be useful (class IIa, level B-R) (3,8,25).

Tranexamic Acid or Epsilon Aminocaproic Acid

Scientific data on patients' blood management are typically focused on reducing red blood cell transfusions through identification and treatment of preoperative anemia, intraoperative blood scavenging, delineation of safe transfusion thresholds, monitoring of the coagulation system, and algorithms for appropriate transfusion practices. Antifibrinolytic use with tranexamic acid with maximum dose of 100mg/kg or epsilon aminocaproic acid is recommended (class I, level A) (3,8,26).

Postoperative strategies

Perioperative Glycemic Control

Interventions to improve and optimize glycemic control are known to improve outcomes after cardiac surgery. Hyperglycemia morbidity after surgery is multifactorial and attributed to glucose toxicity, prothrombotic effects, increased oxidative stress and inflammation. Perioperative glycemic control is recommended (class I, level B-R) (3,8,26,27).

Insulin Infusion

Treatment of hyperglycemia (glucose >160-180mg/dl) with an insulin infusion may be associated with improved perioperative glycemic control. Postoperative hypoglycemia should be avoided. There is supported evidence that insulin infusion protocols to treat hyperglycemia should be used perioperatively (class IIa, level B-NR) (3,8,26,27).

Pain Management

Parenteral opioids were the mainstay of postoperative pain management until recently. Opioids are associated with multiple adverse effects, including respiratory depression, sedation, nausea, vomiting and ileus. There is evidence that multimodal opioid-sparing approaches can adequately treat pain through the additive or synergistic effects of different types of analgesics, permitting lower opioid doses in patients peri-operatively. Nonsteroidal anti-inflammatory drugs are

associated with renal dysfunction. Selective COX-2 inhibitors increase the risk of thromboembolic events. Acetaminophen may be the safest nonopioid analgesic, and when added to opioids produces superior analgesia, independent antiemetic actions and opioid-sparing effect. Intravenous acetaminophen may be better absorbed until gut function has recovered postoperatively. Acetaminophen dosing is 1gr every eight hours. Tramadol has dual opioid and nonopioid effects but with a high risk of delirium. Dexmedetomidine, an intravenous α-2 agonist, reduces opioid requirements. There is sufficient evidence to recommend that pain management should be achieved with usage of acetaminophen, tramadol, dexmedetomidine and pregabalin (or gabapentin) (class I, level B-NR) (3,8,28,29).

Postoperative Systematic Delirium Screening

Delirium is an acute confusional state characterized by inattention, fluctuating mental status, and either disorganized thinking, or altered level of consciousness that occurs in approximately 20 to 50% of patients undergoing cardiac surgery. Delirium is associated with reduced freedom from hospital readmission, reduced in-hospital and long-term survival and cognitive and functional recovery. Early delirium detection is essential to determine the underlying cause (i.e., hypoxemia, pain, low cardiac output, sepsis) and initiates appropriate treatment. A systematic delirium screening tool such as the Intensive Care Unit Delirium Screening Checklist or Confusion Assessment Method for the Intensive Care Unit should be used. At least once per nursing shift delirium screening is recommended in order to identify patients at risk and facilitate implementation of prevention and treatment protocols (class I, level B-NR) (3,8,30).

Persistent Hypothermia

Postoperative hypothermia is the failure to return to or maintain normothermia (>36°C) 2 to 5 hours after admission to the intensive care unit. Hypothermia is associated with increased chance of infection, bleeding, a prolonged hospital stay and subsequently death. Some observational studies suggest that outcomes can be improved if hypothermia is of short duration. Based on this evidence, it is recommended to prevent hypothermia by raising the ambient room temperature, using forced air warming blankets, warming irrigation and intravenous fluids in the early postoperative period (class 1, level B-NR) (3,8,31).

Chest Tube Patency

Most patients have some degree of bleeding immediately after surgery. Retained blood can cause tamponade or hemothorax if left unevacuated. Thus, a pericardial drain is always necessary in order to evacuate shed mediastinal blood. Furthermore, retained mediastinal blood can trigger postoperative atrial fibrillation by blood hemolysis and promotes an oxidative inflammatory process that may further cause pericardial and pleural effusions. Chest-tube stripping has been shown to be ineffective and potentially harmful in some meta-analyses of randomized clinical trials. Another technique used to maintain patency is to break the sterile field to access the inside of chest tubes using a smaller tube to suction the clot out. This technique may be dangerous and potentially damage internal structures, thus increasing infection risk (class IIIA, level B-R). Active chest-tube clearance methods can be used to prevent chest-tube clogging without breaking the sterile field (class I, level B-NR). There are no standard criteria for the timing of safely mediastinal drain removal, but evidence suggests that they can be removed as soon as the drainage becomes macroscopically serous (3,8,32,33).

Chemical Thromboprophylaxis

Vascular thrombotic represent potentially preventable complications after surgery, and events include both deep venous thrombosis, and subsequently, pulmonary embolism. Patients are at increased vascular thrombotic risk because they remain hypercoagulable after surgery. All patients benefit from preventing of deep-vein thrombosis after surgery, achieved with mechanical thromboprophylaxis by compression stockings and/ or intermittent pneumatic compression during hospitalization or until they are adequately mobile even in the absence of pharmacological treatment. Prophylactic anticoagulation for thromboprophylaxis should be considered on the first postoperative day and daily thereafter (class IIa, level C-LD) (3,8,34,35).

Extubating Strategies

Prolonged mechanical ventilation after surgery is highly associated with higher morbidity and mortality, longer hospitalization and increased costs. Prolonged intubation is associated with both significant dysphagia and ventilator associated pneumonia. Early extubating can be achieved with time directed extubating protocols and low-dose opioid anesthesia, within 6 hours of intensive care unit admission. This is a safe protocol even in patients at high risk and is associated with decreased intensive care unit stay, total length of stay and care costs (class IIa, level B-NR) (3,8,36,37).

Kidney Stress and Acute Kidney Injury

Acute kidney injury (AKI) complicates 22% to 36% of cardiac surgical procedures, increasing total hospital stay and doubling hospital care costs. Strategies to reduce acute kidney injury involve by assessing which patients are at higher risk and then implementing strategy and therapies in reducing the incidence. Urinary biomarkers such as insulin-like growth factor-binding protein 7 and tissue inhibitor of metalloproteinases-2) can identify patients as early as 1 hour after CPB who are at increased risk of developing acute kidney injury. The algorithm includes discontinuing angiotensin-converting enzyme inhibitors and angiotensin II antagonists for 48 hours, avoiding nephrotoxic agents, close monitoring of creatinine and urine output, avoiding hyperglycemia and radiocontrast agents, and close monitoring to optimize hemodynamic parameters and volume status (class IIa, level B-R) (3,8,38,39).

Goal-Directed Fluid Therapy

Goal-directed fluid therapy uses monitoring techniques to guide clinicians while administering inotropes, fluids and vasopressors to avoid low cardiac output and hypotension. Goal-directed fluid therapy uses a standardized algorithm for all patients to improve outcomes. Quantified goals include blood pressure, systemic venous oxygen saturation, cardiac index and urine output. Additionally, oxygen debt, oxygen consumption and lactate levels may augment therapeutic tactics. Goal-directed fluid therapy trials consistently demonstrate reduced complication rates and length of stay (class I, level B-R) (3,8,40,41).

Conclusion

The ERAS pathway was initiated in the 1990s by a group of academic surgeons to improve perioperative care for patients undergoing colon surgery, but it is now practiced in most fields of

surgery. Other ungraded ERAS elements include correction of preoperative anemia, intraoperative anesthetic and perfusion considerations, low tidal volume strategy, early postoperative enteral feeding and mobilization.

Although ERAS is relatively new to cardiac surgery, anticipated programs can benefit from these recommendations as they develop protocols to decrease unnecessary variation and improve safety, quality and value for their patients. A successful implementation of ERAS protocols is possible, however, a multidisciplinary, broad-based approach is imperative and vital for success.

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THE IMPORTANCE OF PREHABILITATION PROGRAM FOR THE SUCCESS OF SURGICAL TREATMENT OF THE ELDERLY

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Abstract

With the aging population, surgery is being performed more frequently in progressively older patients and those with a higher prevalence of comorbidities. Prehabilitation has emerged as a crucial strategy for improving outcomes in surgical patients, particularly for older or frail individuals who are at higher risk of morbidity and mortality following surgical procedures. Frailty, characterized by diminished endurance, strength and increased vulnerability to adverse health events, serves as a more accurate predictor of surgical outcomes compared to age alone. Studies, such as Shinall et al.'s investigation involving over 430,000 mostly male patients undergoing noncardiac surgeries, have demonstrated significantly elevated mortality rates among frail patients, emphasizing the importance of preoperative preparation.

Traditional surgical treatment often includes unnecessary elements that exacerbate the body's stress response, such as fasting before surgery, which was initially introduced in the 19th century but continues in some institutions despite updated anesthesia standards.

Multimodal approaches like Enhanced Recovery After Surgery (ERAS) protocols, aim to replace these traditional practices with evidence-based methods to mitigate the surgical stress response. ERAS protocols incorporate various perioperative elements that minimize stress and promote homeostasis, including the avoidance of fasting, leading to improvements in patients' outcomes, such as reduced complications, shorter hospital stays and lower costs, particularly noted in colorectal surgery.

Prehabilitation encompasses unimodal or multimodal interventions aimed at improving patients' overall health status weeks prior to surgery. Various risk factors, including smoking, alcohol consumption, malnutrition and mental health disorders, further exacerbate complications in elderly surgical patients. In addition, a significant percentage of elderly patients experience transient postoperative delirium following surgery or long-term postoperative cognitive dysfunction. These factors underline the necessity of prehabilitation protocols to enhance the patients' health status before procedures and potentially mitigate risks. Interventions focus on modifiable risk factors to improve the physical, nutritional and mental status of the patient. Several molecular effects of exercise have an effect on wound healing by vascular repair, neuroprotection and anti-inflammation.

This prompts discussions about the potential replacement or integration of conventional preoperative and postoperative care, including ERAS protocols, with prehabilitation strategies to optimize long-term surgical outcomes.

Introduction

More than a third of elective surgeries target the older, a proportion expected to rise with population aging (1). Adults above 65 years exhibit elevated rates of postoperative complications, readmissions and mortality, alongside extended hospital stays and more frequent discharge to post-acute care settings, compared to the younger (2). Various factors contribute to these adverse outcomes: age-related shifts in cytokine expression promote a pro-inflammatory state, heightening risks like venous thromboembolism and exacerbating postoperative pain and fatigue (3). Declining organ function further compounds these risks, while comorbid conditions and polypharmacy, affecting nearly 40% of older adults, elevate the likelihood of non-adherence, medication errors and postoperative complications (3). Cognitive, psychosocial and functional impairments among older exacerbate risks, necessitating comprehensive geriatric assessment (CGA) to manage these complexities effectively. Preoperative CGA and geriatric co-management models, like Perioperative Optimization of Senior Health (POSH), demonstrate promise in identifying high-risk patients and improving postoperative outcomes. POSH is a collaborative care model that unites geriatrics, surgery and anesthesiology, where patients undergo comprehensive preoperative evaluation involving multiple disciplines to identify and manage both conventional and geriatric-specific preoperative risk factors (4). Subsequent to surgery, alongside standard care, patients benefit from continued oversight by an inpatient geriatric consultation team. Comparative analysis against a matched historical cohort revealed that individuals enrolled in POSH experienced notable reductions in hospital length of stay and readmission rates, fewer postoperative complications and a higher likelihood of discharge to home rather than a healthcare facility (5).

Frailty

Frailty, a prevalent geriatric syndrome, is described by the diminishment of both physical and cognitive reserves and can be assessed through various measurement tools. The "accumulation of deficits" scale, comprises a comprehensive list of 70 symptoms and disorders utilized to compute a clinical frailty score (6). Alternatively, the phenotypical model delineates deficits across five domains, incorporating both patient-reported data (e.g., involuntary weight loss, self-reported exhaustion, activity level) and objective measures (e.g., grip strength, walking speed) (6). Patients are stratified into robust, pre-frail or frail categories based on these assessments. Notably, research indicates that regardless of the measurement method employed, the presence of preoperative frailty correlates with prolonged hospital stays, heightened risk of complications and increased postoperative mortality.

However, conducting frailty assessments presents challenges, such as the requirement for specialized equipment like a dynamometer for grip strength measurement, which may not be readily available in many clinical settings. Consequently, several expedited frailty screening tools have been developed to address these constraints. For instance, the Frail Non-Disabled Survey and Clinical Frailty Scale (FiND-CFS) combines patient's and clinician-reported items and

has been effectively implemented in settings such as vascular surgery clinics. In this protocol, patient-reported data are collected during check-in, and trained medical personnel utilize the FiND-CFS to assign a frailty score (7). The adoption of such streamlined tools facilitates the swift risk stratification of patients, enabling timely interventions. For those identified as frail, considerations may include subsequent consultations with primary care physicians for health optimization before surgery, as well as nuanced discussions regarding goals of care to ensure a realistic appraisal of surgical risks (8).

Physiology of Surgical Stress

Surgical procedures trigger a physiological reaction known as the surgical stress response. This response involves the activation of afferent nerves and cytokines due to injury, which in turn stimulates the hypothalamic-pituitary-adrenal axis and sympathetic nervous system. These systems work together to restore the body's dynamic equilibrium by orchestrating endocrine, hemodynamic and immune responses. The endocrine response alters metabolic pathways, breaking down body proteins to generate energy and produce inflammatory proteins essential for wound healing. Clinically, this can lead to hyperglycemia and protein catabolism. The hemodynamic response maintains cardiovascular stability by regulating plasma volume and meeting increased oxygen demands, often observed as hypertension, tachycardia and fluid retention (9).

The immune response involves a complex network of pro- and anti-inflammatory cytokines, aimed at minimizing tissue damage, combating infections and initiating the healing process. While this physiological response is a natural survival mechanism, an excessive or prolonged reaction can lead to adverse outcomes, including excessive protein breakdown (10).

Contemporary perioperative strategies focus on moderating the surgical stress response to mitigate its negative effects, such as excessive catabolism while preserving its essential role in restoring the body to a state of normality (11).

Prehabilitation

Prehabilitation is the process of enhancing an individual's readiness for scheduled surgery, aimed at improving the patient's tolerance to upcoming physiological stress (12).

Efforts to mitigate the impact of surgical stress response and metabolic deconditioning, while expediting the return to baseline functional capacity, have historically focused on the intra- and postoperative phases. Traditionally, rehabilitation has been the cornerstone of recovery enhancement, primarily emphasizing the postoperative period. However, it has become evident to physicians that rehabilitation alone does not sufficiently enhance muscular and functional reserve before major surgery. Studies have demonstrated that poor preoperative physical performance is associated with increased mortality, postoperative complications and delayed recovery (13). Without preemptive efforts to improve patients' physical fitness, frail and elderly individuals often possess inadequate reserves to withstand surgical stress, thereby facing heightened risks of morbidity and mortality. Frail patients in particular, experience a more rapid decline in fitness compared to prefrail and fit counterparts. Currently, postoperative rehabilitation serves as the primary intervention for restoring patients' preoperative physical fitness.

Nevertheless, it is imperative to acknowledge that frail patients possess lower baseline fitness levels and diminished reserves, necessitating prolonged recovery periods compared to fitter patients. Given the accelerated loss of fitness observed in frail individuals, preemptive measures to enhance patients' physical fitness prior to surgery are warranted. By elevating the fitness levels of frail patients before surgery, they can accrue greater reserves, potentially transitioning to pre-frail or even fit status, thereby bolstering their capacity to withstand the pitfalls of surgery and expedite recovery (14).

Prehabilitation comprises of three basic modalities: enhancing physical condition, nutritional status and reducing preoperative anxiety. Additionally, there is an initiative for smoking cessation, alcohol abuse cessation, treating anemia, or other potential medical interventions and behavioral counselling to support adherence to the selected program (15).

Physical Condition: Training and Assessment

Physical exercise enhances cardiorespiratory capacity, reduces blood pressure, increases muscle mass, and alleviates stress and anxiety. Metabolically, it decreases peripheral insulin resistance and attenuates the inflammatory response to trauma (12).

Surgery induces significant energy expenditure, challenging patients' physical capacity intraoperatively and during fasting, the inflammatory response, and healing phases postoperatively. Patients in poor physical condition may surpass their anaerobic threshold, utilizing less efficient metabolic pathways and accumulating lactic acid (13).

