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

MJA

Macedonian Journal of Anaesthesia

A Journal on Anaesthesiology, Resuscitation, Analgesia and Critical Care

MJA vol VII No 3
Supplement No 1
CEAA (Committee for European education in Anaesthesiology)

Course 4

MOTHER AND CHILD. ADVERSE REACTIONS
PAPERS
DOJRAN 2023

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

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

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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

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- **Намалување на несаканите ефекти поврзани со монотерапија на NSAID и опоидни лекови**
- **Ублажување на акутна и хронична болка**

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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

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 course.
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

PHYSIOLOGICAL CHANGES DURING PREGNANCY

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During pregnancy, in response to the growing fetus, various changes occur. This affects various organic systems, cardiovascular, respiratory, gastrointestinal, urinary. Factors leading to changes in these systems include changes in hormonal levels, fetal size and physiological needs of the pregnant woman and fetus. Most of the physiological changes return to normal in the postpartum period. It should be pointed out that much of these changes are more pronounced in multiparous patients.

Affected Organic Systems

Endocrine System

Many of the physiological changes associated with pregnancy are due to changes in hormones produced by the placenta. One such hormone is human chorionic gonadotropin (hCG), more specifically, its beta subunit (β-hCG). This hormone is produced by the placental syncytiotrophoblast. It is responsible for stimulating the yellow body to produce progesterone. Progesterone itself is essential in maintainingthe pregnancy (1). β-hCG stimulates and maintains the yellow body, thereby preventing new ovulations. By the end of the first trimester (approximately up to 10–12 gestational weeks), ovaria produce increased levels of estrogens and progesterone. After the first trimester the placenta is mature enough to take over the production of these hormones (2).

In non-pregnant women, the hypothalamus produces and releases thyrotropic releasing hormone (TRH).It stimulates the release of thyroid stimulating hormone (TSH) and prolactin (PRL) from the anterior pituitary gland. In pregnant women, the placenta releases additional TRH, which leads to greater release of TSH and PRL. The production of thyroid hormones in pregnancy increases by about 50%, but free T_3 and free T_4 remain unchanged. This is due to the simultaneous release of thyroid-binding globulin (TBG) (3). These additional thyroid hormones are required for normal brain development and thyroid function of the growing fetus (4).

In pregnancy, the pituitary gland expands by about 135%. This is due to lactotrophic hyperplasia and further raises the level of circulating prolactin (5). Its level increases 10 times during pregnancy. This results in growth of the glandular tissue of the breasts and the production of milk (6).

Relaxin is a peptide hormone that is released from the yellow body in both pregnant and non-pregnant women. In addition, in pregnant women it is releasedfrom the placenta and the decidua. This hormone allows remodeling of the connective tissue and consistent softening of the birth canal. It affects the growth and differentiation of the mammary glands and inhibitsthe uterine contractile activity (7). Relaxin also mediates the release of nitrogen oxide (NO), allowing systemic vasodilation and reducing the blood pressure in pregnancy.

Free cortisol levels are about 2.5 times higher during pregnancy compared to the pre-pregnancy period (9). Increased cortisol levels are particularly important for the normal development of

the fetal brain. However, excessive values of maternal glucocorticoids may be neurotoxic to the fetus, resulting in impaired neuronal development (10).

Concentrations of endorphins and enkephalins also increase during pregnancy. This leads to anincrease in the pain threshold whichis necessary to counter the pain that will be present during birth (11).

Cardiovascular System

The cardiovascular system of pregnant women undergoes significant physiological changes. There is an increase in heart frequency, impact volume, cardiac output and decrease in vascular resistance (12). An increase in the chamber wall, heart contraction and compliance can also be seen.

During the first trimester, vasodilator effects of NO, prostaglandins and progesterone occur. They cause peripheral vasodilation. By the 8thgestational week, it leads to a 20% increase in cardiac output (CO). Additionally, peripheral vasodilation reduces systemic vascular resistance (SVR). This is compensatedby an increase in CO by about 40% during pregnancy. Peripheral vasodilation also leads to a decrease in blood pressure early during pregnancy. The lowest blood pressure values are reached during the 20–24 gestational weeks, leading to physiological hypotension.

Cardiacoutput is a product of the heart frequency and the impact volume. The increase in the cardiac output is mainly due to an increase in the impact volume, and in a smaller percentage of the increase of the heart rate (13). In early pregnancy, the impact volume is responsible for maintaining increased CO. While during the third trimester, the increase in heart frequency becomes responsible for the elevated CO. This directs the blood to the uterus, placenta, kidneys, skin and limbs. During late pregnancy, the blood flow through the uterus increases up to 10 times. The renal blood flow increases by 50%. The blood flow to the liver and brain is minimally affected. Skin flow and flow to the limbs increases the temperature of the mother's skin. This is a mechanism of maternal thermoregulation.

During the active stage of birth, uterine contractions cause "autotransfusion" of approximately 500ml of blood, back into the mother's circulation. Even after childbirth, as a result of a decrease in the compression of the inferior vena cava, the cardiac output increases by 75% (14).

More than 90% of pregnant women will develop systolic murmur in pregnancy that will disappear after childbirth. 18% of pregnant women will develop diastolic murmur. Third heart sound occurs in more than 80% of pregnant women. Fourth heart sound occurs in about 16% of pregnant women (15).

In pregnancy, normal ECG findings can be a small Q-spikes and inverse T-waves in the III line, ST-segment depression and inversion of T-wave into lateral and lower lines, as well as shifting the axis of the QRS complex to the left (13).

Respiratory System

Functional residual capacity (FRC) consists of expiratory reserve volume (ERV) and residual volume (RV). During pregnancy, due to the growing uterus, the rest position of the diaphragm shifts upwards by about 5cm. This reduces ERV and FRC. Vital capacity (VC) remains unchanged, and the reduced ERV is accompanied by increased inspiratory reserve volume (IRV).

Increased concentrations of progesterone, starting in the first trimester, cause the respiratory volume to increase by about 30–50%. The respiratory volume and respiratory frequency product gives the minute ventilation, which will increase by 30–50%.

Progesterone stimulates respiration and can lead to hyperventilation. As a result, arterial partial oxygen pressure (PaO_2) will be up to 105mmHg, while arterial partial carbon dioxide pressure ($PaCO_2$) approximately 30mmHg (16). This change in blood gases results in mild respiratory alkalosis. It is metabolically compensated by increased bicarbonate excretion by the kidneys, approximately 20mEq/L (17). These metabolic changes lead to moving the dissociative curve of oxyhemoglobin to the right. It means that the dissociation of oxygen and oxygen transport through the placenta is facilitated.

During childbirth, minute ventilation increases even by 140–200%, depending on the stage of birth. This causes an even greater decrease in $PaCO_2$ (18). Metabolic oxygen consumption increases, as a result of contractions of the uterus, sympathetic activity and maternal Valsalva maneuver. As oxygen demand exceeds the oxygen supply during the active stage of birth, an anaerobic phase of metabolism and lactate formation occurs (19).

Hematological Changes

In a pregnant woman, renin values in plasma grow, and there is a tendency to reduce the level of atrial natriuretic protein. This leads to systemic vasodilation and increased vascular capacitation. These physiological changes, without compensation, would lead to an unfulfilled vascular system. To compensate for this phenomenon, as well as potential blood loss during birth, the mother's blood volume increases by about 1.5l. The production of maternal erythropoietin increases, leading to an increase in erythrocyte mass by approximately 30%. This increase in plasma volume is greater than the erythrocyte mass, and results in dilutional anemia, or physiological anemia in pregnancy (20).

The increase in erythrocyte mass, combined with increased blood flow through the uterus, leads to optimization of oxygen transport to the fetus. However, increasing erythrocyte mass also means an increase in the physiological need for iron during pregnancy. Approximately 1000mg (1gr) of iron is required during pregnancy. Two-thirds are for the needs of the pregnant woman, and one-third is for placenta-fetal tissue growth and needs. In the first trimester, the iron needs are lower (0.8mg/day). While during the third trimester, the daily iron needs increase (3.0–7.5mg/day) (21).

Pregnancy is a hypercoagulable condition, with increased values of coagulation factors. This is caused by increased levels of estrogens, which play a role as mediators in protein synthesis. As pregnancy progresses, coagulation factors VII, VIII, X, XII, vWF and fibrinogen values significantly increase. As a result of the increase in factor VIII, the activated partial thromboplastic time (aPTT) is typically shortened.The prothrombin time (PT) and thrombin time (TT) remain unchanged. As a result of this hypercoagulable condition, pregnant women are up to five times more likely to develop deep vein thrombosis (DVT) compared to non-pregnant women [22].

Renal Changes

As previously noted, the increase in the heart output leads to an increase in the renal blood flow. Glomerular filtration rate (GFR) increases by about 50% and renal plasma flow (RPF) increases by 80%. This increased GFR leads to a decrease in serum concentrations of creatinine, urea and uremic acid. Due to water containment, the kidneys increase in size and physiological

hydronephrosis occurs. As a result of the influence of progesterone and relaxin on smooth muscles, there is a dilatation of the renal collecting system, which can lead to urinary retention. This phenomenon increases the predisposition to urinary tract infections and pyelonephritis with asymptomatic bacteriuria during pregnancy (23).

Typically, during normal pregnancy, an increase in the level of regulation of the renin-angiotensin-aldosterone system (RAAS) occurs. The formation of estrogen by the placenta stimulates the synthesis of angiotensinogen in the liver. This leads to an increase in the values of angiotensin II. Renin is released from the ovaries and the decidua of the uterus. Approximately around the eighth gestational week, aldosterone values increase. Up to the third trimester of thepregnancythey continue to rise up to 3–6 times from the upper limit of their normal values. The result of these events is a total increase in approximately 1.5l of water in the pregnant woman's body (23).

Gastrointestinal Changes

Gastroesophageal reflux (GER) is a common occurrence in pregnant women as a result of several factors. Increased progesterone values during pregnancy lead to a decrease in muscle tone at rest and the lower esophageal sphincter. It also leads to delayed gastric emptying and an increase in the transit time through the small intestines. These changes, added to the pressure caused by the pregnant uterus, predispose to the appearance of GER (24).

Skin Changes

Increased hormone values of estrogen and progesterone during pregnancy may stimulate increased melanin synthesis. It causes hyperpigmentation of the face, known as melasma. As one of the hyperpigmentation associated with pregnancy is also the dark line, a hyperpigmented line that goes along the middle line of the abdominal wall. It is usually associated with the appearance of hyperpigmentation of areolas, armpits and genitals (25).

Clinical Significance

It is important to remember that many changes in pregnant women during pregnancy affect the pharmacodynamic and pharmacokinetic characteristics of certain drugs (absorption, distribution, metabolism and elimination). If mothers' physiological adjustments during pregnancy are not taken into account, it may lead to an increase in maternal morbidity due to pre-or sub-dosing of a pregnant woman.

Increased renal clearance during pregnancy may increase the elimination of some drugs that have renal elimination. For example, ampicillin, cefazolin, cefuroxime, piperacillin, digoxin, atenolol, lithium.

As soon as pregnancy is confirmed, hypothyroid patients who needed levothyroxine should increase their dose by 30%, and the values of serum thyrotropin should be closely monitored.

Additionally, it is important to understand physiological hypotension during pregnancy, especially when it comes to a pregnant patient who is already hypertensive and receives antihypertensive therapy.