Key tests for assessing patients' functional capacity include the 6-minutes-walk test (6MWT) and cardiorespiratory stress test (ergospirometry). A 6MWT distance of <250m indicates increased morbidity, mortality and hospital stay, with some studies suggesting a threshold of 350m. Ergospirometry assesses cardiopulmonary function and gas exchange, with a low anaerobic threshold (<10mL/kg min) correlating with increased postoperative complications and costs (16).

Training programs vary, but typically involve supervised aerobic exercise sessions with intervals based on heart rate measurements. Home training programs, such as daily walks and breathing exercises, show promise, especially when combined with respiratory exercises for patients with pulmonary conditions (17).

Adaptation processes are typically initiated when the intensity of individual exercise surpasses a certain threshold. While acute exercise bouts often lead to transient metabolic and immunological changes in the blood, structural and functional alterations in the body usually result from longer-term adaptation processes. The specific training modalities significantly influence the location and nature of these long-term adaptations (18).

For instance, research by Schlagheck et al. suggests that endurance training elicits a stronger mobilization of immune cells compared to resistance exercise. Hence, the FITT (Frequency, Intensity, Type and Time) principle outlined by the American College of Sports Medicine serves as a fundamental guideline for prescribing aerobic exercise (19).

According to these principles, one of the key challenges lies in identifying a suitable and personalized training approach tailored to individual performance capacity, risk profile, prehabilita-

tion objectives and the time available until surgery. Nonetheless, the rate and extent of physical adaptation to exercise stress vary among individuals and are influenced in part by genetic factors [33,34]. To address this, performance-based indicators such as VO2max growth and the use of the rate of perceived exertion (RPE) scales can guide interventions, thereby minimizing the likelihood of non-responsive patients (20).

Pre-operative Nutrition

Malnutrition is intricately linked with disease and aging, significantly heightening the likelihood of postoperative complications, prolonged hospital stays and readmission rates (21). Age and digestive neoplasms are notable risk factors for poor nutritional status, with around 50% of colorectal cancer patients being over 65 years old. Preoperative weight loss affects two-thirds of colorectal cancer patients, with one-fifth experiencing substantial (>10%) weight loss (13). Malnutrition prevalence is even more pronounced in esophagogastric neoplasms, reaching up to 19% in gastric cancer patients, and correlating with a doubled incidence of surgical site infections (22). Nutritional assessment involves various methods, including screening, anthropometric measurements, laboratory tests and body composition assessments, all aimed at identifying at-risk or malnourished patients requiring intervention reliably, reproducibly and practically.

Preoperative therapeutic programs for elderly patients undergoing elective abdominal oncological surgery are gaining attention, aiming to optimize nutritional status and reduce postoperative complications. Screening tools like the Malnutrition Universal Screening Tool (MUST) and Nutritional Risk Screening (NRS 2002) assist in identifying patients at risk and guiding interventions (23). The role of sarcopenia in predicting postoperative morbidity has led to increased use of body composition assessment tools, such as bioelectrical impedance and computed tomography. Nutritional interventions, including protein supplementation for 7-14 days preoperatively, are recommended for patients at severe nutritional risk, with potential extensions to 3-4 weeks to encompass prehabilitation (PP). Immunonutrition, with elements like omega-3 fatty acids and arginine, has shown promise in reducing surgical site infections and hospital stay in malnourished patients undergoing oncological surgery, but its standardization within prehabilitation protocols requires further evidence (24).

Reducing Peri-operative Anxiety

The decision for surgical intervention, particularly in the context of a serious condition like tumor pathology, induces a state of uncertainty in patients, impacting not only the procedure itself, but also future life events and family dynamics. This sustained stress activates hormonal systems like the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, leading to elevated cortisol and catecholamine levels, along with immune system alterations mediated by cytokine release. These physiological responses, compounded by symptoms like gastrointestinal issues, tachycardia, palpitations and insomnia, prolong the catabolic phase after surgery, impede healing, and raise the risk of postoperative infections (25).

Given the challenge of quantifying stress accurately using analytical parameters unaffected by circadian rhythms, qualitative questionnaires have emerged as valuable tools for assessing stress levels and evaluating the impact of cognitive interventions. The Hospital Anxiety and Depres-

sion Scale (HADS) and SF-36 have demonstrated validity in screening for psychological distress and assessing health-related quality of life, respectively (26). While cognitive recommendations to reduce preoperative anxiety are integral to prehabilitation, their implementation in multimodal prehabilitation programs often lacks specificity, with the most interventions relying on audiovisual materials and few incorporating face-to-face cognitive sessions.

However, mindfulness-based stress reduction has gained traction as a cognitive intervention method, showing promise in alleviating stress-related symptoms in various conditions, and potentially modulating inflammatory responses. It may apply positive changes to specific markers of inflammation, cell-mediated immunity and biological aging. Additionally, cognitive training programs have proven effective in mitigating agitation and disorientation in dementia patients, offering potential utility in prehabilitation for individuals at risk of delirium, although further research is warranted to establish their efficacy in this context (27).

Prehabilitation and Enhanced Recovery After Surgery (ERAS) Programs

Surgical aggression incites a dual inflammatory response, involving immune system activation through neuroendocrine hormone release and sympathetic hypothalamic system stimulation, resulting in catecholamine and cortisol release. This prompts initial peripheral insulin resistance and heightened protein catabolism (28). The magnitude of this response correlates with the extent of surgical aggression, with larger wounds and tissue dissection eliciting a greater metabolic reaction. ERAS protocols aim to optimize patients perioperatively, mitigating surgical-induced catabolism, insulin resistance, and promoting early anabolic processes, with 70%–80% adherence demonstrating significant postoperative improvement. Moreover, high adherence to ERAS protocols appears linked to better 5-years survival in colorectal cancer patients (29). While ERAS protocols address the immediate perioperative period, prehabilitation anticipates it, initiating patient optimization weeks before surgery to maximize benefits within an intensified recovery program framework.

Several meta-analyses and randomized trials investigating uni- and multimodal prehabilitation have demonstrated clinical and functional benefits (30, 31). However, few studies have specifically examined the clinical benefits of prehabilitation within an ERAS setting. This is partly due to the limited reporting of adherence rates to ERAS elements in these studies. Given that ERAS care itself improves clinical outcomes by reducing surgical stress, it may be challenging to further enhance outcomes with prehabilitation in settings with high ERAS compliance. Nonetheless, evidence suggests that prehabilitated patients demonstrate resilience under ERAS care, characterized by their ability to return to homeostasis after surgery.

Studies have shown that prehabilitated patients, especially those undergoing colorectal cancer surgery, preserve their fat-free mass at both 4 and 8 weeks postoperatively compared to those who receive rehabilitation alone (32). Additionally, prehabilitated patients exhibit superior recovery of functional walking capacity, as measured by the 6-minutes-walk test, at 8 weeks post-surgery compared to patients receiving ERAS care alone (33). These findings suggest that prehabilitation enhances patients' resilience and facilitates a quicker return to normal body structure and function within the context of modern surgical care practices.

A hypothesis, proposed by Gillis et al., suggests that individual patient-related factors influence surgical outcomes by modifying the surgical stress response. ERAS interventions mediate these outcomes by attenuating the stress response, while prehabilitation complements ERAS by targeting preoperative physiological reserve capacity, thereby affecting the stress response and subsequent outcomes (34).

However, it's crucial to acknowledge that individual patient's characteristics can influence the efficacy of prehabilitation interventions. For example, a combined analysis of malnourished colorectal cancer patients indicated that they typically have lower functional capacity before surgery compared to well-nourished patients. Consequently, the likelihood of improving functional capacity through prehabilitation was found to be minimal (21). Despite its potential to enhance physiological reserve and functional capacity, challenges in patient's participation may affect the effectiveness of prehabilitation interventions.

Conclusion

In terms of optimal patient care, the process of rehabilitation begins before surgical incision. Therefore, it is essential to expand the ERAS protocols to the pre-operative period. The three main focuses should be physical activity, proper nourishment with sufficient protein intake and anxiety support. The future of patient care will probably become digitalized and supported by artificial intelligence. It is up to clinicians to utilize it in a day-to-day manner and offer it to a considerable number of patients.

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NARATIVE REVIEW *UDK: 616-089.168-053.9*

PERIPHERAL REGIONAL ANAESTHESIA AND NERVE DAMAGE PREVENTIVE STRATEGIES AND EVIDENCE

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Abstract

Permanent Nerve injuries (PNI) associated with regional anesthesia are very rare, but a disasterous, if and whenever they occur. No evidence exists that the use of ultrasound per se prevents or even reduces the incidence of permanent nerve injuries in peripheral nerve blocks. This review focusses on incidence, pathophysiology and prevention strategies to avoid permanent nerve injury related to peripheral regional anaesthesia.

There is nearly no evidence on PNI after fascia blocks, so this topic will not be covered.

Key Words: *Dual guidance, injection pressure, nerve stimulator, patient's safety, permanent nerve injury, regional anaesthesia, triple guidance, ultrasound.*

Material and Method

Literature research of PubMed/ MEDLINE, Cochrane Database, Google Scholar and NYSORA learning system (nysoralms.com).

Introduction and Presentation of the Problem

Permanent nerve injuries (PNI) associated with regional anesthesia are a very rare event. Early persistant paraesthesias, so called postoperative neurologic symptoms (PONS), may occur in up to 8-15% and resolve quickly in majority of the cases. Transitory neuropathy lasting up to 7 days occurs in 1-3%. However, permanent injury after neuroaxial RA is very rare with an incidence of < 0.04% and even rarer after PNB (1,2). In children, with neuroaxial and peripheral blocks performed under GA, the risk was 1.6- 3.6:10,000 for transient neurological deficits and 0 – 0.4:10,000 for permanent neurological deficit (3). Nevertheless, if permanent nerve injury occurs in connection with regional anaesthesia, it is a disaster for the patient, the anaesthesiologist and the surgeon.

Ultrasound is the superior method of choice to locate nerves and prevent LAST (4), but there is no existing evidence that ultrasound prevents permanent nerve injuries (5). Ultrasound may fail to accurately distinguish between intra- and extraneural needle position and thus, ultrasound alone is insufficient to improve patients' safety with regard to nerve damage after peripheral regional anaesthesia (nerve blocks) (6, 7).

Pathophysiology of Permanent Nerve Injury after Surgery and Regional Anaesthesia

If nerve damage occurs, it is more often related to surgical factors like type of surgery, positioning of the patient, traction, Tourniquet and postsurgical inflammation, and to patients' own risk factors than to RA (8, 9). Careful patient selection is important, as preexisting conditions like alcohol abuse and tobacco abuse or Diabetic neuropathy increase the risk of PNI 10fold ("double or triple crush theory") (2). Different nerves have different risks for injury, with a higher incidence in the upper limb (1). The ratio between neural and connective (epineurium, endoneurium) tissue differs, resulting in more exposed neural tissue and less elasticity, if less connective tissue is present. Thus, for example the interscalene roots are very vulnerable (10). Differences in individuals also play an important role (11). Most case reports of PNI are from interscalene, femoral and sciatic blocks (12). Neurological injury happens in a "triangle of disaster" formed by host's factors, (anatomy, surgery, comorbitities), environmental influences (safe practices, security standards) and causative agents like needle, local anaesthetic or adjuvants (12, 13).

A single center retrospective study by Welch et al., overlooking 10 years and nearly 400,000 patients, failed to establish peripheral nerve blocks as an independent risk factor for permanent nerve injuries, unlike the existing evidence for neuroaxial anaesthesia (14). While mechanisms of PNI can be classified as mechanical, pressure-related, vascular and chemical, damage to the perineurium ("blood- nerve- barrier", Sunderland 1965) is crucial (2). The traditional classifications of nerve damage by Seddon or by Sunderland are schematic and not helpful for the understanding of underlying pathomechanisms leading to nerve injuries by peripheral regional anaesthesia (15). Mechanical disruption of the perineurium by direct needle trauma and intrafascicular injection leads to axonal injury and fascicular leakage. This loss of the protective barrier leads to direct exposure of the axons to higher concentrations of local anaesthetics and hence increases their dose dependent of neurotoxicity. Intrafascicular high-pressure injection leads to mechanical and pressure-related ischemic nerve injury. Vascular damage and microhematomas may also lead to pressure induced ischemia. Inflammation leads to non-specific, peripheral nerve block related neuropathy with formation of adhesions, scar tissue and fascial thickening, which in turn leads to nerve compression (16).

Preventive Strategies

Evidence on Ultrasound

Current ultrasound imaging is often, but not always able to distiguish between an extraneural and an intraneural needle position. In obese patients or deep blocks, due to anatomy or artifacts, this may be challenging (17).

For sure, current ultrasound technology is neither reliably able to distinguish between intraneural- extrafascicular and intraneural- intrafascicular needle position, nor to show or preserve the integrity of the perineurium (18). As even intraneural- extrafascicular injections lead to histological, subclinical damage, any nerve expansion ("swelling") seen on the ultrasound screen during the injection should prompt needle repositioning to extraneural (19). Many nerve injuries remain asymptomatic or subclinical (13).

As it is not predictable in which patient's clinical neurological symptoms will occur, intraneural injection, as seen by nerve expansion in the sonographic image, should be avoided altogether. So, ultrasound alone did not keep all its promises of a safer regional anaesthesia (20, 21) when it comes to permanent nerve damage (22).

The Concept of Dual Guidance

"Dual Guidance" is supported to minimize nerve injuries (2, 9, 23). To combine sonography with nerve stimulators to avoid nerve-needle contact was named "protective nerve stimulation" (24) and helps to improve patients' safety. Nevertheless, the safety threshold of 0.5mA without motor response or paresthesia, to correctly predict nerve contact has been questioned (2, 25-28). Furthermore, no comparitive randomized controlled trials on the incidence of permanent (>1 year) nerve injury with ultrasound guided regional anaesthesia vs. nerve stimulation alone vs. dual guidance have been published yet. As the event is so rare, it will probably need an enormous number of patients to detect a statistically significant difference.

Pressure Monitoring or Triple Guidance

As pressure-related and ischemia-related injuries are closely linked, limiting the injection pressure has been suggested (29-34). Subjective pressure evaluation ("syringe feel") is unreliable, even with experienced anaesthesiologists (35).

Literature tells us that pressure monitoring is very sensitive but not specific for intrafascicular injections (needle contact to tendons, fascia etc.), whereas nerve stimulation is very specific for intraneural needle positions at low currents, but not sensitive enough (2, 15, 18).

ASRA guidelines (36) and NYSORA textbooks (37) advocate for combining ultrasound, nerve stimulation and pressure monitoring ("Triple Guidance").

These techniques are complemetary and hence should be combined. No single best practice to avoid nerve injury is evidence-based.

Further Recommendations to Reduce the Risk of PNI

Unnecessary needle manipulations close to nerves should be avoided. Circumferential LA spread is not mandatory for successful blocks, so we should avoid to "poke" the nerves with a needle (38, 39).

A recent guideline (40) gives detailed advice on how to avoid nerve damage due to impaired coagulation. Superficial blocks in easily compressible areas – in case of vascular puncture – are possible with coagulopthy (intrinsic or iatrogenic), but deep blocks (as well as neuroaxial regional anaesthesia) bear a high risk of of provoking permanent nerve injury by hematoma.

The Role of Different Local Anaesthetics and Adjuvants

All local anesthetics are neurotoxic to different degrees, reduce the neural blood flow and induce inflammation, leading to chemical injury (2, 41). As this is dose-dependent, reducing concentration and volume of local anaesthetics, it reduces the risk of nerve injury. This is a true advantage of ultrasound, since studies found very little volumes required for successful blocks (42, 43). Amide-LAs are less toxic than Ester-LAs. Ropivacaine seems to be the least neurotoxic and caus-

es less vasoconstriction than (Levo)bupivacaine (2). Adrenaline as adjunct worsens the reduction of nerve blood flow (44), while dexmedetomidine as adjunct attenuates perineural inflammation caused by local anaesthetics and dexamethasone, does not alter their neurotoxicity (45).

Puncture and injection through sterile ultrasound gel, alcohol, chlorhexidine and octenidine should be avoided, as they may cause neuroinflammation (16). Sterile normale saline seems to be the best for coupling the probe to the skin.

Is Performing the Blocks in Awake Patients Really Safer?

Most guidelines and textbooks advocate for nerve blocks in awake, conscious adults. Nevertheless, findings in children challenge this paradigm (3, 46) and lead to controversies (47-49). It seems to be clear that possible nerve injury is not reliably displayed by pain during injection, but if it occurs, it must prompt immediate cessation of injection and needle repositioning (2). Nerve injury and intraneural injection is possible without any pain or paresthesia. So, pain and paresthesia are specific but not sensitive and hence unrealiable, even in awake patients.

We do not have conclusive data or sufficient evidence on how to deal with geriatric patients who are not able to communicate because of dementia, but who might benefit from an opioid sparing multimodal pain therapy concept including regional anaesthesia (50). What about the risks of movement during the procedure? We do not know if the benefits outweigh the risks.

To this date, the strongest argument to advocate for performing blocks only in consciouspatients, is to minimize the risk for wrong- sided blocks (WSNB) as a part of the ”stop before you block” campaign (51).

Form and Shape of the Needle

Sharp, long beveled needles penetrate the perineurium more easily than short beveled needles (45°), so short beveled needles reduce the risk of injury (2, 12, 15). However, if such a “blunt” needle penetrates the perineurium, mechanical trauma and axonal damage is worse (52). Experimental animal data show, that the intrafascicular degree of trauma also depends on the needle diameter (Gauge) (53).

In Case of Nerve Injury

In the case of suspected nerve injury after regional anaesthesia, communication with the patient and the surgeon is crucial. A comprehenensively documented neurological examination is necessary.

EMG and nerve conduction studies can be useful and indicated that 95% of sensory changes resolve in 4-6 weeks and 99% in the first year. On the other hand, motor deficits or severe neuropathies need urgent contact to a neurologist and oriented imaging by CT or MRI. After neuroaxial anaesthesia, motor deficits are a time critical, emergent, needing immidiate, neurosurgical consult (54).

Quality of Evidence and Need for Trials

Finally, we should be aware of the fact that much of the evidence on regional anaesthesia and permanent nerve injury results from cadaver studies or animal models and case reports. Clinical

outcomes are often more complex and high-quality evidence from randomized controlled trials is missing (12, 55).

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ORIGINAL ARTICLE *UDK: 616.231-089.819.3-085.214.24*

ACHIEVING HEMODYNAMIC STABILITY DURING INTUBATION USING DEXMEDETOMIDINE BEFORE INDUCTION TO GENERALANESTHESIA

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Abstract

Dexmedetomidine is widely used in operating rooms and ICU circumstances nowadays. It is commonly utilized for light or conscious sedation, analgesia or weaning attempts from mechanical ventilation in the ICU settings, but also in the concept of multimodal anesthesia. Dexmedetomidine can be used prior to general anesthesia induction, intra-operatively or in the postoperative period. It provides hemodynamic and cardio-circulatory stability, while

imposing light sedation and superficial analgesia during these procedures. This was our motive

to use it in the process of induction to general anesthesia, prior to intubation, in order to eliminate the post-intubation spikes in high blood pressure and heart rate, providing a smooth course of the induction process. This case report tries to provide an answer to the common unwanted hemodynamic instability in patients that undergo general anesthesia induction.

The results showed us a more stable general anesthesia introduction after Dexmedetomidine infusion, regarding the NIBP, MAP and HR vital parameters, respectively. Using a continuous infusion of Dexmedetomidine in a dose of 1μg/kg, we succeeded in establishing a smooth induction course, without any drastic fluctuations in blood pressure during the peri-intubation process.

Key Words: Dexmedetomidine, Intubation, General anesthesia, Hemodynamics.

Introduction

Allowing us to extend our clinical examination, we consulted various previously published scientific papers regarding the use of Dexmedetomidine, in correlation to the stabilization and attenuation of hemodynamic response in patients throughout the intubation process or introduction to general anesthesia. Many of them had excellent clinical results.

Some of them have made a comparison in using Dexmedetomidine, given simultaneously with

intravenous Lidocaine and Propofol during tracheal intubation in a randomized controlled study (1). Others have tried to attenuate the sympathomimetic response to laryngoscopy and intubation with Dexmedetomidine, combining it with a short acting Beta-blocker like Esmolol

(3). In some vascular and cardiac surgery procedures there were attempts to numb the response of intubation by combining Dexmedetomidine, Lidocaine and Fentanyl, that also gave excellent results (5). We used Dexmedetomidine as a sole agent in the period before the intubation, not mixing other sedatives, opiates or hypnotics in the process, allowing the dose- dependent mechanism to manifest its results, keeping in mind that the dose and time of infusion are dependent and have a crucial ratio to each other, as seen in other studies, where Dexmedetomidine is used as a solitary agent before intubation (7). There are many mechanisms and pathways through which we could potentially use Dexmedetomidine in the period before intubation and induction to general anesthesia, in order to numb the sympathomimetic response. One of them is using nebulized Dexmedetomidine, as seen in another prospective randomized study (9).

Many variants of the utilization of Dexmedetomidine have been proven to be successful in obtaining hemodynamic stability in patients in the anesthesia induction period. This was our motive to have a chance to use it on our patients, and improve the overall anesthesia induction process, bypass the always present stress-response to stimuli such as laryngoscopy, and have a better patient's outcome at the end.

Material and methods

Through a retrospective analytical method, we studied a single ASA=2 randomized patients (with moderate hypertension) in April of 2023, at the University Clinic for Ear, Nose and Throat diseases – University of "Ss. Cyril and Methodius" in Skopje, Republic of North Macedonia. The exclusion criteria were patients above ASA=2 score (e.g., 3, 4 etc.). We administered Dexmedetomidine via a Braun infusion pump in meticulously calculated concentrations, regarding the patient's physical status and body characteristics. We measured the vital parameters on a Datex-Ohmeda monitor, and closely noted the consequential values that were obtained during the time-period.

Case description

Dexmedetomidine was used in titrated concentrations according to the patients' body weight, age and their entire physiological status. The patient we chose was an ASA=2 male patient, 35 years of age, with normal BMI, that had moderate hypertension (20% above of the average referent value for his age group), scheduled for an elective tonsillectomy procedure. We used Dexmedetomidine in a dose of 1μg/kg, administered through a continuous infusion pump over a period of 15 minutes. We measured systolic, mean and diastolic blood pressure, as well as

the heart rate in six-time intervals: 5-10-15 minutes prior to intubation, and 5-10-15 minutes following. The statistical results regarding the patient's vital parameters showed a significant improvement in hemodynamic stability, completely bypassing the high spikes in blood pressure (BP) and heart rate (HR) during intubation, as shown in Table 1.1. and Table 1.2. in the results section.

Results

1.1 Before intubation:

TIME:	SYSTOLIC:	DYASTOLIC:	MAP:	HR:
5 min	146mmHg	85mmHg	106mmHg	102bpm
10 min	139mmHg	83mmHg	102mmHg	86bpm
15 min	134mmHg	78mmHg	97mmHg	78bpm

1.2 After intubation:

TIME:	SYSTOLIC:	DYASTOLIC:	MAP:	HR:
5 min	119mmHg	68mmHg	85mmHg	82bpm
10 min	120mmHg	65mmHg	83mmHg	68bpm
15 min	114mmHg	62mmHg	80mmHg	65bpm

Discussion

The utilization of Dexmedetomidine before intubation is an ongoing trend in everyday anesthesia practice, especially when aspiring for a multimodal approach. It allows a greater stability in the patient's perioperative hemodynamics. The results we achieved prove that when using this pattern of induction, the patients can experience a safer and more stable induction in general anesthesia, regarding the hemodynamic reaction to painful stimuli and minor

intubation manipulations, if we have a normal, to moderately (ASA=2) hypertensive patient.

This creates opportunities for a more stable and safer general anesthesia induction not only in ENT patients, but in a wide range of surgical cases as well. The multimodal concept in managing a surgical patient has been proven to maximize patient's comfort and minimize perioperative pain. Additionally, improving their overall stress response to the surgical procedure (as shown through their vital parameters), and ensuring a better patient's outcome in the treatment that follows.

Conclusion

Using a continuous infusion of Dexmedetomidine in a dose of 1μg/kg, we succeeded in establishing a smooth induction to general anesthesia, without any drastic fluctuations in blood pressure and heart rate during the peri-intubation process. The concept of multimodal anesthesia is a key factor in establishing a safer and more secure setting for the patients in everyday surgical circumstances, ensuring a smooth introduction to general anesthesia without any hemodynamic instability in correlation to painful stimuli or their level of consciousness. At the end we gain a positive benefit in patients' feedback, which results from minimizing their pain and anxiety in the period before and during introduction to general anesthesia.

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ORIGINAL ARTICLE *UDK: 616.135-089.843-085.273.035.4*

ASSOCIATION BETWEEN PROPHYLACTIC USE OF PROTHROMBIN COMPLEX CONCENTRATE AND THROMBOTIC EVENTS IN THE PERIOPERATIVE PERIOD OF THE THORACIC AORTIC SURGERY - RETROSPECTIVE COHORT STUDY

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Abstract

During cardiac surgery, there is a significant risk of postoperative bleeding due to various factors. It is standard care to replenish the factors perioperatively. On the other hand, the prothrombin complex concentrate (PCC) carries a potential prothrombotic risk.

We hypothesized that prophylactic use of PCC during thoracic aortic surgery increases the potential risk of thrombotic events. We also analyzed the bleeding outcomes in the postoperative period in surgically treated patients for thoracic aorta in 2023 at the University Clinic State Cardio-surgery.

37 patients met the inclusion criteria for retrospective analysis (9/28 f/m, age 61.03±1.57 and BMI 28.638±0.768). 6 had postoperative arterial thrombosis, 4 had CVI, with no difference in age, BMI, duration of surgery (p=0.746), duration of cardiopulmonary bypass (p=0.457), preoperative hemoglobin (p=0.609) to the other group. No difference in blood transfusion (p=0.408) or blood loss (p=0.729). No CVI in any of the patients who received a prophylactic dose of PCC. One had myocardial infarction with elevated troponin and one had arterial thrombosis, and both did not receive PCC.

Eight patients died in the first 30 days after surgery, one received a PCC. There was no difference in the blood transfusion between the groups (p=0.152) and blood loss in the first 24 hours (p=0.580).

Prophylactic use of 1500IU PCC after surgical hemostasis with FFP (10ml/kg TT), 10-20 doses cryoprecipitate and platelets (0.1 unit/kg TT), did not reduce blood transfusion (p=0.12), FFP (p=0.251) or fibrinogen use (p=0.706), nor impacted the blood loss (p=0.696) or the need to revision due to hemorrhage (p=0.913) in the early postoperative period.

Our data show that prophylactic use of PCC did not increase the risk of postoperative thrombotic complications, but also did not impact the blood loss and blood transfusion in the perioperative period.

Key Words: *cardiac surgery, cardiopulmonary bypass, coagulation factor concentrate, prothrombin complex concentrate, transfusion, thrombotic complications.*

Introduction

In cardiac surgery, there is a significant risk of postoperative bleeding due to contact activation of the extracorporeal circulation circuit, degradation of the coagulation factors, dysfunction and activation of the platelets, consumption of fibrinogen, diminished production of factors by the liver, usage of artificial materials and multiple suture lines, as well as open vascular surfaces. The plasma concentration of fibrinogen reduces by mean of 36% and the platelet count by 44%. The activity of factors II, V, VII, X, XI and XIII for 47.0%, 39.9%, 23.5%, 40.3%, 35.6% and 33.6%, respectively (2). Notably, the activity of factors II, VII, IX and X drops exponentially the longer the extracorporeal circulation and the lower the temperature (1).

Traditionally, coagulation factors are replenished using blood products from blood banks, namely red blood cells concentrate, fresh frozen plasma, cryoprecipitate and platelet concentrates. With the availability of commercially available concentrates of coagulation factors like prothrombin complex concentrates and fibrinogen, it is prudent to consider the benefits and their potential risks. The prothrombin complex concentrate (PCC) that we use in our center and that is available in the Republic of North Macedonia is Octaplex, Octapharma and it contains 4 factors (II, VII, IX, X) and protein C and S. Similar to the historic data covering research about the prothrombotic effects of the use of activated factor VII (NovoSeven, Novonordisk), a lot of researches has been dedicated to assess the potential prothrombotic risk of prothrombin complex concentrates available on the market. It is hypothesized that their clinical use carries a potential prothrombotic risk given the high concentration of coagulation factors delivered in the circulation (3,4,8). The thrombosis can be manifested as arterial or venous thrombosis, clinically manifested as cerebrovascular event, myocardial infarction, or as pulmonary embolism or deep venous thrombosis. In one study it was found that in patients with prior history of thrombosis there is a 4.5 higher risk of venous thromboembolism in the 30 days postoperative period when PCC was used (5).

Material and Method

We hypothesized that prophylactic use of PCC during thoracic aortic surgery increases the potential risk of thrombotic events. Secondary to that, we analyze the bleeding outcomes and use of blood products in the postoperative period in surgically treated patients for thoracic aorta. We used retrospective cohort analysis of all operated patients in 2023, both emergency and elective, aortic dissections, aortic root aneurysms, ascending aorta dilation and combination surgery, excluding the patients with hereditary disorders of the coagulation, patients on coumadin or direct factor X inhibitors therapy, and patients who died in the operating theater or could not be weaned from the cardiopulmonary bypass (CPB).

Demographic data were collected, as well as preoperative coagulation and hematologic status, prior risk factors, as prior thrombosis, the type of intervention, intraoperative hypothermia, duration of CPB and duration of surgery, postoperative blood loss, blood products transfusion, thrombotic events in 30 days postoperatively and 30 days mortality.

The variables were analyzed using statistical program Minitab, using descriptive statistics (mean, SD, proportions). Categorical and binary data were compared using Chi-squared test or Mann-Witney test and continuous data using student T test or Fisher test. The risk factors are

expressed as odds ratios (OR) and 95% confidence intervals (CI), and statistical significance of $p<0.05$ was used.

Ethical approval from the Ethics Committee under the University Clinical Hospital State Cardio-surgery, Skopje was obtained prior to the collection of the data.

Results

In 2023, at the University Clinic State Cardio-surgery, 43 patients were surgically treated for surgical repair of the thoracic aorta, out of which 37 met the inclusion criteria for the retrospective analysis. Nine were women and 28 men with mean age of 61.03±1.57 and BMI 28.638±0.768, 15 got interposition of Dacron graft for repair of the ascending aorta, 11 hybrid intervention of the thoracic aorta involving the aortic arch (hybrid frozen elephant trunk), 4 got surgery by Bentall and 7 had combination surgery involving the thoracic aorta. The studied population did not differ by demographics and other risk factors, such as prior thrombotic events, duration of cardiopulmonary bypass, use of hypothermia, thus allowing to analyze the difference in outcomes (Table 1).

Table 1. Demographic data and preoperative characteristics of the studied groups.

	PCC+ blood products (N=6)	Blood products (N=30)	Test	p
Age, median years	53.5	64	Kruskal–Wallis test	0.048
Gender (f/m), n	1/6	8/22	Fisher	0.562
Prior thrombotic events, proportion	1/6	5/30	Fisher	1
Emergency case, proportion	3/6	16/30	Fisher	0.881
Preoperative anemia, proportion	0/6	6/30	Fisher	0.006
Time on CPB, mean minutes	170.7	165.6	t-test	0.826
Redo, proportion	3/6	4/30	Fisher	<0.05

Six patients had postoperative arterial thrombosis, 4 manifesting with ischemic cerebrovascular event (CVI). Among them, there was no difference in age, BMI, duration of surgery (p=0.746), duration of cardiopulmonary bypass (CPB) (p=0.457), preoperative coagulation and hematologic status (p=0.609) in comparison to the patients who did not have postoperative CVI. There was no difference in the postoperative correction of anemia (p=0.408) or blood loss in the first 24 hours (p=0.729). There was no CVI in any of the patients who received a prophylactic dose of PCC.

One patient had postoperative myocardial infarction with elevated troponin, and another one had arterial thrombosis, and both did not receive prophylactic doses of PCC.

Eight patients died in the first 30 days after surgery, one of whom received a prophylactic dose of PCC. There was no difference in age, BMI, duration of surgery (p=0.556), duration of CPB

(p=0.553), preoperative coagulation status and hematological status (p=0.484), in comparison to the patients who survived. There was no difference in the blood transfusion between the groups (p=0.152) and blood loss in the first 24 hours (p=0.580).