It is important that doctors from all medical specialties, especially those in family medicine, cardiology, obstetrics or obstetric anesthesia, understand the physiological changes that occur in pregnant women and appropriately adapt the approach and treatment of these patients.

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Abbreviations:

- β-hCG, beta human chorionic gonadotropin
- TRH, thyrotropic releasing hormone
- TSH, thyroid stimulating hormone
- PRL, prolactin
- TBG, thyroid-binding globulin
- NO, nitrogen oxide
- CO, cardiac output
- SVR, systemic vascular resistance
- FRC, functional residual capacity
- ERV, expiratoryreserve volume
- RV, residual volume
- VC, vital capacity
- IRV, inspiratory reserve volume
- PaO_2, arterial partial oxygen pressure
- $PaCO_2$, arterial partial carbon dioxide pressure
- aPTT, activated partial thromboplastic time
- PT, prothrombin time
- TT, thrombin time
- DVT, deep vein thrombosis
- GFR, glomerular filtration rate
- RPF, renal plasma flow
- RAAS, renin-angiotensin-aldosterone system
- GER, gastroesophageal reflux

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NEURAXIAL TECHNIQUE FOR LABOR ANALGESIA: CURRENT TRENDS

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Intense pain during labor can cause some adverse effects in parturient, like uncoordinated uterine contractions, prolonged duration, or stalled labor, as one of the most important reasons leading to caesarean section (C-S) worldwide. Unrelieved labor pain, which can lead to post-traumatic stress disorder or postpartum depression, in addition to discomfort, causes physiological stress that has an adverse effect on the mother and the newborn. Unrelieved pain stimulates catecholamine release, it causes hyperventilation and hypocapnia, which further constricts uterine blood vessels, reduces ventilation stimulus between contractions, causing a leftward shift of the oxygen dissociation curve; and all these phenomena compromise oxygen supply to the fetus, leading to fetal hypoxemia. Premature "movement down" of the fetus can lead to a canal trauma and injury during childbirth; parenteral opioids may exacerbate maternal respiratory depression, while regional (neuraxial) analgesia may reduce adverse effects of labor pain and sympathetic system responsiveness. Therefore, good labor analgesia aims not only to reduce the pain and suffering of the parturient, but also decreases the risk of fetal acidemia and, in general, makes the labor process safer, both for the mother and neonate.

Although the origin of labor pain is created by two different mechanisms, the process of pain relief should include several stages of pain relief, each of them with different intensity and character, starting from the initial stage and finishing with the final act of childbirth. During the initial - first stage of labor, the pain is the result of uterine contractions and the dilation of the uterine cervix, which radiates to the lower back and the sacrum; painful impulses are transmitted through the efferent nerve fibers that start from the uterus, and together with the sympathetic nerve endings enter the spinal cord at the segmental level from T10 - L1, whereby analgesia covers that segment of pain. During the second stage of labor, there is a strong perineal distension by the fetal leading part, leading to appearance of strong and precisely localized pain that radiates to the vagina, rectum and perineum. It signals the end of the first and the beginning of the second stage of labor, and occurs as a result of the movement of the fetus towards the exit segment. In this phase, somatic pain predominates, which, unlike visceral, is sharp and specific, and is the result of the stretching of the structures from the distal birth canal caused by the delivery of the fetus. In this final phase, additional sacral analgesia is needed at the sensory S2-S4 level.

Traditionally, methods of pain relief have been classified as non-pharmacological, pharmacological and regional (neuraxial) techniques. Hereby, the latest findings and evidence on the efficacy and safety of the most commonly used methods of neuraxial type of labor analgesia are presented.

Epidural technique and regimens -Epidural analgesia (EDA) remains the standard neuraxial procedure for labor analgesia and, as a catheter technique, provides effective and long-lasting analgesia. Its popularity and widespread exploitation are evident, and the concern about an increased rate of C-Ss seems to remain unfounded, because the research excludes such a risk, even when it comes with early initiation of neuraxial blocks (1,2).

After the epidural space is identified by the "loss of resistance" technique (fluid or air), the epidural catheter (EDC) is placed no more than 5cm into the space; the initial loading dose of diluted local

anesthetic with opioid is administered in doses of 5ml, with careful observation and mandatory monitoring of parturient blood pressure and heart rate between the dose bolusing. The epidural technique may require a different dosage of mixture, depending on many factors, but for adequate labor analgesia at the initial period it needs to top-upto 15ml (max. 20ml) of bupivacaine 0.0625 - 0.125 % (ropivacaine 0.08-0.1%) + fentanyl up to 4mcg/ml (or sufentanil). Historically, 3ml of 1.5% lidocaine with 1:200,000 epinephrine was used as a "test dose"; lidocaine makes a rapid proof of spinal anesthesia (motor blockade) and IVepinephrine will cause a transient tachycardia, but the sign is uncertain due to confusion with the tachycardia caused by labor painful contractions. The current trend is to use low dose of local anesthetic without epinephrine as a "test dose", which helps to reduce the motor blockade and to improve the ambulation of the parturient; there is a wide variation with test doses today (from 3-20mg bupivacaine and 15-90mg lidocaine), but any dosing via ED catheter, whether for the initial block or for the treatment of breakthrough pain, should be treated as a "test dose", because ED catheter can migrate intrathecally or IV, despite the initial correct placement in the epidural space (46). Further on, identification of the epidural space in pregnant women could be technically challenging, and even when the ED catheter is inserted without difficulty, unilateral block and missed segments with inadequate analgesia can occur (in 1of 8 parturients).

In the recent period, various EDA regimens have been investigated: continuous epidural infusion (CEI) with low concentrations of anesthetic (bupivacaine 0.1% with fentanyl 2mcg/ml) leads to a significantly higher number of spontaneous (unassisted) deliveries compared to the higher concentrations of the traditional method (0.25% bupivacaine), so it is concluded that "in terms of the method of delivery, the use of traditional epidurals is no longer justified" (3). Manual but more programmed intermittent bolus (PIEB) delivery is a good alternative to CEI for maintaining epidural analgesia, with the note that PIEB may improve the quality and duration of labor analgesia (4).

The patient-controlled epidural analgesia (PCEA) regimen allows the pregnant woman to self-delivering intermittent bolus doses, thus providing flexibility in relation to analgesia requirements as labor progresses. Labor pain is highly variable in intensity, and the character of the pain often changes as the labor process progresses, prompting a sense that parturient could be the best managerof their own pain relief. There is recent evidence that genetic polymorphisms may influence the labor progress and the response to labor analgesia; namely, a μ-opioid receptor gene (OPRM1, A118G), which is believed to be present in 30% of pregnant women during labor, may influence the response to neuraxial-applied opioids (37).

During PCEA, the anesthesiologist takes care of adjusting the delivery program, he namely determines: the bolus and maximum dose delivered, the lock-out interval and the base (background) infusion rate, if there is any. This method of self-titration by the parturient allows improving the dose-requirement ratio in view of the labor progress. From that point of view, PCEA is related both to reduced demand and consumed dosage, especially in the first stage of labor. PCEA can be administered as a single dose-demand regimen (dosing as needed by the parturient) or as a background continuous epidural infusion (CEI), plus dose-demand regimen. Demand dose involves the delivery of a fixed high dose administered by the parturient with pressing the PCEA button without concomitant use of a background CEI. The role of the background CEI in the PCEA regime seems to be still insufficiently explained in the literature: while some studies suggest that CEI with PCEA increases anesthetic consumption without analgesic benefits, other studies show a reduced need for analgesia in the presence of background CEI. Thus, further studies are needed to analyze against background CEI (5).There are observations that the administration of a part (33%) of the maximum hourly demand dose as a background infusion (CEI) in accordance with PCEA, could be the optimal choice for labor analgesia in most of the parturient. However, it can be considered that high-level delivery pumps as the background infusion mode (CEI) improve labor analgesia in the setting of PCEA and as such, it is the best analgesic approach, also recommended by the American Society of Anesthesiologists (ASA) in Obstetric Anesthesia Guidelines (39).

Today, in part of the "smart" pumps, it is possible to analyze the condition of the woman in labor and her analgesia needs in the previous hour (based on the needs of PCEA), whereby the basal (background) infusion is automatically adjusted accordingly. Hence, the basal infusion rate will automatically increase for pregnant women who make more demands, and such a mode of computer analysis and delivery is part of the so-called mode of computer integrated (CI) analgesia, which can also run as CI-PCEA. In some comparative studies between CEI and CI-PCEA, it is shown that CI-PCEA can reduce the incidence of labor breakthrough pain, thereby achieving higher satisfaction in parturient (6).

Effects of EDA on the progress and mode of delivery-The topic has been controversial for many years and there are different opinions on this issue, nevertheless several studies are unanimous in the view that (7,8):

1. The epidural infusion with a low concentration of local anesthetic (0.0625% - 0.125% bupivacaine with 2mcg/ml fentanyl) does not increase the risk of C-Ss nor instrumentally assisted deliveries, although for the latter there are also opposite conclusions especially seen with higher concentrations of local anesthetic;

2. Neuraxial analgesia in early labor (<4cm dilation) does not increase the C-S delivery rate; whereas compared to systemic analgesia, it provides better analgesia and shortened labor duration (9).

The impact of exposure to neuraxial anesthetics on neonate neurodevelopment has not been fully studied and there are not definitive results regarding this item. EDA increases the risk of intrapartum fever in the mother, which may be adverse to neonatal outcome. According to some studies, EDA usage may also cause more frequent neonatal injuries during instrumental deliveries, although long-term adverse events are rarely described. On the other hand, EDA may reduce postpartum depression and, thus, may produce beneficial effects on neurocognitive development in childhood, but definitive evidence for this is still lacking (10).

When should EDA be discontinued? There is insufficient evidence that epidural analgesia should be discontinued in late labor as a means of reducing adverse effects of delivery. In such a way, the rate of inappropriate pain in the second labor stage increases, but a meta-analytic survey of high-quality studies showed no significant differences in the mode of delivery (outcome) with these different approaches to analgesia during the second stage of labor (42,43).

Combined spinal-epidural (CSE) analgesia-The technique is a suitable option for labor analgesia for severe pain, usually associated with more advanced labor. It enables rapid and profound analgesic action (2-5 minutes vs. 15-20 minutes), caused by the spinal dosage. If necessary, the block is potentiated or continued with the additional epidural dosage applied through the epidural catheter.

It is stated that the CSE technique may have certain advantages over EDA: 1. Rapid start of the analgesic block including sacral analgesia, which leads to greater satisfaction of parturient, 2. Confirmation of correct placement of the epidural needle. The appearance of cerebrospinal fluid in the spinal needle during CSE is a confirmation of the correct placement of the epidural needle. This is especially important in those with difficult anatomy or the obese, which results with a higher rate of success. When compared with conventional EDA, the overall failure rate (accidental intravascular placement of the epidural catheter, inadequate epidural analgesia—unilateral or "patchy" block, reduced need for additional bolus doses, reduced total anesthetic dose, repeated catheter replacements) is significantly lower in patients receiving CSE analgesia compared to EDA (12), 3. It allows greater mobility of parturient, 4. Block caused by spinal dose (especially in primiparous women in the early stage of labor) may lead to faster progress of cervical dilatation compared to EDA (11,12), 5. An unsatisfactory spinal block can at any time be corrected, continued or switched in anesthesia for emergency C-S.