Prophylactic use of 1500IU PCC (15-25ml/kg TT) after surgical hemostasis and conversion of residual heparin with protamine sulfate, alongside fresh frozen plasma - FFP (10ml/kg TT), 10-20 doses of cryoprecipitate and platelets (0.1 unit/kg TT), according to our analysis, did not reduce the need for blood transfusion (p=0.12), need to replenish coagulation factors with FFP (p=0.251) or fibrinogen/ cryoprecipitate (p=0.706), nor impacted the blood loss (p=0.696) or the need to revision due to hemorrhage or heart tamponade (p=0.913) in the early postoperative period (Table 2).

Table 2. Difference in blood transfusion and blood loss between studied groups.

	PCC+blood products n=6	Blood products N=31	p
Erythrocytes (units mean±SD/24h)	4.75±1.5	3.207±2.610	p=0.12
FFP (units mean±SD/24h)	4.833±2.317	3.607±1.75	p=0.251
Cryoprecipitate (units /24h mean±SD)	23±8	22±8	p=0.706
Blood loss (ml/24h), mean±SD	975±549	1065±731	p=0.696
Revision, n	2/6	9/31	p=0.913

Discussion

Considering the high prevalence of acquired coagulopathy accompanying cardiac surgery, it is tempting to adopt a more aggressive approach in its correction. However, there is conflicting evidence regarding the efficacy of prothrombin complex concentrate (PCC) versus fresh frozen plasma (FFP) in reducing blood transfusions and blood loss within the first 24 hours post-surgery, based on analysis of high-quality clinical trials (6). On the other hand, we also investigated the inherent risks associated with the use of coagulation factor concentrates. A large meta-analysis involving 1,500 patients found no increased incidence of thromboembolic events associated with the use of PCC (7), which we confirmed in the observation study on our own data. Having this in mind, is there evidence to change the tried and tested treatment, despite the proven safety? PCC may be a preferred option in patients where fluid overload is undesired (6) or where quicker correction of coagulopathy is of essence, without the dreaded side effects. All this without expecting to act as a magic bullet, as is shown not only in our study, but in multicentric, high volume, high quality randomized studies before (6,7,8). There is no data that unequivocally support the use of PCC versus FFP in terms of reducing reoperation for bleeding, mortality, length of stay, ICU duration of mechanical ventilation, acute kidney injury or CRRT (6).

Our study, conducted at a single center with a small patients' cohort and retrospective data, aimed to explore the prophylactic use of PCC in thoracic aorta surgery. The next logical step is to validate these findings on a larger scale and in a randomized controlled trial.

Conclusion

Our data show that prophylactic use of PCC does not increase the risk of postoperative thrombotic complications, but also does not impact the blood loss and blood transfusion in the perioperative period.

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ORIGINAL ARTICLE *UDK: 616.24-008.64:[616.98:578.834(497.11)"2019/2020"*

THE SUCCESS OF THE TREATMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME IN PATIENTS SUFFERING FROM COVID-19 IN THE RESPIRATORY CENTER OF THE GENERAL HOSPITAL LESKOVAC

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Abstract

During the COVID-19 virus pandemia many patients require admission to ICUs. The goal of this study is to evaluate the clinical data of patients suffering from the COVID-19 virus and to compare the success of their treatment with different modes of ventilation. **Material and Method:** The retrospective study included 106 patients who were treated in the Respiratory Center of Leskovac General Hospital from November 2019 to May 2020. They were divided into three groups:

I - patients on NIV,

II - patients transferred from NIV to MV,

III - patients on MV.

The length of treatment, duration of symptoms and comorbidities were secondary analyzed.

Results: In this study, there were 64 men (60.4%) and 42 women (39.6%). Thirty one (46.9%) patients were between 70 and 79 years old. The most common therapy was antiplatelet, antidiabetic and antihypertensive, $p<0.05$. The average time since the onset of symptoms and the time of treatment of the patient did not show differences between the groups, $p<0.05$. Mortality was statistically significantly higher in patients who underwent MV, 81 patients (76.42%).

Conclusion: With NIV, it is possible to avoid intubation and to reduce the mortality rate in patients with COVID-19. This opens up new possibilities for the new treatment of Covid patients.

Key Words: *acute respiratory failure, COVID-19, mechanical ventilation, non-invasive ventilation.*

Introduction

One of the approaches to the treatment of COVID-19 positive patients is based, depending on the course of the disease, on the application of non-invasive (NIV) or invasive mode of pulmonary ventilation, mechanical ventilation (MV) (1). Around 5% of COVID-19 patients develop a critical form of the disease with acute respiratory fail (ARF) indicating ICU admission and delaying intubation may prove fatal for them (2). By evaluating the results of many studies it was determined that the mortality rate of patients who were treated with MV during the pandemic

was higher than 50% (1, 2). Although the effectiveness of NIV in these patients is still controversial, an increasing number of authors emphasize the importance of this mode of ventilation in the initial treatment of COVID-19 positive patients (3). Adding to the controversy, early intubation and mechanical ventilation, within 2 days of ICU admission, for patients with COVID-19 with ARF was associated with increased 60-days mortality as compared to initial use of noninvasive oxygen support (42.7% versus 21.9%) (4).

The goal of this study is to evaluate the clinical data of patients suffering from the COVID-19 virus and to compare the success of their treatment with different modes of ventilation.

Material and method

The retrospective study included 106 COVID-19 positive patients who were hospitalized in the Respiratory Center of General Hospital Leskovac from November 2019 to May 2020. The results of treatment of these patients with one of the modes of pulmonary ventilation with adequate pharmacological treatment were analyzed and compared to each other. Data on the comorbidities of the patients of all three groups, the time from the onset of symptoms to admission to the Respiratory Center and the duration of the patients' treatment were secondary evaluated. All patients, according to the mode of pulmonary ventilation, were divided into three groups:

- Group I - 25 (23.6%) patients who from the beginning to at the end of treatment were on NIV,
- Group II - 70 (66.0%) patients who were transferred from NIV to MV due to worsening condition,
- Group III - 11 (10.4%) of patients who were on MV.

The decision to start NIV was made based on the ratio of the partial pressure of oxygen in the arterial blood (PaO_2) to the fraction of oxygen in the inspired air (FiO_2). NIV was started if the pO_2/ FiO_2 ratio was between 100 and 200mmHg despite ventilation by Venturi mask (FiO_2 60%). If FiO_2 was <50%, respiratory rates (RR) <30 breath/minute, tidal volume (TV) >5ml/kg body mass with the pressure support <10cmH_2O and Positive End- Expiratory Pressure, PEEP <8cmH_2O, NIV would be stopped, and patients would be treated with oxygen by Venturi mask. In order to prolong NIV therapy and avoid endotracheal intubation, NIV was administered with maximum inspiratory airway pressure, IPAP, ("PEEP high" value of positive inspiratory pressure) of 20-22cm H_2O, maximum PEEP of 10 to 12cm H_2O and FiO_2 set to achieve saturation >90%. The possible occurrence of barotrauma was taken into consideration. If it was determined that NIV was not an effective technique, intubation and MV would be undertaken. The decision on endotracheal intubation was made based on the following parameters: persistence or worsening of acute respiratory fail (oxygen saturation 36/minute) despite NIV, development of other organ dysfunctions requiring endotracheal intubation (coma, convulsions, tracheal/ bronchial secretion, hemodynamic or electrocardiographic instability).

The length of treatment, duration of symptoms and comorbidities were secondary analyzed.

Data entry, tabular and graphical presentation was performed using the MS Office Excel program. Statistical calculations were performed using SPSS version 16. The results are presented in tabular and graphical form. The statistical hypothesis was tested at the level of significance for the risk of $\alpha=0.05$, i.e. a difference between samples is considered significant if $p<0.05$.

Results

This retrospective study included 64 men (60.4%) and 42 women (39.6%), Chart 1.

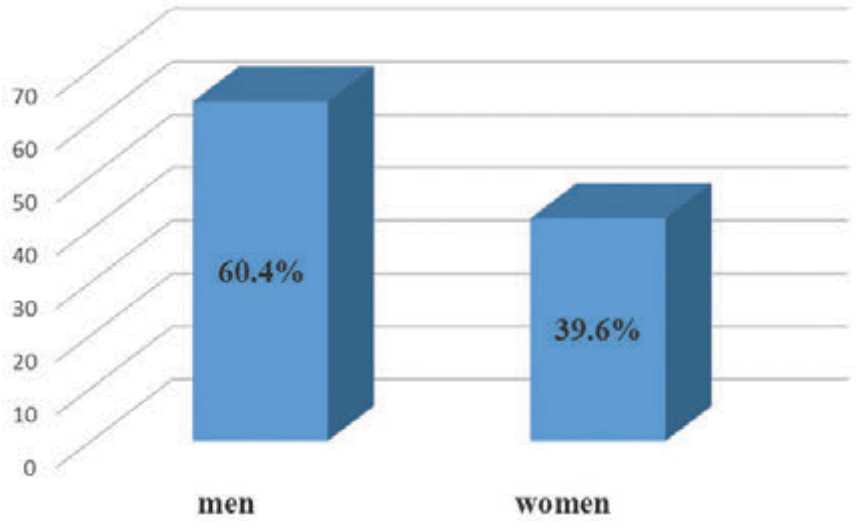

Chart 1. Patients of the study.

The analysis of the obtained results shows that the largest number of patients were aged between 70-79 years, $p<0.05$.

Among comorbidities, hypertension and diabetes had the highest incidence in patients of all three groups.

The analysis of the obtained results showed that there were 61 (57.5%) patients who were previously treated for hypertension, and 34 (32.1%) for diabetes. Also, some of the heart diseases were mostly mentioned in Group II, in 20 (18.9%) patients, 9 patients (8.5%) were treated for chronic obstructive pulmonary disease (COPD), 8 (7.5%) patients had previously changed kidney function, while 5 (4.7%) of patients were already treated for some hematological disease.

The therapy of patients before hospitalization in the Respiratory Center of the General Hospital Leskovac is shown in Table 1. Looking at the obtained results, a statistically significantly high number of patients who used antiplatelet, antidiabetic and antihypertensive therapy before contracting the COVID-19 virus is described, $p<0.05$.

Table 1. Treatment of patients before the disease from the COVID-19 virus.

	I		II		III		Post Hoc	p
	n	%	n	%	n	%	χ^2	
antidiabetic	4	15.4	34	51.5	4	28.6	18.8	p>0.05
anticoagulated	/	/	/	/	/	/		
antiplatelet	5	19.2	36	54.5	5	35.7	20.2	p>0.05
ACE i	7	26.9	56	84.8	6	42.9	28.3	p>0.05

	I		II		III		Post Hoc	p
	n	%	n	%	n	%	χ^2	
β-blockers	5	19.2	30	45.5	4	28.6	14.8	p>0.05
β_2 - agonists	/	/	8	12.1	2	14.3	1.0	p<0.05
corticosteroids	/	/	7	10.6	1	7.1	1.0	p<0.05
antidepressants	/	/	3	4.5	1	7.1	1.0	p<0.05

Analysis of the results of the average time elapsed from the onset of symptoms to admission to the Respiratory Center did not show statistically significant differences between the groups, p<0.05. In Group I it was 8.58±4.12 days long, 7.52±5.51 days in Group II and 5.9±4.87 days in Group III.

The longest treatment of patients in Group I was 45 days, in Group II - 13 days, and in Group III - 9 days. Analyzing the results, no statistically significant differences were found regarding the average length of treatment of patients, p<0.05.

The incidence of deviation of laboratory values of monitored parameters during treatment is shown in Table 2.

Table 2. Number of patients according to the obtained values of laboratory parameter value.

	I		II		III		Post Hoc	p
	n	%	n	%	n	%	χ^2	
Leukocytes	5	19.2	51	77.3	7	50	33.5	p>0.05
Lymphocytes	3	11.5	38	57.6	4	28.6	23.8	p>0.05
Platelets ↓	1	3.8	14	21.2	2	14.3	10.8	p>0.05
Platelets ↑	2	7.7	12	18.2	/	/	1.0	p<0.05
Anemia	2	7.7	10	15.2	1	7.1	3.6	p<0.05
High value of amino transferase	6	23.1	22	33.3	3	21.4	8.1	p>0.05
High value of LDH	24	92.3	66	100	9	64.3	19.8	p>0.05
High value of CRP	24	92.3	64	96.9	10	71.4	20.9	p>0.05
D-dimer >0.5mg/L	12	46.2	56	84.8	11	78.6	31.1	p>0.05

Looking at the obtained results statistically significantly higher parameter values during treatment are described in Group II, p<0.05.

The average treatment time of patients whose treatment had positive results was 7.0±4.5 days. In Group II, treatment with non-invasive mode of lung ventilation lasted 3.36±3.24 days, after which the respiratory function and general condition of the patient worsened. In Group III, the duration of MV was 3.4±3.04 days.

The mortality rate was statistically significantly higher in patients who underwent invasive MV, 81 patients (76.42%). The success of treatment with one of the modes of NIV was recorded in 25 patients (23.58%), Chart 2.

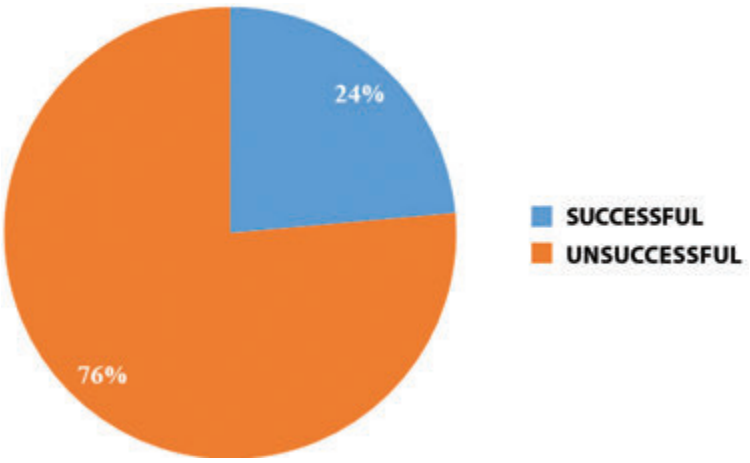

Chart 2. The success of the treatment.

Discussion

Approximately 5% of the patients who have COVID-19 require admission to ICUs (5). They tend to be older, generally over the age of 60 years, with comorbidities such as hypertension, diabetes, cardiac disease and obesity (6, 7). Gamberini et al. (8) during their study studied the risk factors that prevent the extubating of a patient infected with the COVID-19 virus. According to them, these are: age of the patient, organ system dysfunction assessed by scores used in intensive care units, pulmonary compliance, PaO_2/ FiO_2, renal and cardiovascular complications. The analysis of the results of this study showed that the patient's age and comorbidities were the main risk factors for unsuccessful treatment. The largest number of patients who underwent MV after NIV was aged between 70 and 79 years, 31 (46.9%).

During earlier studies, it was shown that hypertension is the leading risk factor for unsuccessful treatment of COVID-19 patients. Zhou and colleagues (9) described hypertension in 14.3% and diabetes in 8.9% of treated patients. Similar results were obtained by this study.

Looking at the results in the time period from the onset of symptoms to the beginning of treatment at the Respiratory Center, no statistically significant differences were found between the groups. The average time until the beginning of treatment at the Respiratory Center in Group I was 8.58±4.12 days, in Group II 7.52±5.51 days, and in Group III the average time until admission was 5.9±4.87 days. Similar to these, are the results of the study by Menzell et al. (10). The analysis of the results of their study showed that the average time from the onset of symptoms to the start of NIV was 10.6±4.3 days in the group of patients in whom NIV was successful, and 9.9±6.2 days in the group of patients in whom NIV did not give satisfactory results. Marti et al. point out that the average period from the onset of symptoms to hospitalization was 2 days (1-4 days) for all patients in whom NIV gave positive results (11). The results of this study showed that the longest period from the onset of symptoms to arrival at the Respiratory Center was 11 days, and the shortest was one day for patients in whom treatment with one of the NIV modes resulted in recovery. The longest period until the start of treatment at the Respiratory Center was 21 days in Group II, and 14 days in Group III where non-invasive ventilation was unsuccessful, and treatment was continued with MV. There were no statistically significant differences between the groups in the average length of treatment for patients. This differs from the study

by Zhou et al. (9) who pointed out that patients who required MV had a longer period of hospitalization (26 versus 7 days, p<0.001).