The same regime of intrathecal component from the spinal (single-shot) analgesia can be used in the CSE method (1-2.5mg 0.5% Bupivacaine + Fentanyl 15-25mcg), with the possibility of an additional epidural dose. This synergistic action allows analgesia lasting 90–120 minutes, with the presence of minimal motor block, while intrathecal opioid (ITN) can provide satisfactory analgesia in the early latent phase, but almost always requires the additional analgesia (bupivacaine) in the mixture for satisfactory analgesia in advanced labor. Some studies suggest using lower opioid and local anesthetic doses (max. 15μg fentanyl, 5μg sufentanil), but despite the increasingly widespread use of this technique, as well as numerous published studies, the optimal intrathecal regimen of the mixture has not yet been defined. An intrathecal (spinal) dose provides satisfactory analgesia until the onset of therapeutic analgesia levels caused from the epidural dose or infusion, which can sometimes begin soon after the spinal injection, thus creating a "perfect" transition from spinal to epidural analgesia. The regime of epidural infusion of bupivacaine (0.0625-0.08- 0.125 + Fentanyl 2mcg/ml, at a rate of 8-15ml/h, which can be activated later (i.e. 30-40 minutes after spinal injection or before the end of its analgesic effect), is the most often used. Serious maternal side effects from the recommended doses of this regimen are rare.

The most common side effects of CSE in practice still remain the following: 1. Fetal bradycardia (FB), which is not accompanied by a higher risk of C-Section, and 2. Pruritus. It is hypothesized that FB is caused by uterine hypertonus induced by decreased circulating catecholamines and could be avoided by a reduced dose of intrathecal opioid. Unsettled FB can usually be treated with the usual procedures that include repositioning (left lateral tilt), IV bolus fluids, IV terbutaline, ephedrine or phenylephrine. Itching after CSE usually subsides after 45–60 minutes and can be minimized with reduced fentanyl doses (10-15mcg); small IV dose (5mg) of nalbuphine (mixed agonist-antagonist) which successfully relieves the effect without reducing analgesia. Concerns about an increased risk of infection or PDPG associated with spinal needle dural puncture are unfounded.

Although the functionality of epidural catheters placed during CSE at the beginning of the block cannot be accurately determined (due to the nonfunctional test dosage), evidence suggests that ED catheters placed via CSE are more reliable than ED catheters placed during a standard ED procedure.

Better satisfaction among parturients, faster onset of action and general impression, may account for the wider use of CSE, but whether there are definitive reasons for favoring CSE over EDA remains undefined. An extensive Cochrane study (e.g. 19 studies, 2,658 pregnant women) suggests that there is little basis for offering CSE over epidurals, despite the reported positive effects and overall impression of it (13). In practice, the choice between conventional epidural and CSE is usually dictated by the clinical situation, institutional protocols, equipment availability and anesthesiologist's experience, i.e., depending on the preferred method.

Dural puncture via epidural (DPE) is gaining more popularity in the last decade. The procedure is similar to the CSE technique, but the intrathecal administration of anesthetic is omitted. Intentional dural perforation is thought to allow some passage of the epidural dose intrathecally, thereby improving the epidural function. Studies regarding the superiority of DPE over traditional EDA are equivocal. A recent systematic review concludes that there is a lack of clear benefit over EDA (14), the next one notes that although "overall results remain equivocal," epidural puncture with 25-G spinal needles (not 26- or 27-G) provide higher success rates compared to standard EDA without dural puncture (15).The remaining two studies are also unanimous that DPE puncture results in fewer unilateral blocks and better sacral coverage compared to traditional epidural analgesia. When compared to CSE, DPE results in comparable analgesia (onset 11 min. vs. 2 min.) although with fewer maternal and fetal side effects (pruritus, hypotension, fetal bradycardia) (16).

Both techniques are useful to localize the epidural space, when the possibility of identification is limited, unclear or difficult to recognize. The flow of CSL through the spinal needle provides reliable evidence that the tip of the epidural needle is close to the dura, confirming the correct identification of the epidural space.

Spinal (singleshot) analgesia is an alternative method to the epidural which is usually applied where the epidural is not possible for various reasons, and that in the advanced stage of birth, preferably in multiparous mothers. The limited duration, as well as the impossibility of additional analgesia in the second stage of labor, represent limiting factors for more frequent application. The advantages come from the simple and practical performance, the low dose, as well as the rapid onset of action with immediate sacral analgesia. Side effects occur as a result of dural puncture (nowadays, very rare due to small atraumatic needles) and limited analgesic duration and possible impact on fetal ejection. Changes in the fetal heart rhythm are mostly of the FB type. The spinal cocktail of local anesthetic and opioid has a mutual synergistic effect, which deepens and prolongs the analgesic effect, reduces the total amount of local anesthetic and the risk of possible complications (2.5mg 0.5% bupivacaine plus fentanyl 25μgr has a synergistic effect with a duration of 90-120 minutes). The addition of a low-dose hydrophilic opioid (morphine ≤ 200μg) provides prolonged analgesia for up to 4 hours (17,18). Studies suggest that the addition of epinephrine to the combination of a standard intraspinal dose of bupivacaine and fentanyl (in CSE), provides a significant prolongation of single spinal analgesia.Out of the 4 doses tested (12.5-25-50-100μgr), it appears that 12.5μgr of epinephrine may be the optimal dose for this clinical purpose (45).

Continuous spinal analgesia -This technique can provide rapid analgesia or anesthesia with less amount of local anesthetic, but in expense with more difficulties and failure during spinal catheter insertion, compared to epidural analgesia. It is theoretically advantageous in the management of morbidly obese parturients, those with significant comorbidities who cannot tolerate hemodynamic instability, and those with a potentially difficult airway undergoing C-S. It allows for gradual dose titration and a slower onset of subarachnoid block. However, this technique is still less frequently used, due to the risk of more frequent occurrence of PDPH, as well as neuraxial infection (40).

Intrathecal opioid application (intrathecal analgesia, ITN) has its advantages, but also side effects. The application of spinal opioids in the recommended doses, does not cause sympathetic blockade or mobility affection, nor does it affect the expulsion of the fetus in the second stage. From that aspect, it is useful in high-risk parturients, where functional spinal sympathectomy represents a risk (hypovolemia, aortic stenosis, tetralogy of Fallot, pulmonary hypertension, etc.).It causes fewer emetic complaints and less fetal affection when compared with IV analgesia.

ITN is usually insufficient to relieve labor pain in the second stage of labor, thus remaining a potential problem in most of the cases, so the addition of a local anesthetic is of great benefit. Nausea and vomiting, itching, respiratory depression and fetal bradycardia may occur. Repeated opioid doses result in poor results due to the development of tachyphylaxis. Liposoluble fentanyl is the most widely used intrathecal opioid for labor analgesia, primarily because of its rapid onset of action and deep analgesia without motor blockade. It is the most often used liposoluble opioids: fentanyl 10-25μg, sufentanil 5-10μg or 10-12mg meperidine (pethidine) possibly in combination with low-dose water-soluble morphine (max. 200μg), providing longer-lasting analgesia in the first birth stage (17,19).

Local anesthetics and adjuvants for labor analgesia -Local anesthetics such as ropivacaine and levobupivacaine, although having less potential for cardiotoxicity and motor blockade, are significantly more expensive than racemic bupivacaine. With the widespread use of dilute anesthetic concentrations, as well as with the CSE method, the likelihood of systemic toxicity caused by higher concentrations of bupivacaine remains very low. Clinical studies have also failed

to show that ropivacaine or levobupivacaine offer any advantage over bupivacaine in terms of placental transfer and neonatal outcome, and therefore it appears to have little justification for their use in daily practice, so the popularity of bupivacaine as one of the most widely used local anesthetics remains largely unchanged (20,21).

An important progress in the quality of labor analgesia is the addition of the "adjuvant drugs" in the anesthetic mixture, with the intention of maintaining or improving the quality of analgesia at the expense of reduced doses and concentration of local anesthetic administered, which would result in less motor block and fewer instrumental interventions. Many adjuvants have been tested, such as midazolam, magnesium, ketamine, meperidine (Dolantin) and dexamethasone, but concerns about side effects and minimal efficacy have prevented wider testing and use, particularly in the obstetric population. However, some adjuvants have already gained popularity and wider application, such as the alpha agonists clonidine and dexmedetomidine, as well as neostigmine and epinephrine. Since opioids, alpha-agonists and neostigmine produce analgesia through different mechanisms of action, combining all these adjuvants may have the effect of further improving the quality and duration of analgesia, in terms of reduced local anesthetic dosing. For example, the addition of dexmedetomidine (an alpha2-adrenoceptor agonist, 0.5μg/mL) to epidural solutions has been shown to provide superior labor analgesia with fewer side effects (pruritus, nausea and vomiting) compared to opioid adjuvants (sufentanil) (22).Studies evaluating the safety, efficacy, optimal dose and method of drug delivery (PIEB, PCEA) with clonidine (α2-agonist) and (or) neostigmine (as adjuvants to a local anesthetic), with or without an opioid, consider that an epidural clonidine 75μg with neostigmine 750μg are effective in initiating labor analgesia without inducing motor or sympathetic block (23,24). However, further research is needed to definitively evaluate their effectiveness and side effects before they are put into official use in obstetric anesthesia.

Complications from neuraxial anesthesia - Technical problems during needle insertion, unintended dural perforation and blood vessel injury (dural, bloody tap), hypotension and unsatisfactory block remain the most common adverse complications in obstetric neuraxial analgesia. The excessive motor block can have a prolonged effect on the course of the second labor stadium and increases the risk of instrumental delivery. PDPG develops in about 52-60% of parturients in whom inadvertent dural puncture is caused by an epidural needle, while it is, usually, much less common after dural perforation caused by spinal needles (from 0.5-2% with atraumatic needles). Recent studies show that PDPG in obstetric cases is mostly rare, but its association with a serious type of neurological complications (such as, for example, cerebral venous thrombosis, subdural hematoma, bacterial meningitis and other complications, persistent lower back pain, chronic headache) cannot be ruled out, emphasizing the need for early diagnosis and prompt treatment (25).

The occurrence of high neuraxial block is identified as one of the most common serious complications of neuraxial anesthesia in the obstetric population (1 in 4,336 procedures)(26). This serious complication usually occurs as a result of incorrect placement or migration of the ED catheter from the epidural space during labor, but it can also occur after spinal anesthesia for C-S, administered after a non-functional epidural labor analgesia (14%). Therefore, it is justified to warn the parturient that the placement of the ED catheter cannot be fully guaranteed, so the catheter may be placed again if the relief of labor pain is partial or unsuccessful. More recent knowledge about factors that contribute to failed epidural conversion, early replacement of dysfunctional catheters and their management during labor etc., can significantly help in reducing this type of complications (27,28).

Conversion of epidural labor analgesia to surgical anesthesia for C-S - The recommendation "early epidural analgesia for labor should be considered whenever possible, in order to reduce the risks associated with general anesthesia, especially in the setting of emergency C-S" implies the active involvement of the anesthesiologist from the very beginning of the laborprocess, familiarization

with the health condition and possible comorbidities of the pregnant woman, as well as early and timely placement of ED catheter especially in those who have less chances to deliver spontaneously. The importance of this recommendation was emphasized during the COVID-19 pandemic, and soon afterwards it was affirmed by the Societies of Maternal-Fetal Medicine (SMFM) and Obstetric Anesthesiologists and Perinatologists (SOAP) (26).