The most frequently previously used therapy among patients were ACEi, antiplatelet, β-blockers and antidiabetic therapy. In Group II, 84.8% of patients used ACEi, 54.5% antiplatelet therapy, 45.5% β-blockers, and 51.5% antidiabetic therapy. These results are similar to the results of the study by Menzell et al., who described that 53.7% of the patients in the group of failed NIV were on ACEi therapy, while antiplatelet therapy was used by 31.7% of the patients, and β-blockers were used by 34.2% of the patients (10).

The incidence of leukocytosis, lymphocytopenia, thrombocytopenia and thrombocytosis, was lower in Group I than in patients of the other two groups. The largest number of patients in whom high values of C reactive protein (CRP), transaminase and lactatdehydrogenase (LDH) were described, were in Group II. Marti et al. (11) related their treatment's success results to these parameters. According to them, patients with failed non-invasive ventilation had statistically significantly higher values of leukocytes, platelets and hemoglobin, than those whose hypoxia was resolved with NIV and High Flow. Wang et al. (12) examined the behavior of six laboratory parameters. Several significant differences were noted between patients who needed admission to the ICU and those who did not, especially encompassing higher white blood cell (WBC) count (1.5-fold), higher neutrophil count (1.7-fold), lower lymphocyte count (0.9-fold), as well as higher values of LDH (2.1-fold), alanine aminotransferase (ALT) (1.5-fold), aspartate aminotransferase (AST) (1.8-fold), total bilirubin (1.2-fold), D-dimer (2.5-fold).

Lippi et al. demonstrated that hepatic factors that were predictive in patients with an unfavorable course of COVID-19 requiring ICU admission, included an increase in levels of ALT (1.5-1.8-fold), AST (1.8-fold), total bilirubin (1.2-1.3-fold) and decreased albumin (0.8-fold) (13).

Lui et al. (14) found that disease severity could be predicted by lymphopenia, neutrophilia, low values of albumin, as well as by increased values of LDH and CRP. Tang et al. (15) found that coagulation parameters were more frequently deranged in those who died that in those who survived. Specifically, the values of PT, D-dimer and fibrin/fibrinogen degradation products (FDP), were found to be 1.4-, 3.5-, 1.9-fold higher in non-survivors than in survivors, respectively.

During this retrospective study, failure of noninvasive ventilation was recorded after 3.36±3.24 days. Menzella et al. (10) describe the inability to further ventilate the patients with non-invasive ventilation and the continuation of treatment with invasive modes of ventilation after 2.95 days.

The mortality rate was statistically significantly higher in patients who underwent invasive mechanical ventilation, 81 patients (76.4%). The success of treatment with one of the modes of NIV was recorded in 25 patients (23.6%). The results of other studies describe the mortality rate in MV patients between 52.4% and 86.5% (15, 16). The results of several studies (15) showed that by using NIV in patients with acute respiratory disease, the use of MV can be avoided in 70% of patients. A similar study of COVID-19 patients described mortality in 86% of intubated and 57% of patients on NIV (16). In a retrospective review (17, 18), it was confirmed that the incidence of mortality was higher in the group of intubated patients (96%) than in the group of patients ventilated with NIV (92%).

Conclusion

The results of this study showed that the incidence of mortality among patients with COVID-19 was higher in patients who underwent MV due to respiratory insufficiency. The leading risk factors were hypertension and diabetes. The incidence was directly dependent on age, comorbidities and previous therapy. The period from the onset of symptoms to admission to the Respiratory Center and the length of the patient's treatment were not significant. Initial NIV treatment of respiratory insufficiency in patients suffering from COVID-19 reduces the degree of mortality. Based on the obtained results, it is possible to contribute to the improvement of the treatment of these patients and enable new approaches in their treatment.

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PERIPHERAL NERVE BLOCKS AS A SOLE TECHNIC FOR INTRAOPERATIVE ANESTHESIA

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Abstract

Introduction: Peripheral nerve blocks can be used to provide regional anesthesia for operations involving the upper or lower extremities, alone or combined with general or spinal anesthesia. The use of ultrasound optimizes the technique of peripheral blocks and the amount of local anesthetic used.

Successful regional anesthesia for upper limb surgery is reliant on appropriate patient selection. Peripheral nerve blocks are advantageous in patients undergoing extensive surgery and those prone to postoperative nausea and vomiting, at risk of postoperative respiratory depression or the ones intolerant of opioids. Primary patients' exclusions are patient's refusal, infection at the proposed nerve block site and local anesthetic allergy.

Material and Method: As a sole technique for intraoperative anesthesia, we used peripheral nerve blocks of plexus brachialis-interscalene or supraclavicular, in a few cases. General anesthesia was associated with high risk of intraoperative complications. These patients were admitted for upper limb surgery, and they had a lot of comorbidities.

Cases: The first case was 39-years-old male patient admitted for orthopedic surgery with Dg. Contractura cubiti l.sin. He had a history of car accident 1.5 years ago, and he was tracheostomized then.

The second case was 78-years-old male patient admitted with Dg. Fractura of proximal part of left humerus, with history of HTA, AFF, COPD. General anesthesia and sitting position were with high risk of complications in this patient.

The third case was 72-years-old male patient admitted with Dg. Laesio n. radialis reg cubiti for decompression, with history of HTA, AFF, Diabetes Mellitus.

The last case was 48-years-old male patient, with Dg. Laesio ommae l.sin for arthroscopy and tenodesis BCL ommae. This patient insisted on being awake and to see the surgery.

Our patients were stable during surgery and did not feel any pain.

Conclusion: In cases where General anesthesia is with high risks for patients, peripheral nerve blocks can be good choice for intraoperative anesthesia and postoperative analgesia.

Key Words: *peripheral nerve blocks, postoperative analgesia, regional anesthesia, ultrasound.*

Introduction

Regional anesthesia and peripheral nerve blocks (PNBs) have an important role as an anesthetic technique for intraoperative anesthesia, prolonged postoperative analgesia and fast discharge of patients after surgery. Peripheral nerve blocks can be used to provide regional anesthesia and analgesia for operations involving the upper or lower extremities (1).

Peripheral nerve blocks can be used alone or in combination with general anesthesia for intraoperative analgesia. It depends on the type of surgery, duration and extensivity of surgery, and acceptance of the patient. Prolonged procedures can be done with general anesthesia combined with regional anesthesia or peripheral nerve blocks. In combination with peripheral nerve blocks, both the depth of general anesthesia and the dose of opioids are reduced, so the patient has an early return of their full cognitive function and fast transition to postoperative pain control compared to general anesthesia alone (2).

As part of a multimodal analgesia for postoperative pain management, peripheral nerve blocks with long-acting local anesthetic can provide prolonged analgesia (3).

The anatomy-based techniques, nerve stimulation, palpation, landmarks, paresthesia and trans-arterial approaches, did not give us good monitoring of the local anesthetic dispersion. Ultrasound guidance has become very popular for performance of peripheral nerve blocks and offers a lot of practical advantages. Ultrasound allows good visualization of the anatomy of the region, more informed guidance for the needle pathway to the nerve, avoiding structures that can be damaged by the needle. But the most important is that ultrasound guidance allows good visualization of local anesthetic delivery and distribution, with the potential to change the needle tip position to optimize local anesthetic distribution (4).

Regional anesthesia and peripheral nerve blocks have been shown to improve the cardiovascular, pulmonary, gastrointestinal, coagulative, immunological and cognitive functions, especially in elderly and high-risk patients undergoing surgery (5).

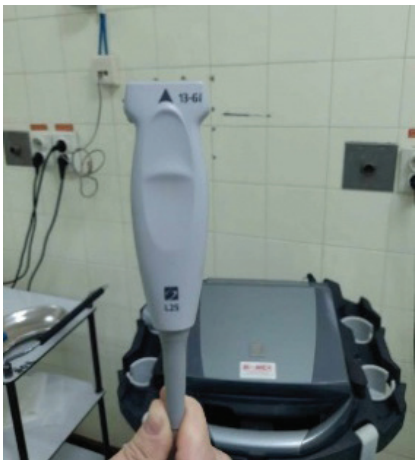
Plexus brachialis blocks for upper extremity surgery have an obvious place as a sole anesthetic technique or in combination with general anesthesia, reducing the need for analgesics intraoperatively and providing good postoperative pain relief (6).

Compared to systemic analgesia, regional anesthesia provides improved postoperative analgesia, reduced pain intensity, less postoperative nausea and vomiting (PONV), and increased patient's satisfaction. But, for successful regional anesthesia for upper limb surgery appropriate patients' selection is needed. Absolute contraindications are patient's refusal, skin infection at the nerve block site and local anesthetic allergy. Relative contraindications include patients with a pre-existing neuropathy or receiving anticoagulant therapy.

Material and methods

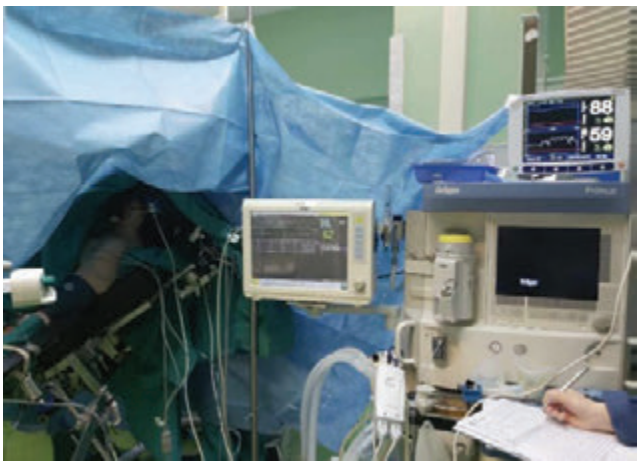
In our hospital we have been performing ultrasound guided peripheral nerve blocks (PNBs) for a few years. Most of the blocks were performed in orthopedic department, for upper and lower extremity procedures, combined with spinal or general anesthesia. But plenty of our patients that were admitted for upper limb surgery, elective or with fractures, were old and with

a lot of comorbidities: arterial hypertension (HTA), aorto-coronary by-pass, stenting, COPD, Asthma bronchiale, Diabetes Mellitus, Atrial fibrillation (AFF), CVI. General anesthesia was associated with a high risk of complications. Because of that, our choice for type of intraoperative anesthesia and analgesia in these patients were PNBs. We have done a lot of these operations only with peripheral nerve block, but here we will present only four cases. The nerve blocks were performed usually 15 to 30 minutes before the surgery. SonoSite ultrasound machine and Stimuplex needle by B/Braun were used (Picture 1).

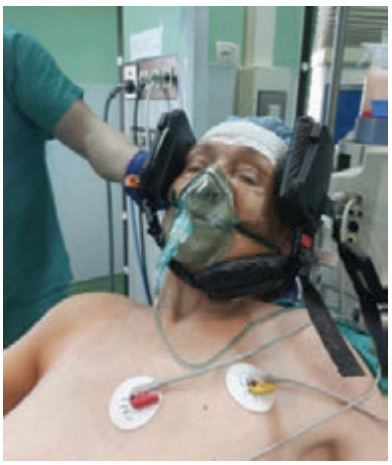


Picture 1.

The procedure was explained to all patients. They were monitored and intravenous canula was inserted with infusion of 0.9% Saline. Bupivacain 0.5% was used in a dose depending on the type of PNBs and the patient. Dexamethason 4mg was given intravenous in the operating room. Intraoperatively patients were oxygenated with facial mask, and blood pressure, EKG and SpO2 were measured (Picture 2, 3).

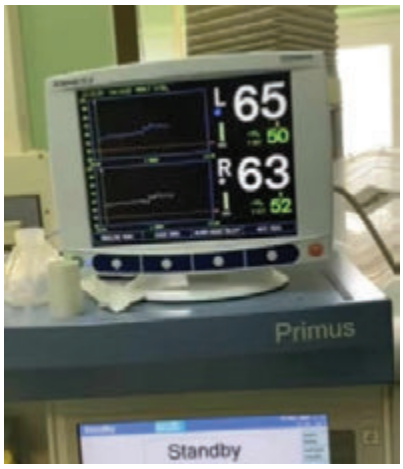


Picture 2.



Picture 3.

If the patient was in a sitting position, NIRS monitor was used for cerebral oxygenation measurement of both hemispheres (Picture 4).



Picture 4.

As a sole technique for intraoperative anesthesia, we used peripheral nerve blocks of plexus brachialis-interscalene or supraclavicular nerve block.

Cases

Our first case was 39-years-old male patient, admitted in our hospital for orthopedic surgery with Dg. Contractura cubiti l.sin. He had a history of a car accident 1.5 years ago, was hospitalized in Intensive Care Unit for 2 months, he was on mechanical ventilation, and he was tracheostomized. When the patient was admitted for surgery, he was breathing normally, without difficulties, and his tracheostoma was closed. Because of that, we decided to give him supraclavicular nerve block. We explained to him all the advantages of this type of anesthesia, and he accepted it. Ultrasound-guided supraclavicular nerve block was performed with complete anesthesia of the upper limb. Bupivacain 0.5% 20 ml was given. The surgery was done in a supine position, lasted 1 hour and the vital signs of the patient were stable. Postoperative analgesia lasted around 19 hours. No complications or side effects were reported. The patient was very satisfied, and the next day was discharged home in a good condition and without pain.

The second case was 78-years-old male patient, admitted in our hospital with fracture of proximal part of the left humerus. The patient had medical history of HTA, AFF, COPD. Chest X-ray showed pulmonary fibrosis and emphysema. He was a smoker. General anesthesia and sitting position were with a high risk of intraoperative complications for this patient. So, the best choice of intraoperative anesthesia in this case was peripheral nerve block. The surgery was done with ultrasound-guided interscalene nerve block, in sitting position. 10ml Bupivacain 0.5% was given. The anesthesia of the arm was excellent and complete, with stable vital signs intraoperatively. The patient was sedated with midazolam. NIRS monitor was used, with stable cerebral oxygenation during surgery. Next day the patient did not complain of any pain, and on the second day he was discharged home in a stable and good condition.

The third case was 72-years-old male patient admitted for elective surgery, with Dg. Laesio nervus radialis regio cubiti, for decompression. The patient had a medical history of HTA, AFF, Diabetes Mellitus. Ultrasound-guided supraclavicular nerve block was performed, with 20ml

Bupivacain 0.5%. Intraoperative anesthesia and analgesia were excellent. The patient was in a supine position, sedated with midazolam, with stable vital signs all the time. Next day he was discharged home in good condition.

And the fourth case was 48-years-old male patient. He was admitted to our hospital with Dg. Laesio ommae l.sin for arthroscopy and tenodesis bicipitalis ommae l.sin. This patient was without any comorbidities, but he insisted on being awake and seeing the surgery. His wish was fulfilled. Surgery was performed with ultrasound-guided interscalene nerve block, with 10ml Bupivacain 0.5%. Intraoperative anesthesia and analgesia were excellent. The surgery was done in a sitting position, NIRS monitor, and vital signs were monitored and were stable during the procedure. Our patient was very satisfied and discharged home the next day with no pain.

Discussion

Ultrasound-guided regional anesthesia has become very popular in recent years because of the benefits that the method offers to patients. The use of ultrasound optimizes the technique of peripheral nerve blocks and reduces the dose of local anesthetic used (7).

Compared to systemic analgesia, regional anesthesia gives better postoperative analgesia, reduced pain intensity, less postoperative nausea and vomiting (PONV), as well as increased patient's satisfaction. But, for successful regional anesthesia for upper limb surgery it is required to have good patients' selection. If the patient is not cooperative, especially if the sitting position is needed, regional anesthesia is not recommended (2).

In our cases, regional anesthesia was the best choice for intraoperative anesthesia. Mild sedation with midazolam had a good effect in our cases. Postoperative analgesia lasted almost 18-20 hours. D'Alessio et al. demonstrated reductions in nonsurgical intraoperative time by 20 minutes and PACU time by 30 minutes among patients who received an interscalene block in a preoperative area compared to those who received general anesthesia (8). The interscalene block group also had fewer unplanned readmissions for treatment of pain, sedation or PONV.

Our patients received interscalene or supraclavicular block depending on the type of surgery. No complications were found from performing the blocks. From the operating room they were discharged directly to the ward in a stable condition, no complaints of pain, nausea or vomiting. After 4 hours they were allowed to get up, walk and drink. Next day the patients were discharged home. Readmissions were not reported in our cases.