Several precautions should be taken when converting a neuraxial labor block to anesthesia for C-S and the first step of the set of measures is 1. The verification of the functionality of the ED catheter and the eventual presence of reduced labor pain. The inability to obtain satisfactory analgesia, i.e. the presence of a unilateral or inadequate (patchy) block and the need for an increased number of bolus doses to maintain satisfactory analgesia, indicates the non-functionality of the ED catheter and, in principle, it should not be used for further conversion; 2. The visual inspection of the site of the inserted catheter is also essential, as well as;3. Careful aspiration through it, in order to exclude possible migration outside the epidural space (subdural or spinal location).Unrecognized spinal migration is one of the most common and serious complications in obstetric anesthesia - almost 1/4 of high neuraxial blocks are the result of unrecognized spinally inserted catheters, and even 93% of them refer to obstetric cases (26); 4. during the conversion to C-S, the timing since the last epidural dose should be taken into account- if the interval is less than 30 minutes, the possibility of high spinal block may be increased if spinal anesthesia is used for C-S (36).

The location or the place to administer the initial epidural dose for C-S can be the delivery box or the operating room, which in themselves have their own risks or benefits. The administration of the epidural dose in a labor box facilitates the rapid onset of surgical anesthesia, but may delay the diagnosis and management of possible complications (high spinal block, hypotension, systemic toxicity), whereas the initiation of the epidural dose in the operating room can delay the onset of surgical anesthesia. The final decision is made depending on the urgency of the C-S, as well as the possibilities for adequate monitoring and resuscitation during transportation. From a practical point, it may be the best to administer the initial epidural dose in the labor box through a fractionated test dose of 3-5mL 2% lidocaine with epinephrine (or 3% 2-chloroprocaine) and then immediately to transport the parturient to the operating ward, accompanied by an anesthetist and monitoring; after positive confirmation of progressive spread of bilateral cephalic block, an additional epidural dose is administered to achieve the desired block height (Th4).

Adjuvants for rapid conversion to C-S -Commonly used adjuvants are epinephrine, sodium bicarbonate and opioids that increase the speed, duration and quality of anesthesia. Epinephrine intensifies the surgical block, as a result of α2-adrenergic receptor stimulation located on the superficial laminae of the spinal cord.It is more effective when combined with lidocaine than with bupivacaine, and the concentration is 5mcg/mL (1:200,000).The addition of epinephrine to 2-chloroprocaine, although prolonging the duration of epidural analgesia and motor block, is not routinely used (35). Addition of 1mL of 8.4% sodium bicarbonate (1mEq/mL) to 10mL of 2% lidocaine increases its rate of action - by raising the pH of the solution to its pKa value, more of the ionized molecules are available for passage across neuronal lipid membranes. The time is shortened to 5.2 minutes when bicarbonate is added, vs. 9.7 minutes With the mixture of lidocaine-epinephrine-fentanyl (29). The addition of bicarbonates to bupivacaine (ropivacaine or levobupivacaine) causes precipitation and should not be used. Alkalization with 2-chloroprocaine slightly increases the speed of onset of epidural analgesia (12 minutes with bicarbonate vs. 14 minutes), although there are no studies with definitive results (33). Common practice is to use epidural 2-chloroprocaine in a higher (3%) concentration and without any adjuvant. It ensures a faster onset of action and avoids the delay in preparing the mixture when time is of the critical essence.

Opioids and new adjuvants -Lipophilic opioids such as fentanyl (50-100μg) and sufentanil (10-20μg) are commonly combined with a local anesthetic for rapid conversion to epidural anesthesia.

They increase the speed of action, improve the quality of anesthesia and provide synergistic analgesia for the treatment of intraoperative visceral pain (34). The neuraxial addition of clonidine, dexmedetomidine, neostigmine, ketamine and magnesium have been suggested to improve analgesia for C-S. Clonidine can cause hypotension, bradycardia and sedation at higher doses and is therefore not recommended in US obstetric patients. However, the neuraxial use of these agents is not yet officially indicated, as further studies of their neurotoxicity, analgesic superiority and side effect profile are needed before they can be officially recommended as neuraxial adjuvants for labor analgesia.

Conversion failure for C-S -There are 3 main failure factors commonly reported in the literature, and these include: 1. The administration of the epidural by a non-obstetric anesthetist; non-obstetric anesthesiologists are more likely to induce GA and less likely to manipulate the ED catheter or option for another type of neuraxial technique when conversion fails (28,32); 2. The number of additional epidural boluses for labor pain relief. A non-functioning ED catheter may result in pain requiring additional bolus doses, and such a catheter is unlikely to be useful for surgical conversion (with parturient who receive 1 or more additional unplanned boluses, the failure rate is increased 3-fold)(32).It should be noted that breakthrough labor pain can also indicate a dysfunctional delivery, which necessitates an obstetrical evaluation of the progress of the delivery;3. Urgency of the C-S- is an important risk factor because there is less time to manipulate the epidural block, therefore conversion to GA is highest in most-urgent C-Ss (32).

Key recommendations to reduce the risk of failed conversion are: 1. Active communication with the obstetrician in order to identify women in labor at risk of C-S; 2. Removal of the inappropriate labor epidural blockade with timely optimization or replacement of the ED catheter that does not work with a new epidural or combined spinal-epidural anesthesia (CSE); 3. The confirmation of the location of the ED catheter by visual inspection and by the administration of a test dose before transport in the operating room; 4. Assessment of the block in the operating room - do not administer more than half of the full dose of local anesthetic if the block does not progress cephalically and bilaterally; 5. Application of an alternative anesthesia technique in case of failure, as said, one should always use the fastest-acting local anesthetic i.e. 2% lidocaine-epinephrine-bicarbonate with an opioid for C-S emergencies or 3% 2-chloroprocaine (35,36).

Management of failed epidural conversion - In most of the cases of C-S, the woman in labor should be trusted if she complains of pain and the anesthetic failure accepted. In general, epidurals have a higher failure rate compared to spinals. Not always the epidural block can provide 100% anesthesia even after the correctly performed procedure and its active management. The treatment of pain during C-S is extremely important because the inability to deal with it can lead to complications of psychological disorder (including post-traumatic stress disorder, 11%) and that can affect the long-term well-being of the patient (37). Moreover, according to a review of litigation on inadequate anesthesia during C-S, pain during neuraxial anesthesia for C-S is one of the most common causes of these disputes in UK directed against obstetric anesthesiologists (35).

There are no complete practice guidelines for the optimal management of failed epidural anesthesia for C-S, but an option remains IV supplementation of fentanyl 25–50μg or alfentanil 250–500μg, and ketamine 10mg bolus doses, or conversion to GA. From that point of view, it is necessary to ensure an adequate neuraxial blockade before starting the surgical incision.

Intralipid infusion - Anesthesia safety becomes greater with the availability of intralipids as a countermeasure for local anesthetic toxicity. Intralipids bind with an amidoanesthetic molecules in the plasma, while reducing the free toxic fraction that depresses the heart muscle. It has become a widely accepted procedure and is part of resuscitation protocols for local systemic anesthesia-induced toxicity and should be readily available in all units practicing neuraxial analgesia (41).

Conclusion

There is no doubt that neuraxial analgesia is the most effective method for relieving labor pain and it remains the main analgesic approach in obstetric practice. In addition to eliminating labor pain, which is described as one of the strongest pains that a human being can experience, modern neuraxial analgesia allows minimal motor disability and enables ambulation during labor, minimal impact on the progress of labor, as well as safety and security of both mother and neonate. Decreasing the concentration of bupivacaine from 0.5% to 0.065%, and adding neuraxial opioids allowed achieving effective labor analgesia while minimizing potential adverse effects on labor progress, as well as less motor blockade. The techniques of epidural analgesia controlled by parturient itself are rapidly evolving to enable more flexible analgesia that is adaptable to the individual needs of women in labor (during the different stages of labor), while "smart" pumps and computer systems are being refined to a degree to provide maximum analgesia and comfort, starting from the initial block until the final act of laboring. Ultrasound (US) identification as part of the assessment of the depth of the epidural space, as well as for scanning the interfacial structures during truncal blocks, is also widely used in the obstetric population. Pre-procedural US reduces the risk of failed epidurals and traumatic insertion and is therefore approved by the US Institute of Health (NIH). New adjuvant drugs that improve the synergism and effectiveness of local anesthetics, while reducing the side effects of single high doses of local anesthetic, are already part of routine practice in obstetric anesthesia.

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REVIEW ARTICLE *UDK: 618.5-089.888.61-089.5*

ANESTHESIA FOR CESAREAN SECTION: CURRENT TRENDS

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Cesarean section (C-S) is one of the most common operations in the world, with a current average rate of 21.1%, which means that one in 5 pregnant women delivers in this way. The percentage of C-S is different around the world and varies widely, from an average of 5% (sub-Saharan Africa) to 42.8% in Latin America and the Caribbean. At the global level, the trend of C-S is constantly increasing and it is estimated that by 2030, 28.5% of pregnant women in the world will be delivered with C-S. This means that even now, and even more in the future, a huge part of the population will be exposed to surgical termination of labor, which dictates that the risk of operative morbidity and mortality should be minimized, along with the possibility of other complications related to C-S. Furthermore, unlike spontaneous delivery, where there is no need for anesthesia and the presence of an anesthesiologist, the increasing number of C-Ss globally, implies that it will very likely have an impact on the workload of obstetric anesthesiologists in general, as well as their increased demand (1).

Although the choice of general, endotracheal anesthesia (GA) is a risky choice for C-S, it cannot be completely excluded from use, especially in emergency situations or the presence of contraindications for the performance of neuraxial anesthesia. The primary area of concern with the use of GA in pregnant women are the possible complications during the induction of endo-tracheal anesthesia as well as the risk of difficult or impossible intubation. It is generally accepted that pregnant women have a higher risk of difficult or unsuccessful intubation with rapid development of hypoxemia, as well as the risk of aspiration of gastric contents; the failed intubation in obstetrics is higher than in the nonpregnant, whereas the aspiration pneumonitis, although rare, is one of the most serious complications associated with GA for C-S (2,3,4). In a recent multicenter observational study in a series of over 2500 C-S deliveries, the incidence of failed intubation was reported to be 1:312 (5); in addition, specific changes in the respiratory system (reduced FRC, increased minute ventilation and metabolic index) put the pregnant women at risk of rapid onset of deep hypoxemia, incomparable to other surgical patients (6); from that aspect, the possibility of increasing oxygen reserves in pregnant women during the preoxygenation phase with the help of high-flow nasal oxygen (HFNC, with max. 60 L/min) is considered by some to be justified and necessary, but its definitive application in practice remains to be confirmed (7,8). Considering these facts, in less developed countries, exposure to GA for C-S triples the odds of maternal mortality and doubles the odds of perinatal mortality, so off-label general endotracheal anesthesia should be avoided whenever possible, because apart from the association with higher mortality, it is also associated with a higher risk of morbidity as a result of numerous anesthetic complications, including surgical infections, venous-thromboembolic complications, etc. (9,10).