There are a lot of studies that confirm the benefits of PNBs use:

- improvement in postoperative pain control and reduction in the use of opioids (9);
- reduction in hospital length of stay (10);
- prevention of hospital readmissions (11);
- reduction in postoperative nausea and vomiting (9);
- faster movement to recovery and/or post-anesthesia care unit (12);
- earlier participation in physical therapy (10);
- improved patient's satisfaction (9).

Conclusion

In cases where general anesthesia has a high risk of intraoperative complications for patients, peripheral nerve blocks can be excellent and safe choice for intraoperative anesthesia and postoperative analgesia.

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CENTRAL VENOUS CATHETER PLACEMENT IN A PATIENT WITH ABNORMAL VENOUS ANATOMY

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Abstract

For critically ill patients, central venous catheter insertion is a routine and frequently requires procedure. The internal jugular vein is the most commonly used central vein. We describe a case of 70-years-old female, with severe obesity, (BMI >30kg/m2), and a medical history of hypertension, DM2ID, AFF, thyrotoxicosis. The patient was stationed in the ICU due to progression of thyrotoxicosis. On admission she was unconscious, hypoxemic, dyspneic and hemodynamically unstable. Acid base status was interpreted as metabolic acidosis. Shortly after admission in ICU she was intubated and put on mechanical ventilator. Central venous catheter insertion was indicated. We chose the internal jugular vein for CVC. After multiple unsuccessful attempts, we decided to use ultrasound for better visualization of the anatomical structures. We found out displacement of the internal jugular vein about 3cm lateral presentation due to thyroid gland enlargement. The CVC was successfully inserted after the first attempt without further complications. To help with orientation of the deep path of CVC insertion, there are surface anatomic landmarks. But the proportions and anatomical relationships vary by gender, alter with normal aging, and are affected by conditions like high BMI. In our instance, the patient had an enlarged thyroid gland that was not clinically apparent. Despite the blind technique, the usage of ultrasonography in this particular situation proved to be successful on the first attempt. The case highlights the effectiveness of ultrasound in improving the success rate and safety of central venous catheter insertion, particularly when anatomical variations pose challenges.

Key Words: *central venous catheter, landmark, thyroid gland, ultrasound.*

Introduction

For critically ill patients, central venous catheter insertion is a routine and frequently required procedure. Numerous access methods and tools were created for a variety of purposes, such as administering medication, administering total parenteral nutrition, administering dialysis, administering plasmapheresis and monitoring hemodynamics (1). The internal jugular vein, the subclavian vein and the femoral vein are all vessels utilized for catheterization. The operator's experience and factors related to the patient, influence the selection of which vein to use (2). Guidelines from medical societies strongly suggest the use of ultrasound for placing a central

venous catheter in the internal jugular vein, based on clinical study evidence (3).

Case Presentation

We describe a case of 70-years-old female, with severe obesity, (BMI> 30kg/m2) with a medical history of hypertension, Diabetes mellitus type 2 insulin dependent, AFF, thyrotoxicosis. The patient was first admitted in the department of Endocrinology due to severe thyrotoxicosis. Couple of days after she was initially admitted in the department of Endocrinology and non-responsive to medicaments treatment, the patient became unconscious, hypoxemic, dyspneic, tachycardic and hemodynamically unstable. Acid base status was interpreted as metabolic acidosis. The patient was transferred to the intensive critical care unit for further investigation and treatment. Shortly after admission in ICU she was intubated and put on mechanical ventilator. Central venous catheter insertion was indicated. We chose the internal jugular vein for CVC. Seldinger technique was used. Ten minutes after multiple unsuccessful attempts, we decided to use ultrasound for better visualization of the anatomical structures. We found out displacement of the internal jugular vein about 3cm lateral presentation due to thyroid gland enlargement. The CVC was successfully inserted after the first attempt without further complications.

Discussion

Landmark techniques, which rely on anatomic structure knowledge and the palpation of arteries next to the veins, are traditionally used for CVC placement. Anomalies at the CVC insertion site cannot be taken into account by these landmark techniques. For the internal jugular vein (IJV), subclavian vein (SV) and femoral vein (FV), anatomic variations to the "normal anatomy" have been reported in a significant proportion of patients (3). The internal jugular vein can be accessed by three different percutaneous methods: anterior, central, and posterior. The central approach is the method of internal jugular cannulation that the authors recommend. The boundaries of Sedillot's triangle, the clavicular head of the sternocleidomastoid laterally, the sternal head of the sternocleidomastoid muscle medially and the superior border of the medial third of the clavicle inferiorly, make up the important surface anatomy**.** The first step in cannulation is a cutaneous puncture at the triangle's superior apex (4). However, the dimensions and anatomical linkages are gender specific, change with normal ageing, and are impacted by disorders such as elevated body mass index (5). In our case, the patient was obese, with BMI>30kg/m2, with enlarged thyroid gland that was not clinically evident. We found no success in multiple attempts using the blind technique and following the anatomical landmarks. Therefore, the decision to use real-time ultrasound for better visualization of the anatomical structures was made. The addition of ultrasound guidance to the technique has shown great improvement considering the finding of displacement of the internal jugular vein about 3cm lateral presentation due to thyroid gland enlargement. The knowledge from US-guided CVC placement and the knowledge from anatomic landmark techniques must be integrated and combined to reach the optimal skill level for CVC placement (4). Prior to and during the insertion of the catheter, the operator can see the intended vein and the surrounding anatomic structures thanks to real-time ultrasound guidance of CVC insertion. This technique seems to increase the rate of success and decrease the rate of complications related to CVC implantation (6). It is reported that approximately 15% of central venous line placements result in complications overall. There is a reported 33 percent incidence of mechanical issues, which are frequently operator-dependent. Arteri-

al puncture, catheter malposition, pneumothorax, subcutaneous hematoma, hemothorax and (extremely rare) cardiac arrest, are among the complications associated with CVL placements. The complication rates associated with this procedure can be considerably reduced by utilizing real-time ultrasound guidance (7). In our case, the CVC was inserted after the first attempt using ultrasound guidance without further complications. Several medical societies' guidelines strongly advise using US for CVC placement in the IJV based on data from clinical studies. The use of US in clinical practice and the available evidence and guidelines still differ, according to data from survey studies (3).

Conclusion:

Good anatomical knowledge and recognition of anatomical landmarks combined with the US skills of the user are crucial for success in the procedure of CVC placement. Our case highlights the effectiveness of ultrasound in improving the success rate and safety of central venous catheter insertion, particularly when anatomical variations pose challenges.

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CASE REPORT *UDK: 616.132.2-089.843:616.61-006.6-089.87*

SIMULTANEOUS SURGERY FOR ADVANCED RENAL CELL CARCINOMA AND CONCOMITANT DOUBLE VALVE AND CORONARY ARTERY DISEASE: A RARE CASE REPORT

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Abstract

Introduction: Cardiovascular and neoplastic diseases are the main causes of death in Europe. Renal cell carcinoma is a kidney cancer that originates in the lining of the proximal convoluted tubule.

Case Report: A 74-years old patient with severe aortic valve stenosis, severe mitral valve regurgitation and coronary artery disease was diagnosed with malignant renal carcinoma in advanced stage with intravascular extension as tumor thrombus into the inferior vena cava and right atrium. A multidisciplinary team, consisting of cardiac surgeons, urologists and anesthesiologists, has successfully performed a simultaneous curative surgery consisting of aortic valve replacement, mitral valve repair, double coronary artery bypass and open radical nephrectomy, lateral cavotomy and thrombectomy under cardiopulmonary bypass. The procedure was rendered as a very high-risk procedure. In the postoperative period, due to oligo-anuria, the patient was placed on continuous veno-venous hemodiafiltration, with subsequent resolution of left kidney function. The pathohistological finding revealed Clear renal cell carcinoma in the IV stage, pTNM= pT4 G3 (WHO/ISUP) pNx pM1 L1 V1 R1. The patient was discharged on the 15th postoperative day in good and stable condition.

Conclusion: Patients with renal tumors in advanced stage and cardiac disease can be treated successfully with surgery and benefit from early intervention by a simultaneous approach. This is a rare case report in which extensive cardiac surgery procedure and urologic procedure were performed. The multidisciplinary approach is the key factor for successful outcomes.

Key Words: *cardiac disease, cardiac surgery, renal cell carcinoma, simultaneous surgery.*

Introduction

Cardiovascular diseases accounted for around one-third of all deaths in Europe in 2021(1). Cancer was the second most common cause (1). Renal cell carcinoma (RCC) is a type of kidney cancer that is formed in the epithelial cells in the proximal convoluted tubule. It represents around 3% of all cancers, and is responsible for 80% to 90% of all primary renal neoplasms. It is the most common type of kidney cancer in adults, predominantly in men. The incidence of tumor thrombus in inferior vena cava is 4% to 10%, whereas extension of the tumor thrombus to the right atrium is 0.3% to 1.0% (2).

Initial treatment for renal cell cancer is surgical, consisting of radical nephrectomy or partial nephrectomy, involving regional retroperitoneal lymph nodes. Extension of tumor thrombus in inferior vena cava or rarely the right atrium, requires additional multimodal techniques for tumor extraction, such as liver mobilization, control of the vena cava, right heart veno-venous bypass and cardiopulmonary bypass with or without circulatory arrest (3).

The number of patients who have both cardiac disease and cancer has been rising as the proportion of elderly in the general population increases. Surgical procedures for cardiac disease and renal tumors can be performed in stages or simultaneously (at the same time). Over the last years, simultaneous operations are favored and treatment of choice to achieve a long-lasting remission (4).

Case Report

A 74-years-old patient with symptoms of fatigue, dyspnea, swelling of both lower legs, high blood pressure and ascites, performed heart echocardiography revealing ejection fraction of 44%, severe aortic stenosis, severe mitral regurgitation, moderate tricuspid regurgitation and suspect thrombosis of inferior vena cava (Figure 1).

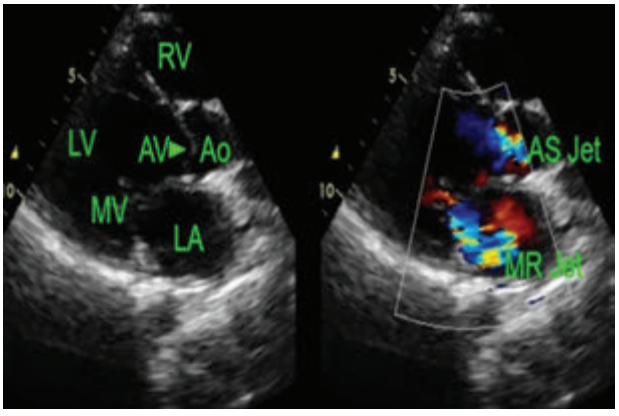

Figure 1. Echocardiographic findings.

Coronarography finding resulted in LAD proximal stenosis 80-90% and RCA prox 100% with collaterals (Figure 2).

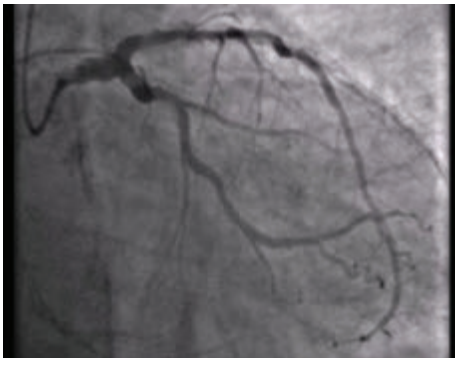

Figure 2. Left anterior descending artery stenosis an chronic occlusion of right coronary artery.

The blood test results revealed hemoglobin 60g/L. The patient was substituted with red blood cells transfusions. The CT scan showed right kidney tumor mass which penetrates the cortex and partially spreads retroperitoneally. The tumor is spreading into the renal vein and additionally to the inferior vena cava proximally in length of 82mm, to the right atrium. Inferior vena cava lumen is narrowed around 90%. The left kidney, liver and spleen, are normal. There are no enlarged retroperitoneal lymph nodes (Figure 3).

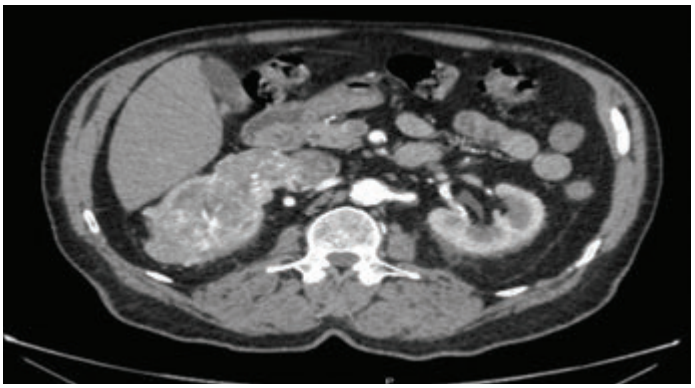

Figure 3. Right kidney tumor invading the inferior vena cava in CT scan.

The pulmonary function tests showed moderate to severe degree of combined type of ventilatory failure (FEV1 52%, SpO2 93% without oxygen).

Afterwards, the patient was properly preparing for three months, including diuretic therapy, antihypertensive drugs, bronchodilator therapy and correction of anemia. The procedure was rendered as a very high-risk procedure.

A multidisciplinary team, consisting of cardiac surgeons, urologists and anesthesiologists, has successfully performed a simultaneous curative surgery consisting of aortic valve replacement, mitral valve repair with ring annuloplasty and double coronary artery bypass, and open radical nephrectomy, lateral cavotomy and thrombectomy under cardiopulmonary bypass (Figure 4).

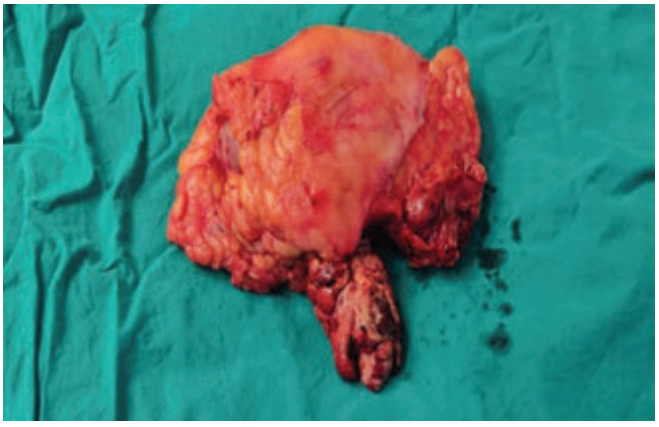

Figure 4. Intraoperative figure of right radical nephrectomy along with the tumor thrombus extending to the vena cava and right atrium.

In the postoperative period, due to oligo-anuria the patient was placed on continuous veno-venous hemodiafiltration, with subsequent resolution of left kidney function and satisfactory diuresis. Antibiotic therapy was administered including piperacillin/ tazobactam, linezolid and antifungal medication fluconazole, adjusted according to eGFR. Catecholamine and vasopressor support were gradually reduced in the postoperative period and discontinued. After extubating he was placed on non-invasive mechanical ventilation, and intensive physical and respiratory therapy was performed. The pathohistological finding revealed Clear renal cell carcinoma in the IV stage, pTNM= pT4 G3 (WHO/ISUP) pNx pM1 L1 V1 R1. Postoperative echocardiography showed good function of the implanted aortic valve and annuloplasty of the mitral valve without residual regurgitation or paravalvular leak. The patient was discharged on the 15th postoperative day in good and stable condition.

Discussion

As the aging population increases, presentation of cancer patients who are simultaneously affected by a cardiac disease requiring surgery is increasing (4). The first case of simultaneous surgical treatment in patients with cardiac disease and extracardiac tumors was reported by Dalton et al., in 1978 (5). However, there are only a few reports in the literature of cardiac disease and concomitant kidney tumor requiring surgical treatment.

Litmathe et al., in 2004 (6), presented series of six patients who had undergone concomitant surgery using cardiopulmonary bypass and kidney tumor resection. Two of the patients had undergone nephrectomy and aortic valve replacement, while four patients had undergone nephrectomy and coronary artery bypass surgery. All six patients had satisfactory long-term survival.

In 2017, Andrushchuk et al. (3), published the largest series of simultaneous (15 cases) and staged (14 cases) surgeries for concomitant cardiac diseases and kidney tumors. Their experience revealed that simultaneous approach is a preferred option when the tumor is invading the inferior vena cava, while the staged surgery should be used for localized kidney tumors.