Indications where GA is considered "unavoidable and necessary", including obstetric indications (postpartum hemorrhage), certain contraindications to the performance of neuraxial analgesia (anticoagulation or coagulopathy) as well as the refusal of pregnant women for regional anesthesia, are still the most common indications for C-S and nowadays. Pregnant women with urgent obstetric indications for C-S, such as placental abruption, prolapsed umbilical cord, antenatal placental hemorrhage, fetal distress, fall under greatest risk for GA, where rates for GA (of this type of emergency) climb to 20%. However, several professional associations believe that the average rate of pregnant women delivering with GA for C-S should be less than 5%

(SOAP), and others recommend that it should be lower than 1% for elective C-S and less than 5% for emergency deliveries (RCOA) (11,12,13).

In the last decade, the positive experiences with the application of supraglottic devices and especially video laryngoscopy in the field of obstetric anesthesia are becoming numerous and clear, and the benefits became evident. The invention of the GlideScope and its competitors, the C-MAC, King Vision, McGrath, and Airtraq video laryngoscopes, represented a major advance in the field of difficult airway treatment, whereas the popularity of fiberoptic intubation slowly declined, along with the availability of video laryngoscopy. Today, safety standards are at a higher level, and from that point of view, the Association of Obstetric Anesthesiologists and Difficult Airway (OAA,DAS) recommends that every physician performing laryngoscopy for endotracheal intubation should have immediate access to a video-laryngoscope as a backup option in case of difficult intubation. Moreover, the application of video laryngoscopy in obstetric anesthesia is already recommended by some centers as the first attempt at intubation with general anesthesia for C-S, instead of direct laryngoscopy (14).

GA at labor is associated with worse outcome in newborns compared with neuraxial anesthesia (15,16). Despite allowing the shortest period of time to surgical incision in emergency C-S deliveries, GA is not associated with better neonatal outcomes, as evidenced by several studies (17). More recently, questioners have arisen regarding maternal exposure to GA and the possibility of potential complications in the newborn in later development; the risk of fetal neurotoxicity with neurological consequences of short or long-term type is mentioned. However, these studies do not have evidentiary evidence for such accusations yet (18,19,20).

When applying GA for C-S, anesthesiologists should pay more attention to the depth of anesthesia, because the period until cord clamping and fetal extraction is vulnerable (opioid analgesics and other depressants are avoided) and may lead to a higher incidence of mother awareness, compared to other surgical procedures. Although rare, the consequences of intraoperative awareness after C-S can be serious, commonly including post-traumatic stress disorder and sleep-disturbances . Careful titration of doses and gas delivery, as well as the ability to monitor the depth of anesthesia, help to prevent complications; there are views that an initial dose of propofol of 2.5 mg/kg is sufficient to prevent maternal awareness during C-S, although it causes worse fetal effects and a greater reduction in blood pressure compared to thiopental, e.g. (21,22).

For over 50 years the use of succinylcholine as an induction agent for C-S continues, primarily due to its rapid onset and ultra-short duration, but the severity of its side effects and the need for more advanced drugs, lead to searching for a new alternative of neuromuscular relaxant for rapid-sequence intubation (RSI) in C-S. In that context, parallel to the emergence of sugammadex, rocuronium starts to replace succinylcholine as the first choice in obstetric patients for C-S, whereas the exact dose for that purpose is still debatable. However, used under normal circumstances, it seems that a dose of 1,0 mg/kg is an appropriate intubation dose for C-S (23). Sugammadex, as a long-awaited agent for the reversal of neuromuscular paralysis, reached the market in 2016 and according to several analyses, the drug is well accepted; it reverses rocuronium paralysis in less than a minute, almost as quickly as succinylcholine does, and also eliminates complications caused by residual muscle paralysis. Time and experience show that its (combined) application for endo-tracheal intubation in C-S nowadays finds justification.

More recent research reports that maintenance of anesthesia, can also be achieved with total intravenous anesthesia (TIVA), which can replace inhalation anesthetics, among other, because of the lower degree of uterine relaxation enabled by propofol as the only hypnotic that should be used in TIVA for C-S. Dexmedetomidine has recently been reported to improve oxytocin-induced uterine contractility after delivery, and thus its positive effect on postpartum blood loss,

so it is expected that its use in the maintenance of anesthesia after fetal extraction will become more frequent 24).

Neuroaxial anesthesia for C-S: The superiority of neuraxial anesthesia for elective C-S over GA has been proven and established, and it continues to be the main, gold approach for C-S delivery (25). Avoidance of the risks inherent in airway manipulation, and in particular the "can't intubate, can't ventilate, can't oxygenate" scenario, has contributed to the widespread use of neuraxial techniques in obstetric anesthesia. It is generally associated with better maternal and fetal outcomes, i.e.it is attributed to improved postoperative analgesia, less blood loss, and overall greater satisfaction among parturient compared to GA (1). It could be a more desirable choice than GA from both a social and emotional point of view, because the parturient is fully aware and experiences the newborn delivering(the partner should be encouraged to be present in the operating room), and the skin-to-skin contact is established quickly, i.e., immediately after delivery.

The choice of neuraxial anesthesia for elective C-S mainly lies in spinal, epidural or possibly combined spinal-epidural anesthesia, but spinal-intrathecal is the most commonly used technique for C-S, which provides a rapid onset of action and an efficient and reliable anesthetic block. The duration of spinal anesthesia is variable and depends on the drugs used, but usually adequate surgical anesthesia is achieved in about 90 min., enough to perform C-S.

Hyperbaric spinal anesthesia with 0.5% bupivacaine (10-15 mg) in a combination with opioids remains the gold standard for elective C-S, although some clinical effects cannot be fully predicted. The challenge of spinal anesthesia lies in the balance between the lowest possible dose that produces adequate surgical anesthesia and minimal side effects, especially spinal hypotension and the risk of inadequate anesthesia. A meta-analytic study evaluated that hyperbaric 0.5% bupivacaine at low doses (≤8 mg) led to a significant reduction in intraoperative hypotension and nausea and vomiting, but this advantage was negated by a significantly increased need for additional analgesia and the need for conversion to GA (26); therefore, if a low dosage, ≤ 8mg, is chosen, it mandates the use of a combined spinal-epidural technique (CSE), in order to allow prolongation or deepening of anesthesia, if necessary. The difference in the therapeutic profile between the opioids allows the option of an intrathecal combination of fentanyl and morphine as an adjunct to the local anesthetic. A dose of fentanyl (15-20 μg) would supplement local anesthetic effects and analgesia during the operative procedure, while morphine (50-150 μg) would provide long-lasting postoperative analgesia (13-33 h). The addition of long-acting opioids is the basis of postoperative analgesia in C-S and is recommended from the international guidelines (SOAP, ERAS, PROSPECT); The American Society of Obstetric Anesthesiology and Perinatology (SOAP) recommends that at low doses of intrathecal morphine in healthy pregnant women (0.05-0.15 mg; ED 1-3 mg), respiratory monitoring (O2 saturation) is not required, but only monitoring the respiratory rate and the level of sedation, the first 12 h; more frequent and prolonged monitoring (O2 saturation) is recommended only in those at high risk of respiratory depression, such as the obese, parturient with obstructive sleep apnea, preeclampsia or those who receive additional sedatives, opioids, Mg, GA, etc. (27,28).

More recent studies show that compared with fentanyl (meta-analysis, 639 patients), dexmedetomidine as an adjuvant to spinal anesthesia in surgical patients prolongs the duration of spinal anesthesia, improves postoperative analgesia, reduces the occurrence of pruritus, and does not increase the frequency of hypotension and bradycardia (29); another meta-analytical study (278 pregnant women), which refers to obstetrical patients exposed to C-Sin bupivacaine spinal anesthesia, shows that dexmedetomidine as a spinal adjuvant at local anesthetic, can effectively reduce the occurrence of shivering without causing nausea and vomiting; in addition, bradycardia and hypotension are not incease indicating that its spinal administration during

pregnancy has a stable effect on hemodynamics, with fewer side effects (30).Additionally, more recent clinical studies of obstetric spinal anesthesia with prilocaine report that hyperbaric (2%) prilocaine, compared with bupivacaine, induce more reliable but shorter motor block, faster recovery, and more stable hemodynamics in healthy pregnant women (31,32).

The performance of spinal anesthesia is technically easier than the epidural one and, in most cases, the help of additional technology is not required. However, in the last decade, the use of ultrasound (US) in regional anesthesia is becoming a widespread practice, and the analysis of the economic and overall benefits is going in a positive direction. US is also widely used in obstetrical anesthesia, both for identification of the lumbar space (especially for pregnant women with problematic anatomy, obesity, scoliosis, etc.), and for scanning the fascial blocks (TAP and QLB) in accordance with multimodal treatment protocols for postoperative pain in C-S. The first-attempt success rate of ultrasound-guided obstetric epidurals has been reported to be 30-60% higher compared to the traditional method, and the inclusion of US in lumbar scanning in daily clinical practice in pregnant women is thought to be beneficial and could significantly improve the success of epidurals and thus the safety and comfort of parturient undergoing C-S (33,34).

Neuraxial anesthesia for emergency C-S: recently it has been reported that in emergency C-S, in the lack of time, standard spinal anesthesia can be transformed into the so-called rapid sequence spinal technique (RSS), which is actually a simplified and accelerated spinal procedure, with the goal of avoiding the risk of GA (35). Rapid sequence induction for GA is the fastest technique for anesthesia in C-S for fetal distress (category 1), but the goal of RSS is also to quickly and safely achieve anesthesia for C-S cat.1, without further compromising of fetal oxygenation and be prepared for eventual GAin case of failure. Training of junior anesthetists and obstetric ward staff in the implementation of RSS is crucial in order to ensure rapid and safe practice, avoid any unnecessary delay and safely avoid the risks associated with GA in C-S cat.1. It involves training and performing a series of rapid planned procedures that include, among others: no-touch technique, rapid and shortened field disinfection, omission of spinal opioid (higher dose of anesthetic), limitation of spinal attempts, allowing surgery to begin before full recovery and checking the block, simultaneous preparation for conversion to GA if there is a need, etc. Performing RSS anesthesia safely and promptly is a cooperative team action that requires adequate plan of action, with proper training preparation and practice.

C-S in pregnant women with a previous labor epidural: It is a common practice to "top up" the epidural to convert labor analgesia to surgical anesthesia for C-S (about 18% of emergency C-Ss in U.K. are undertaken using this technique, 36). Key considerations in ensuring an effective and safe management of epidural conversion for C-S revolve around the questions: which epidurals to top up, what drugs to use, and where to initiate the conversion (see in: Neuraxial technique for labor analgesia: current approach).

Management of spinal hypotension in C-S: hypotension following spinal (or combined spinal epidural) anesthesia in normal labor or C-S is common and, if prolonged and uncorrected, can cause adverse maternal and fetal effects. Dealing with it, the most important thing is to use prophylactic measures,correlated withthe professional guidelines regarding this problem (37). State-of-the-art protocols mandate usage of preventive infusion of alpha 1 vasopressor, instead of the current mixed agonists (ephedrine). Phenylephrine is the vasopressor of choice, although norepinephrine is also mentioned, along with measures of pre- or co-hydration and relief of aorto-caval obstruction in the pregnant woman (using the left lateral tilt).

Prevention and management of pain during C-S under neuraxial anesthesia: Although well performed neuraxial anesthesia is in general painless and safe procedure, it may sometimes be associated with the occurrence of intraoperative pain. In such cases, the only remaining option

is the supplementation of IV fast acting agents: fentanyl 25–50 μg, alfentanil 250–500 μg or ketamine 10 mg bolus doses or conversion to general endotracheal anesthesia, with all associated risks from it. From that aspect, it is necessary to ensure an adequate neuraxial blockade before starting the surgical incision.

Postoperative pain after C-S: Although latest and modern analgesic modalities and drugs for postoperative analgesia treatment for C-S have been introduced in the recent years, a review of the literature suggests that we are far from achieving the goals of optimal postoperative analgesia. The administration of IV opioids after C-S is still widely used and their side effects have made the incorporation of non-opioid analgesic regimen to be mandatory. Fascial blocks and especially the TAP block have been the most researched modalities in the last decade, but also QLB block has gained popularity. The analgesic efficacy of fascial blocks as part of a multimodal analgesia approach has been established as an integral part of analgesic regimes after C-S, but only where neuraxial morphine was not used or parturient had received GA. Nonsteroidal anti-inflammatory drugs (including COX-1 inhibitors) in combination with IV paracetamol have been found to be beneficial in the postoperative analgesic regimens, whereas perioperative use of ketamine may be beneficial if C-S was performed under neuraxial anesthesia. It is evident that the guidelines of the multimodal type of analgesia including paracetamol, NSAIDs and spinal morphine (ITM) as adjuvant to bupivacaine, are the most effective regimen for postoperative analgesia in C-S; recent research suggests that a dose of 50-75 μgr ITM balances the desired analgesia with fewer side effects compared to higher morphine doses (100-150 μgr). Further studies are needed to define the role of: gabapentinoids, dexamethasone, ketamine, wound infiltration (infusion), and ilio-iliac and ilio-hypogastric block (II or IN NB) for regular post-analgesic regimens in C-S (38,39).

Recovery from anesthesia after C-S: regardless of the method of anesthesia, all patients must receive the same standard of care for recovery as after recovery from anesthesia in any other surgical specialty, i.e. with staff trained in post-anesthetic care and an environment containing adequate space and equipment to provide safe and effective care for both beings. The basic equipment should include blood pressure measurement, ECG, oxygen saturation and, if necessary, capnography monitoring.

Spinal anesthesia for C-S after failed epidural conversion: some anesthesiologists decide to give spinal anesthesia after failed ED conversion, which mainly has the potential for at least two risk conditions: the risk of failure and the risk of high neuraxial block. The epidural space can be filled with local anesthetic from the previous dose and its compression of the dural compartment can lead to difficulties in obtaining CSL; the epidural local anesthetic can flow back through the spinal needle and be misidentified as CSL. On the other hand, if the dural puncture is successfully done, the injected anesthetic can cause a high spinal block, as a result of compression of the dural sac or partial passage of the anesthetic through the dural hole into the spinal space; the risk of such a block is avoided by injecting a reduced dose of anesthetic, at least 30 minutes after the last epidural bolus and by delaying the supine position. However, the optimal dose of spinal anesthetic is not known, and delaying the supine positionmay be impractical. Cases of high spinal block have also been reported 40 minutes to 1 hour after the last epidural bolus (40).

ERAC protocol in obstetric anesthesia: operative delivery with C-S is a common surgical procedure, which means that a large part of the (pregnant) population is exposed to potential operative risk and complications, which should be minimized. The postoperative period is unique and specific because new mothers have to balance from recovering of surgery (often unplanned) and also taking care of the newborn and breastfeeding. ERAC (Enhanced Recovery After Cesarean) is a term that denotes a multidisciplinary, evidence-based approach that implies

a strategy, i.e. a set of evidence-based on practical measures and recommendations, with a focus on the components related to anesthesia and the perioperative period, and refer to optimizing and accelerating recovery of the mother (and the newborn) from C-S. Its purpose is to minimize the physiological response from the operation and to optimize the final outcome of the patients, by reducing the risk of postoperative complications. ERAC extends the principles of ERAS (Enhanced Recovery After Surgery) in obstetric problems; the guidelines were introduced in 2018, much later than the ERAS protocols that apply to other surgical specialties. ERAC incorporates recommendations from existing guidelines issued by professional associations, such as American College of Obstetricians and Gynecologists (ACOG), American Society of Anesthesiologists (ASA), SOAP, etc. (41).

The preoperative recommendations and instructions for the ERAC protocol refer to pregnant women who will be scheduled as elective C-S; the obstetrician starts educating program from early 10-20GW of pregnancy and explains the goals of the protocol in relation to the upcoming period (42). It mainly refers to comorbid conditions that should be optimized before delivery, including possible anemia and iron deficiency, as well as glycemic function for pregnant women with diabetes (43). The period of starvation before C-S is also emphasized; the last light meal is allowed up to 6 hours before surgery (up to 8 hours for a solid meal) and (clear) liquids up to 2 hours before anesthesia; for unplanned or emergency delivery with C-S, the preoperative pathway is narrowed to a 30- to 60-minute interval (44).

Intraoperative recommendations are focused to minimize the surgical complications and to preparethe pregnant for a safe perioperative course and a successful discharge from the hospital stay. Prophylactic IV antibiotic should be administered in the first 60 min., preferably before the surgical incision and before clamping the umbilical cord; in doing so, the effectiveness of the drug is improved which poses no risk for the fetus; cephalosporins of the first generation (cefazolin) are recommended for all pregnant women without allergies or for those at risk (ruptured amnion) the addition of azithromycin is suggested (45); disinfection but also adequate drying of the skin before the surgical incision is mandatory; preoperatively, pregnant women should receive at least two IV antiemetics with a different mechanism of action, from the group of ondansetron, dexasone and/or metoclopramide.

Neuraxial technique is the gold standard for anesthesia with C-S; spinal anesthesia results in a faster and shorter onset of action compared to epidural; neuraxial morphine (intrathecal or epidural) should be given for better postoperative pain control (46); truncal interfascial block (TAP or QLB) is used in those parturients who do not receive neuraxial morphine. Administration of non-steroidal anti-inflammatory analgesics (NSAIDs) should begin immediately after closure of the peritoneum and begin with early non-opioid analgesia (acetaminophen). Such a multimodal approach to pain control aims to reduce IV opioid use and it side effects they cause (ORADEs), especially undesirable in pregnant and newborns; the use of non-opioid analgesics prevents gastrointestinal and other side effects associated with opioids (nausea, vomiting, constipation, reduced intestinal motility, sedation of newborns, etc.); less sedating analgesics may also improve early maternal mobility as well as breastfeeding.

A preventive infusion of vasopressors (phenylephrine, possibly noradrenaline) is recommended immediately after spinal puncture, in order to prevent spinal hypotension and maintain normal blood pressure in pregnant women (47). For adequate euvolemia IV fluids should be limited to less than 3 liters; it is recommended that oxytocin be limited to the minimum dose necessary to achieve and maintain adequate uterotone, but also to avoid side effects (tachycardia, hypotension, ischemia, hyponatremia), bronchospasm (prostaglandins) or hypertension (ergot alkaloids), and. C. bolus dose of 1 - 3 i.e. (intrapartum C-S), continued with an infusion dose (48). Intraoperative hypothermia can have adverse effects for both mothers and newborns

(including coagulopathy, possibility of infection, arrhythmia, etc.), therefore, forced warming of the mother, warm IV fluids and increasing the temperature in the operating room (23 degrees), as well as adequate drying of newborns are necessary (49).

The ERAC guidelines also address immediate care of newborns after delivery-clamping of the umbilical cord for full-term newborns should be delayed for at least 1 min, while for preterm infants it should be delayed for 30 seconds (50); the routine use of oxygen and suctioning of the newborn's airway is avoided, except in cases of obstructed airway; skin-to-skin contact is encouraged immediately after delivery, as well as promoting early breastfeeding during the first hour of life (51).

Postoperative guidelines refer to the postoperative outcome, which depends on the steps taken during the preoperative and intraoperative period. The primary goal is to ensure that pregnant women return to preoperative baseline functions and to ensure an early and successful hospital discharge. Early mobility after neuraxial anesthesia is considered to reduce the risk of thromboembolic events and is one of the initial steps to return the pregnant woman to preoperative functional status; in addition, prophylaxis with mechanical pneumatic compression is beneficial for women not receiving pharmacologic thromboprophylaxis. Maintaining euvolemic status and preventive treatment of spinal hypotension reduces the risk of emetic complaints in the postoperative period; early oral fluid intake should begin within 60 min. after admission to the recovery unit; women in labor are encouraged to resume a light diet within 4 hours after surgery, if there are no contraindications. Published guidelines recommend early removal of Foley catheters, if there is no need to monitor diuresis; it is believed to be beneficial for early mobility of the women and leadsto reduction of the risk of symptomatic urinary tract infections (52).

Ideally, a multimodal analgesia regimen that begins in the operating room with neuraxial anesthesia, continues postoperatively; the prolonged effect of morphine, added with IV acetaminophen and non-steroidal anti-inflammatory drug has an advantage over others regimens. Before discharging the patients, it is recommended to monitor the anemic patients, i.e. hemoglobin level on the 1st and 2nd postoperative day, but only in those with more extensive blood volume lossesand those with anemia. Mothers should receive appropriate measures to support breastfeeding during the hospital stay and finally, to get information regarding outpatient help for the period that follows.

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UROLOGICAL SURGICAL AND ANESTHETIC CHALLENGES IN PREGNANCY

ANESTHESIA FOR NON-OBSTETRIC SURGERY DURING PREGNANCY

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Non-obstetric surgery during pregnancy is a rare occurrence, with an incidence ranging from 0.2% to 2%. Maternal physiological, hormonal and anatomical changes affect cardiovascular, respiratory, hematological, gastrointestinal, endocrine and urinary systems, posing increased risks. Complications, such as premature birth, are prevalent, making diagnosis and treatment complex. The American College of Surgeons' National Surgical Quality Improvement Program reports an overall postoperative complication rate of 5.8%. This includes reoperation within 30 days (3.6%), infections (2%), respiratory complications (2%), wound site complications (1.4%), thromboembolism (0.5%), bleeding (0.2%) and a mortality rate of 0.25%. A literature review from 2017 to 2022, using PUBMED and VHL, highlights key insights on anesthesia and surgery during pregnancy. Neuraxial techniques in the first trimester, general anesthesia in the second trimester for abdominal surgeries, and surgical procedures in the third trimester pose specific risks, including low birth weight and premature delivery. The findings stress the importance of precise planning, management, and intraoperative fetal monitoring to optimize outcomes for both mother and baby.

Non-obstetric surgery during pregnancy may be indicated for various conditions, including acute intra-abdominal infections, acute appendicitis, cholecystitis, ovarian cysts and trauma. Additionally, urological issues, such as symptomatic urolithiasis, iatrogenic injuries of the urethra and bladder, as well as rare conditions like placenta percreta with bladder invasion, pheochromocytoma and bladder tumors, may necessitate surgical intervention.In managing anesthesia during pregnancy, understanding physiological changes and altered pharmacokinetics is crucial. Preoperatively, emphasis on hemodynamic stability, oxygenation, thromboprophylaxis and airway management is vital. Careful .selection of anesthesiology techniques, patient positioning and consideration of hematological changes is necessary. Intraoperative fetal monitoring is essential, with operation time linked to gestational age. Recognizing inherent risks, both anesthetic and surgical, throughout pregnancy highlights the critical nature of essential and emergency operations. Notably, surgical procedures in the second trimester show better fetal outcomes, emphasizing the importance of strategic decision-making in maternal and fetal care during operations.