There are other isolated case reports which give emphasis to simultaneous surgery, such as Budrikis et al., 2012 (4), with performing simultaneous operation with technique of extended sternotomy, Erdem et al., 2022 (7), presenting multidisciplinary open surgical treatment of renal cell carcinoma with venous tumor thrombus extending to the right atrium, Quang Fu et al., 2017 (2), surgical treatment of renal cell carcinoma and coronary artery bypass surgery.

All reviews for treating patients with cancer and simultaneous cardiac disease show the importance of submitting every challenging case to the assessment of a multidisciplinary team, in order to have the most comprehensive evaluation and results (8).

Conclusion

In our case a simultaneous procedure was a good and feasible option for patient's treatment. Moreover, such a complex operation consisting of aortic valve replacement, mitral valve repair with ring and double coronary bypass grafts, open radical nephrectomy, lateral cavotomy and tumor thrombus extirpation, is very rare in the literature. Our patient is recovering well in the two-years follow up. A multidisciplinary team approach consisting of cardiac surgeons, urolo-

gists and anesthesiologists is the hallmark of success in such complex cases.

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PULMONARY FAT EMBOLISM AFTER FEMORAL FRACTURE IN 20 YEARS OLD BOY - CASE REPORT

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Abstract

Introduction: A fat embolism (FE) syndrome is a rare condition when a piece of intravascular fat lodges within a blood vessel and causes a blockage of blood flow. It commonly occurs after fractures to the long bones particularly the femur, tibia and pelvis, besides the anticoagulants. The fat droplets don't have to be present in urine to set up the diagnosis when itis based on clinical symptoms.

Case Report: 20-years-old patient was hospitalized after a fall from a one-meter height with Dg. Fra diaphysis femoris sin cum dislocation; Fra ossis naviculare sin. In a few hours, operation was performed(Osteosynthesis intramedularis femoris) and the patient was transferred at the Department of Trauma. After two days the same patient was transferred to the ICU as his condition deteriorated (HR >140/min, SaO2<70%, dyspnea, hyperventilation >30/min.). Despite symptomatic therapy the patient's condition became worse and he was intubated. CT and CT angiography were performed (ARDS diffusa bill; Mass fat pulmonary embolism suspected). COVID-19 test was made (positive +), and also AB status, hemostasis and hemoculture were made. Fat droplets were not found in urine. After 3-4 days the patient's condition was satisfactory and he was extubated.

Discussion: In case of this patient because fat droplets were not found in urine, mass pulmonary embolism was diagnosed only clinically. Differential-diagnostically it is possible ARDS to occur after trauma, and ARDS after COVID pneumonia.

Conclusion: There is no cure for fat embolism and there is no standard treatment. The main goal is to provide supportive care and prevent further complications. Whatever, early though on fat embolism always provides good outcome for the patients.

Key Words: *ARDS , fat droplets, fat embolism.*

Introduction

Fat embolism syndrome (FES) is a complication of long bone fractures and polytrauma. FES can lead to potentially respiratory failure in the form of rapidly developing acute respiratory distress syndrome (ARDS) (1).

The development of FES is caused by the release of fat emboli and leads to occlusion of the microvasculature, which triggers an inflammatory response clinically manifested by dermatologic,

pulmonary and neurologic dysfunction.

The pathophysiological mechanisms of FES are still controversial. The development of FES is explained by two theories: mechanical and biochemical. The mechanical theory explains that a fat embolus can cause mechanical blockage in the pulmonary blood vessels and can stimulate the release of lipase by peripheral vascular endothelial cells, which increases the free fatty acids level and leads to vascular permeability changes, pulmonary artery pressure increases, and pathological changes result in ARDS (2-4).

Case Presentation

A 20-years-old patient was hospitalized after a fall from a one-meter height with Dg. Fra diaphysis femoris sin cum dislocation; Fra ossis naviculare sin. In a few hours an operation was performed(Osteosynthesis intramedularis femoris) and the patient was transferred to the Department of Trauma. After two days the same patient was transferred to ICU as his condition deteriorated (HR >140/min, SaO2<70%, dyspnea, hyperventilation >30/min.). The patient was treated with symptomatic therapy. The patient's condition became worse, and he was intubated and put on mechanical ventilation. Fat droplets were taken from urinary sediment (negative) and a CT and CT angiography were performed (ARDS diffusa bill; Mass fat pulmonary embolism suspected). COVID-19 test was made (positive +). An AB status, hemostasis and hemoculture were made. The ABS showed the following: pH 7.261, pO2 93.4 mmHg, pCO2 46.1mmHG, HCO3 20.9mmol/L, PO2/FIO3 422.5mmHg. The lab test showed low Hemoglobin 89g/l and Hematocrit 0.27l/L, low Potassium (3.3mmol/L), hypoproteinemia (55g/l) and hypoalbuminemia (35g/l). The treatment included antibiotics, corticosteroids, and anticoagulant therapy with heparin. The patient was extubated after three days. In the following days, there was improvement in the clinical state and the control CT showed improvement. The patient was discharged from the ICU after 14 days.

Discussion

FES is commonly related to orthopedic trauma, mainly in long bone fractures of the lower extremities, particularly the femur.

Population-level data from the National Hospital Discharge Survey found an FES incidence of 0.17% in patients with isolated or multiple orthopedic fractures. The incidence increased to 0.54% in isolated femoral fractures and 1.29% if multiple fractures including the femur were present (5).

FES is characterized by multisystem dysfunction. Pulmonary manifestations are among the most common and frequent initial signs of FES and include dyspnea, tachypnea, hypoxemia and respiratory failure. In 1 large series of patients with FES, hypoxemia was the most common finding, affecting 96% of the patients. The most common nonspecific findings include fever and retinopathy. Thrombocytopenia and unexplained anemia are common hematologic manifestations seen in 37% and 67% of the cases (6).

Fat emboli cause acute lung injury, altering pulmonary vascular resistance and decreasing systemic blood pressure, cardiac output and intraoperative arterial oxygen saturation, while in-

creasing pulmonary permeability and mean pulmonary arterial pressure. Pulmonary dysfunction following FE is also reported to be aggravated by secondary problems such as hypoxia, hypovolemia, pulmonary vasoconstriction, pre-existing pulmonary disease or massive blood transfusions. The bone marrow fat is primarily filtered by the lungs, which makes it the first organ to be affected when no intracardial shunt is present. Respiratory dysfunction within 12-72 hours following injury in a patient with musculoskeletal trauma without pulmonary injury, indicates the development of FES (7).

The diagnosis is made by the characteristic clinical presentation and chest X-ray findings of bilateral patchy infiltrates consistent with acute respiratory distress syndrome.

Because FES is a heterogeneous disease with a wider spectrum of features, its diagnosis can be challenging. Gurd proposed clinical criteria for diagnosing FES in 1970, later modified by Wilson (8)..

Table 1: Gurd and Wilson's criteria for FES

- Respiratory distress
- Cerebral symptoms in non-head injury patients
- Petechial Rash

Minor criteria

- Tachycardia (>110 bpm)
- Fever (>38.5 C)
- Jaundice
- Renal changes
- Retinal changes
- Drop in hemoglobin
- New onset thrombocytopenia
- Elevated ESR
- Fat macroglobulinemia

2 major criteria or one major criteria and four minor criteria suggest a diagnosis of FES.

Figure 1. The Gurd and Wilson`s criteria for FES (8).

Laboratory and imaging tests can help in the diagnosis but they are nonspecific. Patients will be hypoxemic while on room air on arterial blood gas. Chest X-ray shows diffuse interstitial infiltrates and chest CT scan shows diffuse areas of vascular congestion and pulmonary edema. Biochemical test of lipase, free fatty acids and phospholipase A2 have all been shown to be elevated in patients with FES. However, this elevation is nonspecific in patients with lung injury. Also, microscopic examination of blood, urine or sputum may show fat globules, but again this finding is nonspecific.

Bronchoalveolar lavage (BAL) has been used as a diagnostic tool for FES. Lipid inclusions within macrophages can be quantified BAL. But because it is an invasive and time intensive, it has not become widely used in diagnosing FES (8)(9).

The presented patient met the diagnostic criteria proposed by Gurd, with the respiratory symptoms and positive signs of lung imaging changes, showed in CT of thorax and with the second-

ary features which included tachycardia (>120 beats/min), and an acute decrease in hemoglobin <100 g/L.

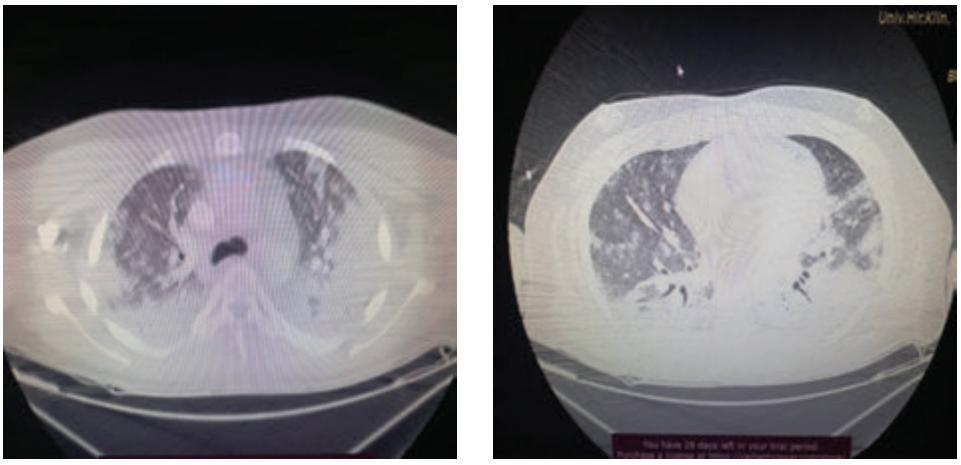

Figure 2, 3. CT findings of ARDS in the patient.

There is no specific treatment for FES. The management includes symptomatic treatment of FES and secondary ARDS, corticosteroids and anticoagulants (11-13).

Conclusion

FES is a common complication of long bone fractures with no specific demographic presentation. There aren't specific test for diagnosing FES still, it relies on clinical signs, chest X-ray and CT findings. The main goal is to provide supportive care and prevent further complications. However, early recognition of clinical signs of fat embolism and ARDS always provides a good outcome for the patients.

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ANESTHETIC CONSIDERATIONS DURING LABOR AND DELIVERY IN PREGNANT WOMAN WITH A HEREDITARY ANGIOEDEMA

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Abstract

Hereditary angioedema (HAE) is a rare inherited disorder, characterized by C1 esterase inhibitor (C1-INH) deficiency, manifested with episodes of swelling attacks. Pregnancy is a potential triggered factor that may aggravate the attacks, leading to serious complications during childbirth. A 39 years-old pregnant woman at 37th gestational week, diagnosed with HAE type I at the age of 32 presented at our institution due to labor pains. She had a history of thrombophilia and three spontaneous labors, two of them were stillbirth. None of the labors were complicated by an acute attack. Although the attacks were infrequent and the last one occurred 1 year ago, she had a history of an upper respiratory tract swelling episode. The head of the National Angioedema Center recommended administration of prophylactic dose of C1-INH and avoidance of fentanyl in case of anesthesia. The patient had a spontaneous vaginal delivery without anesthesia. She was observed in ICU for 48h and discharged after 72h without any complications. Although this patient had normal delivery, we emphasize the necessity of anesthetic readiness in several aspects. Up to available data, regional anesthesia is preferred technique whenever possible. The use of fentanyl is debatable due to its potential interaction with the components of innate and adaptive immune system. Due to drug availability and above-mentioned risk factors, the patient received high dose of C1-inh, although prophylaxis is not obligatory and lower dose of 1800U (20U) is considered efficient. The appropriate planning and close multidisciplinary cooperation contributed to a positive outcome in our case.

Key Words: *HAE, labor, C1 inhibitor, prophylaxis.*

Introduction

Hereditary angioedema (HAE) is a rare inherited disorder that arises from autosomal dominant genetic mutation (SERPING gene), resulting in lack or impaired function of C1 esterase inhibitor (C1-INH) (1). One of the major roles of C1-INH is inhibition of the steps in the kinin-gen-

erating pathways, which is the most directly related proposed mechanism in the pathogenesis of HAE (2). This disturbance leads to excess of bradykinin production which results in increased permeability of blood vessels. HAEs are classified into three types. HAE type I is caused by C1-INH deficiency; HAE type II is characterized by normal levels, but unfunctional molecules of C1 –INH, while HAE type III most recently described in 2020 is associated with gene mutations. The main disease manifestation is unpredictable swelling attacks of subcutaneous and submucosal tissues. Swellings usually develop slowly over a few hours, although in some patients they may progress quickly and usually persist for one to five days (3). Most commonly affected areas are skin, gastrointestinal tract, face and upper airway tract with larynx and oropharynx involvement. Several factors may provoke an acute attack, including stress, infection, increased concentration of estrogen, surgical trauma and anesthetic airway instrumentation (4). Therefore, pregnancy is a potential trigger factor that may aggravate the frequency of attacks, leading to serious complications during childbirth. In addition, severe attacks may lead to complete airway obstruction. Epinephrine and other anti-anaphylactic drugs are not helpful in these cases. In affected patients who require intubation, it is often performed with topical anesthesia on awake or lightly sedated patients (5). We report a woman in labor with HAE type I and describe the management during labor and delivery with an accent on the role of the anesthesiologist.

Case Report

We report here a 39-years-old pregnant woman at 37th gestational week, diagnosed for HAE type I at the age of 32. The diagnosis was confirmed by immune genetic analyses, which showed decreased concentration of functional C1INH, C3 and C4 complement components. She presented at our institution due to labor pains. She had a history of thrombophilia and three spontaneous labors, two of them were stillbirth. In the second pregnancy, the patient was prescribed short term prophylaxis with C1 INH before delivery. None of the labors were complicated by an acute attack. Although the attacks were infrequent and the last one occurred 1 year ago, she had a history of upper respiratory tract swelling episode. The patient described the attack with pain and tightness as if she had a lump in her throat. Intubation was not required for the management of this attack. In general, her attacks were manifested by migrating painful swellings, edema of the face and mouth. She denies family history for HAE. The patient is reported in the Rare Disease Registry, she was educated and owns license for preparation and self-administration of the prescribed medication. The patient is obliged to have at any time sufficient amount of medication for at least two acute attacks of HAE. Given the unpredictability of the disease and the impending delivery, we established online conversation with the allergist/ immunologist for instructions of using the therapy. The recommendation was to administer 2 vials recombinant human C1INH (one vial contains 1200U). Each vial should be dissolved in 14ml of aqua and both vials together to be given within 5 minutes. If symptoms appear, another dose can be given after 2 hours of the application of the first dose. If contrasts, if symptoms affecting the respiratory system with edema and difficulty breathing occur, the dose should be repeated after 20 minutes. In addition to the specified instructions, she recommended us to avoid fentanyl in case of anesthesia. In presence of the anesthesiologist, obstetric, neonatologist and auxiliary medical staff, the patient received prophylactic dose of 4200U of recombinant human C1INH (rhC1INH – Ruconest) before delivery. The patient had a spontaneous vaginal delivery without anesthesia. She was observed in ICU for 48h and discharged from hospital after 72h without any complications.

Discussion

Hereditary angioedema is an autosomal disorder that is manifested by unforeseeable episodes of swelling attacks of the skin and mucous membranes. The attacks vary from mild to life threatening in case of swelling of the airway structures which may lead to asphyxia. Alterations in female sex hormones during pregnancy are considered to have an impact on the frequency and severity on swelling attacks (6). However, obstetrics complications, such as premature births, spontaneous abortions and cesarean deliveries, are not associated with HAE (1). A study has shown that although the attacks in pregnancy are more frequent, they do not increase in severity (7). We assessed our patient to have an increased risk of airway swelling due to several reasons. Her most affected areas were the face and the mouth, which are the initial symptoms of upper airway edema in 15-30% of the patients (8). An additional risk factor is the age between 11-45 years old (8). However, in our case the last attack occurred a year ago, which means that she did not have a single attack during her pregnancy. Still, the possible seriousness of an eventual attack, the need of pharmacology preparation and multidisciplinary approach including specialists familiar with disease pathology, especially in a case of intubation, additionally increases the risk of disease complications.