The American Heart Association and American College of Cardiology recommend utilizing echocardiography for evaluating congenital heart disease, impaired valve function and non-physiological murmurs. In pulmonary assessments, altered respiratory dynamics, like decreased functional residual capacity (FRC), increased minute volume (MV) and tidal volume (TV) may lead to respiratory alkalosis, favoring rapid induction with inhalation anesthetics. Vigilance is crucial for complications such as tachypnea, pulmonary embolism, physiologic anemia affecting oxygen delivery, airway edema and assessing difficult airway and aspiration risks. Failed endotracheal intubation, with a 10 times higher incidence than the general population,

requires adherence to The American Society of Anesthesiologists' guidelines for managing difficult airways in obstetrics. Factors like Mallampati class 3, fiberoptic intubation and strong recommendations to prevent atelectasis are integral components in ensuring safety for both the pregnant patient and the developing fetus during non-obstetric surgery. Thromboprophylaxis is crucial during non-obstetric surgery in obstetric patients due to a 6-10 times higher risk of deep vein thrombosis. Low molecular weight heparin (LMWH) is preferred for its lower bleeding and thrombocytopenia risk. Gastroesophageal reflux prevention involves prokinetics, antacid drugs and the anti-Trendelenburg position.

Considerations for timing and type of surgery are essential, especially to prevent fetal hypoxia in the third trimester. Laparoscopic procedures, commonly performed in the first trimester (42%), adhere to safety recommendations in general surgical literature. However, caution is warranted when considering the inclusion of endourological surgery due to potential gaps in existing research. In non-obstetric surgery for pregnant patients, the recommended positioning is a 30° left lateral decubitus. Intraoperative fetal monitoring, recommended after 22 weeks of gestation, involves continuous monitoring with a focus on uterine contractions. In non-obstetric urological surgical patients, physiological changes during pregnancy are noteworthy. The right-sided hydronephrosis, occurring in 50% to 90% of the cases, is prominent in the second and third trimesters. This is attributed to hypertrophy of Waldeyer's sheath, progesterone effects, communication between the right ovarian vein and the ureter and the protective arrangement of the left ureter with the sigmoid colon, along with a dextrorotated uterus. These changes lead to an increased capacity of the collecting system (200-300ml) causing urinary stasis.

Pregnancy also induces an elevation in glomerular filtration rate, heightened excretion of sodium, calcium and uric acid, increased levels of 1.25 dihydroxy vitamin D, bladder displacement, hypervascularization of pelvic organsand a tendency towards coagulopathy. Symptomatic urolithiasis in pregnancy, the most common non-obstetric indication for urological surgery (1:200 - 1:1500), presents diagnostic and treatment challenges and numerous complications. Diagnostic modalities such as renal and bladder ultrasound (RBUS) and computed tomography without contrast (NC-CT) are employed, while interventions like ureteral stents and percutaneous nephrostomy may be necessary. Guidelines from prominent urological associations (EAU, AUA, ACR) recommend an early multidisciplinary approach, thromboprophylaxis and a meticulous management plan. The initial evaluation includes pain and nausea therapy along with fetal monitoring, utilizing RBUS, RI and transvaginal ultrasonography. Interventions depend on clinical urgency, focusing on reducing radiation exposure. Therapeutic measures include pain relief, hydration, expulsive therapy, and the use of selective alpha 1 blockers, such as tamsulosin. For urgent decompression in cases of septic obstructive urolithiasis during pregnancy, the preferred method is a ureteral stent, that is deemed safe for both the mother and fetus. Percutaneous nephrostomy (PCN) is the intervention of choice in situations involving previous urinary tract reconstruction, septic shock, large stones, or prone positioning for percutaneous nephrolithotomy (PCNL), where accessing the airway and fetal monitoring may pose challenges. Changing ureteral stents every four weeks is standard until the final treatment. Ureteroscopy with laser lithotripsy stands as the first-line treatment, offering an advanced surgical technique with a single-session approach, avoiding undue anesthesia exposure. Notably, neuraxial anesthesia is preferred, supported by a retrospective study spanning 16 years, which found no significant increase in reduced birth weight during general anesthesia (Devroe S., Bleeser T et al., ObstetAnesth Ang., 2019, 39:74-81).

Pheochromocytoma in pregnancy has anincidence of 0.007%(in 30,246 pregnancies during 20 years). Despite autopsy studies indicating a potentially higher occurrence, more than 50% result in maternal and fetal mortality. Improved outcomes are observed with advanced anesthetic and surgical approaches. Primary management focuses on early diagnosis, preventing

hypertensive crises and ensuring timely delivery with definitive surgical intervention.Early diagnosis of pheochromocytoma in pregnancy is vital to significantly reducemortality. Despite its complexity due to association with pregnancy symptoms, various tools like ultrasound, CT, MRI and laboratory analyses measuring metanephrine levels in blood and urine, contribute to timely identification. Hypertensive crises can occur due to mechanical factors like tumor compression and non-mechanical factors, such as gestational hormones. Surgical procedures pose particular risks including moving a patient to an operating chair, induction under general anesthesia, endotracheal intubation, changes in intra-abdominal pressure, pneumoperitoneum and surgical manipulations. These situations can lead to uteroplacental insufficiency, fetal hypoxia and fetal death. In managing pheochromocytoma during pregnancy, cesarean delivery is preferred, and vaginal delivery is considered only for previously treated cases. Adrenergic blockade is administered for fetal maturity and spinal anesthesia is chosen during childbirth to reduce adrenal stimulation. Swift surgical intervention, especially before the 24th week of gestation, is recommended. Laparoscopic adrenalectomy, after prior pharmacological treatment, is preferred, but caution is needed due to potential fetal acidosis and hemodynamic changes with CO_2 pneumoperitoneum. General anesthesia during surgery involves IV lidocaine, opioids, a short-acting vasodilator, desflurane and remifentanil.

Placenta percreta with bladder invasion represents the most severe form of placenta accreta, where the placenta penetrates the uterine wall and attaches to another structures. The incidence, often associated with a history of previous cesarean sections, remains unclear. It carries a high maternal mortality rate of 9.5%. Diagnostics involves ultrasound, dopplerography and MRI. Serious complications occur in 72% of cases, including cystectomy, hysterectomy, vesicovaginal fistula and massive bleeding. The latter involves extrauterine blood vessels, non-blood vessel formation, complete penetration of chorionic villi into the myometrium and adjacent organs and potential complications during surgical separation or application of endovascular procedures such as occlusion or embolization. Pre-operative planning involves assessing blood loss, monitoring vital parameters (CVP, IAP), ensuring hemodynamic stability, maintaining body temperature, and implementing a massive transfusion protocol. Correcting coagulopathy and electrolyte imbalances, along with preoperative optimization of iron and hemoglobin are essential components for comprehensive patient's preparation. Anesthesia techniques for obstetric patients include general and regional anesthesia. General anesthesia ensures ventilation control, hemodynamic stability and facilitates longer operative treatment with muscle relaxation for careful surgical dissection. Postoperative epidural analgesia is commonly employed in this context. On the other hand, regional anesthesia offers benefits such as postoperative analgesia, lower risk of aspiration and blood loss, and reduced exposure of the fetus to anesthetics. However, it may pose challenges related to hemodynamic instability. The choice between these techniques depends on various factorsand careful consideration is given to optimize patient's safety and comfort during obstetric procedures.

Bladder tumors during pregnancy are exceptionally rare, with an incidence of 0.0013%. The first reported case dates to 1927, and fewer than 50 cases have been documented in the literature. Transitional cell carcinoma (TCC) is the most common type, accounting for 70% of the cases, presenting symptoms like hematuria, nocturia, frequent urination, cystitis and pain. Diagnosis challenges often lead to delayed or incorrect identification. Various diagnostic tools including ultrasound, MRI and flexible cystoscopy are employed. The role of pregnancy in either protecting against or increasing the risk of tumor occurrence and spread, remains a topic of consideration in these infrequent cases. The treatment considers the trimester and malignancy stage. Early Transurethral Resection of Bladder Tumor (TURBT) is crucial, safely performed in all trimesters with lowest risk in the second and third. Using spinal anesthesia and a bipolar technique ensures safety. Delivery method (vaginal or cesarean) varies. Intravesical therapy is delayed until after delivery for maternal-fetal well-being.

In conclusion, advanced surgical techniques can be safely applied to obstetric patients undergoing non-obstetric surgery, with a complication rate comparable to non-obstetric patients. The choice of anesthetic techniques and standard doses demonstrates minimal impact on fetal development, ensuring control of hemodynamics, oxygenation, and maintenance of utero-placental perfusion and uterine relaxation. The multidisciplinary approach, coupled with close communication within the team comprising a gynecologist, anesthesiologist, surgeon and internist, is deemed essential for ensuring safety and achieving successful treatment outcomes.

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EMERGENCIES IN OBSTETRICS' ANESTHESIA

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In obstetric anesthesia emergencies, the anesthesiologist and obstetrician-gynecologist must focus their attention on the well-being of both the mother and the unborn child. To maintain the well-being of the child, the mother's vital functions must be stable at all times.

There are several emergency conditions, but in this presentation, we will focus first on postpartum hemorrhage and hypertensive disorders in pregnancy, as the most common causes of maternal mortality, and further on cardiopulmonary arrest and cardiopulmonary resuscitation of a pregnant woman as the most urgent condition.

Postpartum hemorrhage

Postpartum hemorrhage (PPH) is an obstetric emergency and is one of the top five causes of maternal mortality in both developed and developing countries, although maternal mortality is significantly lower in developed countries (1). It is estimated that PPH is responsible for approximately 100,000 deaths annually. In general, PPH occurs in 1-3% of deliveries, with a tendency of constant increase.

Timely recognition, availability of appropriate resources and appropriate response are key factors to prevent death.

The World Health Organization defines PPH as blood loss ≥500mL within 24 hours of birth, while severe PPH is defined as blood loss ≥1000mL within the same time frame. However, the classic definition of PPH is the most often used for diagnosis: estimated blood loss is ≥500mL after vaginal birth or ≥1000mL after cesarean delivery.

Primary or early PPH refers to PPH that occurs within the first 24 hours after delivery, and secondary or late PPH refers to bleeding that occurs 24 hours to 12 weeks after delivery.

Many risk factors for PPH have been reported and the same are often interdependent. The greatest risk factors associated with the highest chances of PPH are abnormal placentation, placental abruption, hypertensive disorders in pregnancy, intrauterine fetal death, lacerations, instrumental termination of birth, large newborns.

Whenever possible, patients with risk factors for PPH should be identified. Preparation for PPH is an early detection of PPH, and availability of all resourcesat all times. Coordination and multidisciplinary cooperation are essential.

After delivery, vaginal or cesarean, all patients with persistent excessive bleeding should be immediately evaluated by the obstetrician who led the delivery. Assessment primarily involves quantifying blood loss using graduated volumetric containers and weighing scales or using visual aids.

On time recognition of PPH followed by prompt determination of the cause and initiation of appropriate treatment is critical to prevent death, as nearly 90% of deaths due to PPH occur within four hours of delivery. That's why it's important to recognize the warning signs and intervene early. In order to recognize alarm signs, monitoring of vital signs, determination of shock index, examination of coagulation status, fibrinogen and thrombo-elastography (TEG), should be performedwhere available.

Insight into the medications the patient is receiving, should always be maintained, as some medications may have unexpected hemodynamic side effects and simulate a false scenario (for e.g.,beta blockers, antihistamines).