We emphasize the necessity of anesthetic readiness in managing patients with HAE in several aspects. The upper aerodigestive tract is a predilection place and highly vulnerable during instrumentation in these patients, which may lead to fatal obstruction. Death rates from untreated acute laryngeal oedema can reach 15–33%, whereas in patients with confirmed diagnosis and cautious management, these rates drop to 4–6% (9). According to studies, asphyxiation can happen between 20 minutes and 14 hours after the onset of symptoms (10). Upper airway edema (UAE) is an emergency condition where primary is to recognize the onset of attack. In addition to pharmacological treatment, the anesthesiologist should also take care of supporting treatment: to ensure airway, oxygenation, intravenous fluids to prevent hypovolemia due to vasodilatation, and leak of fluids in the interstitial place. If intubation is not required, the patient should be placed in a recovery position. In unconscious hypoxemic patients, with stridor and dyspnea, intubation is necessary. Difficult airway equipment and tracheostomy set is obligatory in pregnant woman, considering the alterations in anatomy and physiology, the increased risk of aspiration and gastric reflux, and the harmful consequences of hypoxia on the developing fetus. If intubation or tracheostomy fails, cricothyroidotomy should be performed. The inner diameter of the intra venous catheter must not be less than 3mm to ensure sufficient gas exchange (8).

Spontaneous vaginal delivery is the safest way to give birth. Up to available data, regional anesthesia is preferred technique whenever possible (11). The epidural catheter may reduce the labor pains and avoid the harmful effects of general anesthesia, in case of emergency caesarian section (7). This procedure was not performed on our patient, as she was admitted at the hospital with labor pains at the end of the first stage of labor. We did not administer any anesthesia. There are many studies and reports published so far, where regional anesthesia was successfully used in patients with HAE undergoing any intervention (7,11,12).

Despite that there is not current evidence-based medical contraindication for using opioids (1,11), the use of fentanyl is debatable due to its potential interaction with the components of innate and adaptive immune system and possible damaging effect on mucosal membranes. The available literature data show that opioids may induce mast cell degranulation, reduce TNF – alpha levels and damage the mucous membranes (2,11,13). In our case the recommendation

of the national manager of ACARE (Angioedema Centers of Reference and Excellence) was to avoid fentanyl. There are not contraindications of using other anesthetics, but patients should not take Angiotensin Converting Enzyme (ACE) inhibitors and non-steroid anti-inflammatory drugs. The first ones catabolize bradykinin, while the second inhibit prostaglandin synthesis, both causing skin mast cell degranulation (11).

Pharmacological treatment for HAE is used for acute attacks, on-demand therapy, like short-term prophylaxis (STP) before invasive procedures and like long- term prophylaxis (LTP) (14).

Approved on-demand medications are Plasma derived C1INH concentrates (*pdC1INH*, Berinert) and recombinant human C1INH (*rhC1INH*, Ruconest), plasma kallikrein inhibitor *ecallantide* and bradykinin B2 receptor antagonist *icatibant*. For short-term prophylaxis can be used pdC1INH, anabolic androgen and rhC1INH (1). Considering that anabolic androgens are contraindicated, while ecallantide, lanadelumab and icatibant are not approved for use in pregnancy, C1INH is recommended for acute attacks or STP. Due to the unpredictability and rarity of the disease in many hospitals the drug is not available, so the patient must be supplied, with no exception, with at least 2 standard doses of a Food and Drug Administration (FDA) - approved on-demand medication (1), as it was the case for our patient. Fresh frozen plasma (FFP) for acute attacks and STP, tranexamic acid and epsilon-aminocaproic acid for LTP can be used, if none of the FDA approved medicines is available (13,14,15). However, our patient was diagnosed with thrombophilia, and antifibrinolytics are contraindicated in such patients (13). Although the FDA approved first line medication is pdC1INH, to date literature support the use of rhC1-INH in pregnancy as safe and effective. There are a few case series on rhC1-INH application in pregnant women for STP and acute attack with no adverse effects been reported (16,17). Current guidelines point out the use of rhC1-INH at a dose of 50U/kg up to 4200U (1,17), although some studies report the dose of 10-20u/kg for STP 30-60 minute before surgical procedure as efficient (11). Because there are no rigid criteria whether to use prophylactic therapy in spontaneous uncomplicated labor (1) in consultation with ordinating immunologist, we decided to use the full dose of rhC1INH (4200U/kg). The patient had enough vials of rhC1INH (Ruconest 2100U) for intravenous use.

Conclusion

The aim of this report is to point out that pregnant patients with HAE should always be managed with a comprehensive strategy, including close follow up of the patient, multidisciplinary cooperation and prophylactic therapy in certain situations. The role of the anesthesiologist is essential, and all the possible complications always should be taken in account, and possible solutions and preparations should be planned upfront.

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CORONARY ARTERY BYPASS SURGERY IN PATIENT WITH HEMOPHILIA B

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Abstract

Introduction: Hemophilia B is inherited X-linked recessive genetic bleeding disorder caused by low concentrations of coagulation factor IX. Cardiac surgery alone poses a high intra and postoperative coagulation risk.

Case Report: Our patient is a 58- years-old man suffering from mild form of hemophilia B presenting with symptoms of unstable angina pectoris. The preoperative level of factor IX was 52 units/dl (normal range 50-150 units/dl). In consultation with hematology specialist, 9000IU of AIMAFIX plasma coagulation factor were administered. A multidisciplinary team, consisting of cardiac surgeons, anesthesiologists and hematologists has successfully performed and managed the coronary artery bypass surgery. Six hours after surgery the level of factor IX was 102 units/dl, so 4500IU of coagulation factor IX were administered every 12 hours in the first three postoperative days. On the third postoperative day the level of factor IX was 84units/dl, so 4500IU of coagulation factor IX were administered each day in the fourth and fifth postoperative day. The patient was discharged on the sixth postoperative day. Later the administration of coagulation factor IX was 4500IU daily for the following seven days. In the postoperative period and at home, the patient was treated with Clopidogrel 75mg daily, and Enoxaparin Sodium 40mg/0.4ml every 12 hours for the following 7 days.

Conclusion: In this case report, cardiac surgery with cardiopulmonary bypass was successfully and safely performed in a patient with hemophilia B without hemorrhagic or thrombotic complications. The multidisciplinary approach is the key factor for successful outcomes.

Key Words: *cardiac anesthesiology, coagulation, coronary artery bypass surgery, hemophilia B.*

Introduction

Cardiopulmonary bypass (CPB) has allowed surgical procedures to be taken, but the risks that accompany can be significant and must be expertly managed. One of the foremost risks is altered normal coagulation. Increasing levels of bleeding at the time of separation from CPB are associated with poor outcomes and mortality. CPB-associated coagulopathy is typically multifactorial, and include heparinization, prolonged cardiopulmonary bypass time, acidosis, hypothermia and preexisting bleeding disorders. The management of coagulopathy implies maintenance of the normal physiological conditions for coagulation, treatment of hyperfibrinolysis, reversal of excess heparinization, maintaining normal levels of coagulation factors and transfusion of

platelets, if thrombocytopenia or platelet dysfunction occurs. Important adjuncts to avoid transfusion include perfusion practices such as red cell salvage, sequestration and retrograde autologous priming (1).

The clinical management of hemophilia patients and dilemma lie in the maintenance of the balance between anticoagulation and hemostasis under conditions associated with blood loss, factor replacement therapy and hemodilution (2).

Hemophilia B patients who undergo cardiac surgery need to maintain hemostasis with recombinant factor IX during all treatment stages. The World Federation of Hemophilia guidelines recommend factor IX activity levels of 60–80 IU/dL prior to major surgery and continuous factor IX replacement during the 14-days postoperative period (40–60 IU/dL during the first 3 days, 30–50 IU/ dL 4th to 6th day, and 20–40 IU/dL from days 7 to 14) (3).

Case Report

Our patient is a 58-years-old man suffering from mild form of hemophilia B presenting with symptoms of unstable angina pectoris. The patient had chest pain one day before admission, so he underwent coronarography revealing significant three vessel coronary artery disease: Left anterior descending artery (LAD) proximal and mid segment 80% stenosis, Circumflex artery (CX) ostial 80% stenosis, and right coronary artery (RCA) proximal 95% stenosis, with dominance of right coronary artery vascularization area (Figure1 and Figure 2).

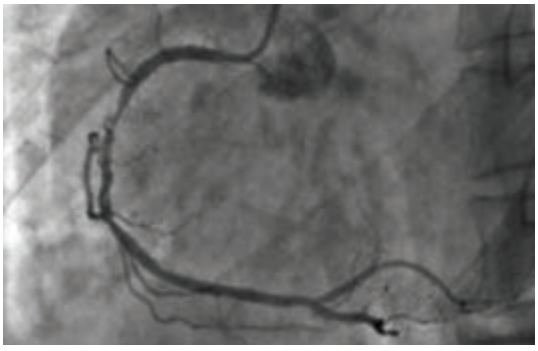

Figure 1. Right coronary artery stenosis.

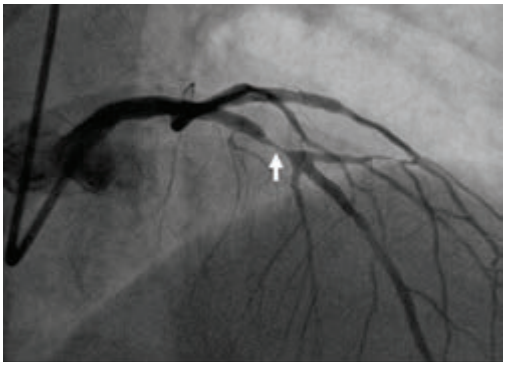

Figure 2. Left coronary artery stenosis.

The patient was also suffering from hypertension, dyslipidemia, non-insulin dependent diabetes mellitus on oral treatment and anxious disorder. About 23 years earlier, the patient had undergone crural amputation of right leg due to peripheral vascular disease and diabetic foot, necessitating walking with a prosthesis. He was also a long-term smoker.

The preoperative echocardiography revealed ejection fraction of 70%, normal dimensions of left and right ventricle, without regional drop in kinetics and normal findings of valvular apparatus (Figure 3).

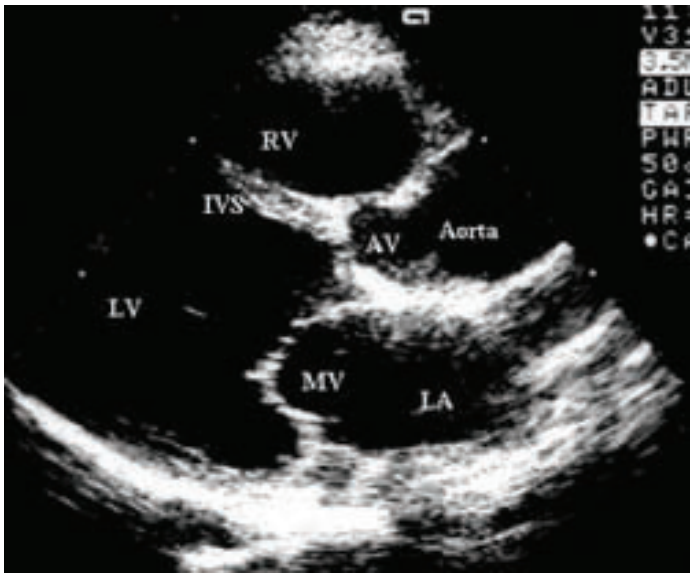

Figure 3. Echocardiographic findings.

Laboratory findings on admission were as follows: white blood cells 7.94 10^9/L, hemoglobin 153g/L, thrombocytes 258 10^9/L, urea 4.2mmol/L, serum creatinine 70umol/L, AST 55 U/L, ALT 94 U/L, CK 313 U/L, CK-MB 25 U/L, Troponin 0.032ng/ml. The coagulation status, aPTT 22.6s, Prothrombin time 10.3s (111.9%), INR 0.85, Fibrinogen 2.78 g/L, D-dimer 0.46 ug/ml F.E.U.

The preoperative level of factor IX was 52 units/dl (normal range 50-150 units/dl). In consultation with hematology specialist, 9000IU of AIMAFIX plasma coagulation factor were administered.

The patient underwent cardiac surgery procedure - CABGx3 (LIMA-LAD, SVG-PDA, LRA-Cx) the same day with good perioperative course. The patient received tranexamic acid intraoperatively. He was extubated a few hours after the operation. Six hours after surgery the level of factor IX was 102 units/dl, so 4500IU of coagulation factor IX were administered every 12 hours in the first three postoperative days. On the third postoperative day the level of factor IX was 84 units/dl, so 4500IU of coagulation factor IX were administered each day in the fourth and fifth postoperative day.

The postoperative course was uneventful. The patient had sinus bradycardia in the postoperative period, the control laboratory and echocardiography examinations were within normal limits.

The patient was discharged on the sixth postoperative day. Later the administration of coagulation factor IX was 4500IU daily for the following seven days. In the postoperative period and at home, the patient was treated with Clopidogrel 75mg daily, and Enoxaparin Sodium 40mg/0.4ml every 12 hours for the following 7 days.

Discussion

The progress in the hemophilia treatment has resulted in a near normal life expectancy, and as a result hemophilia patients are now more likely to be faced with age-related cardiovascular diseases, such as coronary artery or ischemic heart disease and valvular heart disease. Secondary to arthropathy and limited mobility, hemophilia patients are even more susceptible to certain cardiovascular risk factors such as obesity and hypertension (4,5).

Currently, the best treatment approach is to introduce a policy of multidisciplinary teamwork and individualize the treatment protocol (5).

The use of cardiopulmonary bypass induces multi-factorial changes in coagulation and inflammation. Most of the coagulation factors and inhibitors are decreased by approximately 30% to 40% after moderately complex cardiac surgery cases (6).

The current literature regarding the long-term anti-thrombotic treatment is limited for these patients following cardiac surgery. Adopting the current guidelines from the general population to hemophilia patients could be associated with increased bleeding risk. However, several case studies reported safe anti-thrombotic treatment. According to the experience of the Dutch Group, the recommendations for anti-thrombotic treatment should be the same as those adopted in the general population, providing that there is adequate replacement therapy. There are still few data on the appropriate dose and duration of anti-thrombotic and anticoagulation therapy. Therefore, close cooperation between all the specialists is essential in order to minimize the bleeding risk and optimize treatment for such patients (7,8).

Indeed, data and reports of cardiac surgery in patients with hemophilia, especially hemophilia B, are very scarce, and are limited to small series and case reports, or expert opinions and reviews. Most recent expert opinions and reviews have been focused on perioperative management but fail to address optimal strategies for managing these patients during surgery (8,9).

Most experts agree that cardiac surgery in such patients requires a multidisciplinary and individualized approach for each patient, with the participation of surgeons, hematologists, anesthesiologists, laboratory specialists and intensivists.

Conclusion

In this case report, cardiac surgery with cardiopulmonary bypass was successfully and safely performed in a patient with hemophilia B without hemorrhagic or thrombotic complications. This experience demonstrated the importance of multidisciplinary approach and preoperative planning for the care of complex patients undergoing cardiac surgery.

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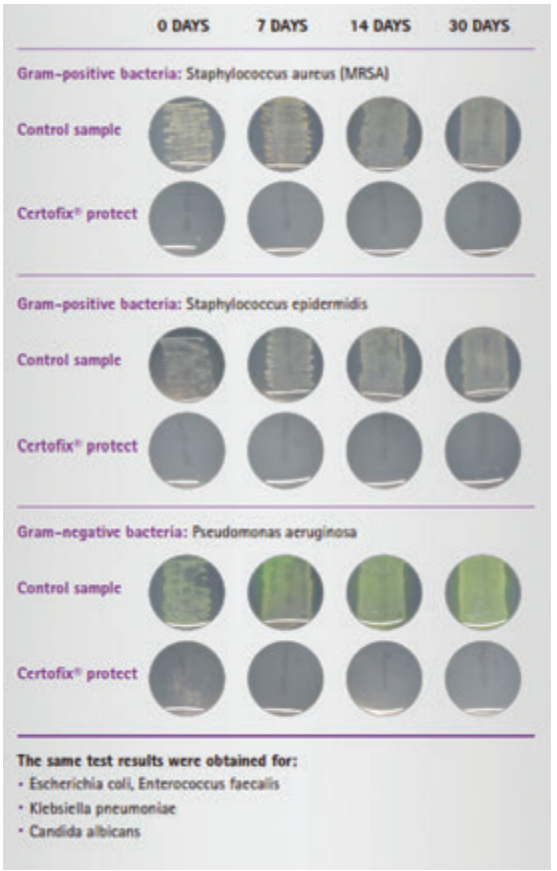

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