In the prevention of PPH, active management of the third birth period plays the biggest role. It usually consists of drug prophylaxis just before or after birth along with controlled traction of the umbilical cord. The most important prophylactic intervention is slow intravenous administration or a short infusion of 3 - 5 I.U. oxytocin (Syntocinon) after the delivery of the child.

Treatment of PPH is based on a combination of factors, but the key to managing postpartum hemorrhage is to recognize excessive bleeding before it becomes life-threatening, identify the cause, and initiate appropriate interventions. Initial interventions include:

- Calling for help because the treatment of PPH requires a multidisciplinary approach;
- Monitoring vital signs and quantifying blood loss;
- Moving unstable patients to the operating room.
- Establishing adequate intravenous (IV) access - with two lines, with high volume for administration of fluids, blood and drugs;
- Resuscitation with controlled amounts of crystalloids while the preparation for obtaining blood and blood products continues. Regardless of the cause of PPH, initial circulatory support with crystalloids is required in all patients. Early recourse to blood and blood product replacement is recommended when bleeding is severe in order to rapidly replace lost platelets and coagulation factors and minimize the risk of dilutional coagulopathy, electrolyte imbalance, and hypothermia;
- Provision of adequate analgesia;
- Inspection of the lower genital tract and uterus to determine the cause of bleeding and start of surgical treatment of the cause of bleeding;
- Administration of 1g of tranexamic acid in the first 3 hours from the start of PPH. Tranexamic acid is an antifibrinolytic and is useful in the early stages of major postpartum and traumatic bleeding when increased fibrinolytic activity and depletion of fibrinogen are common. Delay in treatment, even if short, reduces the benefit of tranexamic acid administration (2).

If bleeding continues:

- Transfusion of erythrocytes (Er) and fresh frozen plasma (FFP) according the recommendations for the Er: SSP ratio vary. Usually, 1 SSP per 1 or 2 units of Er, or 4 SSP per 6 units Er is recommended. At times when massive transfusion is required, the recommended Er: SSP: Tr ratio is 1:1:1 (3,4);

- Correction of fibrinogen. The normal level of fibrinogen in pregnancy is almost twice as high as in nonpregnant patients and falls to a critical low level earlier than other coagulation factors during PPH and is a more sensitive indicator of ongoing major blood loss. Although SSP contains small amounts of fibrinogen, cryoprecipitate and fibrinogen concentrate are preferred for the treatment of hypofibrinogenemia;

- Prothrombin complex concentrate - (PCC) can be used as an alternative to SSP. Perceived advantages are reduced risk of volume overload, no need for thawing or blood typing, and reduced risk of transfusion-related acute lung injury (TRALI) and allergic reactions;

- Maintain oxygenation with oxygen >95% by giving O_2 (10-15l/min). The anesthesiologist should assess the patient's airway and breathing and intubate if indicated. A high flow mask and correct flow rate is important as a low oxygen flow rate can result in CO_2 retention and worsen the condition;

- Avoidance of hypothermia and acidosis, which increase the risk of clinically significant bleeding. Blood products should be properly warmed, and patient's warming devices should be used.

In patients with blood loss >1500mL and ongoing excessive bleeding refractory to medical and minimally invasive interventions, it is important to move quickly to more aggressive treatment, including laparotomy, hysterectomy, which should not be delayed if bleeding cannot be promptly controlled. Massive bleeding requires additional preparations: placement of two large-bore IV catheters for volume administration, placement of a central venous catheter for administration of vasopressors, coordination of the planned massive transfusion with the blood bank, and consideration of the use of the intraoperative blood cell salvage device.

Ensuring adequate anesthesia is also an important factor in the treatment of patients with PPH. Neuraxial anesthesia is usually the preferred technique for cesarean section and most procedures performed for postpartum hemorrhage. It may be appropriate for patients who are hemodynamically stable and without evidence of coagulopathy. Neuraxial anesthesia causes sympathectomy and vasodilation and may cause severe hypotension or hemodynamic collapse in patients with clinically significant hypovolemia and may be contraindicated in patients who develop dilutional or consumptive coagulopathy.

But if PPH is serious or likely to become serious, general anesthesia is preferred. Advantages of general anesthesia for patients with severe PPH include the following: secure airway, muscle relaxation, easier vascular access, unconscious patient. Induction of general anesthesia should not be delayed once the need for it is determined, as ongoing IV fluid resuscitation can cause airway edema and difficulty with endotracheal intubation. Induction of anesthesia can cause cardiovascular collapse in severely hypovolemic patients, so continuous IV volume resuscitation and administration of vasopressors should be maintained if necessary. Etomidate (20mg IV) or ketamine (0.5 to 1mg/kg IV) is recommended instead of propofol for induction to minimize the risk of hypotension. Airway edema and difficult airway should be expected.

Key things in the management of PPH include recognizing excessive bleeding before it becomes life-threatening, identifying the cause and appropriate intervention.

Hypertensive disorders in pregnancy

Hypertensive disorders in pregnancy belong to obstetric emergencies and are one of the main causes of maternal mortality.

The most common 4 hypertensive disorders that occur in pregnant patients are: preeclampsia, eclampsia, HELLP syndrome, gestational hypertension, chronic hypertension, and preeclampsia superimposed on chronic hypertension.

In this presentation, we will focus on the treatment of preeclampsia with severe features, eclampsia and HELLP syndrome, because these disorders usually require urgent treatment.

The definitive treatment of preeclampsia, eclampsia and HELLP syndrome, is delivery to prevent maternal or fetal complications from disease progression. In certain premature pregnancies with preeclampsia, expectant management is preferred, but if the risks associated with expectant management are greater than any potential benefits, immediate delivery is recommended (5).

Treatment of these patients includes:

- Administration of magnesium sulfate for seizure prophylaxis, as well as for neuroprotection of the newborn in case of premature delivery (6);
- Frequent monitoring of blood pressure, given the risk of severe hypertension;
- Careful recording of fluid intake and urine output, considering the risk of pulmonary edema (7);
- Laboratory analyses, including complete blood count, electrolytes, degradation products, liver enzymes, coagulation factors. Laboratory tests are repeated every 6 to 12 hours, while the patient is in the intensive care unit;
- Acute treatment of severe hypertension. Labetolol and hydralazine are drugs of choice in the treatment of severe hypertension (8);
- Magnesium sulfate ($MgSO_4$) – For patients with eclampsia, treatment with intravenous magnesium sulfate is recommended. A 6-gram initial dose over 15 to 20 minutes, followed by a 2-gram/hour continuous intravenous infusion, is commonly used as a maintenance dose. Maintenance doses may be increased or decreased, and deep tendon reflexes, respiratory rate, and urine output should always be monitored.

Anesthesiology Approach to Hypertensive Disorders in Pregnancy

Anesthesiologists should generally evaluate patients with preeclampsia early in the labor period. Evaluation should focus on airway, hemodynamic status and coagulation abnormalities. Particular attention is paid to airway assessment due to airway edema associated with preeclampsia and eclampsia.

For anesthesia, neuraxial techniques are always recommended and preferred if not contraindicated. Thrombocytopenia and other coagulopathies in association with preeclampsia/eclampsia/HELLP may preclude neuraxial anesthetic techniques due to the risk of spinal epidural hematoma. Apart from the number of platelets, the dynamics of the number of platelets

over time is also very important. In the absence of other coagulopathies, an epidural catheter is safe to place in patients with a platelet count >75,000/microL, it is not safe if the platelet count is ≤50,000/microL, and individualized decisions are needed for patients with a platelet count between 50,000 and 75,000/microl (9). In terms of analgesia for painless delivery, placement of an epidural catheter early in labor is preferable, especially for patients with declining platelet counts. Continuous epidural analgesia attenuates the hypertensive response to labor pain, reduces circulating catecholamines, and provides a means of rapid conversion to surgical neuraxial anesthesia and avoidance of general anesthesia. Prophylactic, titrated administration of a low-dose infusion of phenylephrine is recommended to prevent hypotension induced by neuraxial anesthesia in these patients, while ephedrine is alternatively recommended in patients with bradycardia.

Caution is needed with fluids in patients with preeclampsia/eclampsia/HELLP and limitation of intravenous fluids to avoid pulmonary edema. Recommendations are 80-100mL/hr IV, also restrictive fluid volumes during initiation of neuraxial analgesia or anesthesia.

Neuraxial techniques are preferred for caesarean section anesthesia whenever possible. The most important advantage of neuraxial anesthesia is that it avoids severe hypertension, which can be life-threatening. On the other hand, it also avoids the need for endotracheal intubation, which can be particularly difficult in these edematous patients, and avoids the need for the administration of neuromuscular blocking agents. Induction of general anesthesia for these patients should always include steps to minimize or eliminate the hypertensive response to intubation.

The anesthesiologist's choice of a particular neuraxial technique is based on many factors, including the urgency and expected duration of labor. The obstetrician and the anesthetist should discuss these factors before starting anesthesia.

Cardiopulmonary resuscitation in pregnancy

Cardiopulmonary arrest (CPA) in pregnancy is a rare, life-threatening condition that affects two patients: the mother and the fetus. The treatment of these patients requires a rapid multidisciplinary approach. Basic and advanced life support algorithms should be implemented to manage these patients, but the physiological and anatomical changes of pregnancy require certain modifications to these protocols. Randomized trials on the treatment of pregnant women with cardiopulmonary arrest are lacking, and therefore, recommendations for these modifications are based on expert opinion and data from small case series and small cohort studies involving patients with cardiopulmonary arrest during cesarean delivery.

The prevalence of cardiopulmonary arrest in pregnancy ranges from 1 in 20,000 to 1 in 50,000 pregnant patients.

Etiological CPA in pregnant women can be the result of conditions characteristic of pregnancy, but also conditions unrelated to pregnancy. The most common causes of CPA are pulmonary embolism, hemorrhage, sepsis, peripartum cardiomyopathy, preeclampsia/eclampsia, complications related to anesthesia (difficult or impossible intubation, high spinal block, toxicity of local anesthetics), amniotic fluid embolism, myocardial infarction, preexisting heart disease, trauma.

Cardiopulmonary resuscitation (CPR) includes the following maneuvers and interventions performed simultaneously:

- Activation of the team for resuscitation of a pregnant woman and team approach (anesthesiologist, obstetrician, neonatologist, cardiologist);
- Manual displacement of the uterus laterally and to the left if the uterus is at or above the umbilicus to minimize aortocaval compression, optimize venous return, and ensure adequate stroke volume during CPR. Manual displacement of the uterus allows the patient's upper torso to remain supine, which allows for more effective chest compressions, improves airway, intravenous access, and improves defibrillation access;
- Starting with chest compressions (100-120 compressions per minute) with the same hand position as in non-pregnant women (10);
- Early intubation is recommended to secure an airway, but always consider a difficult airway and have additional devices for difficult intubation ready. Pregnant women are at increased risk of rapid development of hypoxemia due to reduced functional residual capacity and increased oxygen consumption, as well as increased intrapulmonary shunting. Smaller volume ventilation with 100% O_2 (approximately 350 to 500mL) is recommended in large pregnancies with a uterus above the umbilicus;
- Do not delay defibrillation and administration of drugs;
- Adrenaline 1mg every 3-5 minutes in patients with asystole, antiarrhythmics, discontinuation of $MgSO_4$, lipid emulsion in the treatment of toxicity from local anesthetics;
- Intravenous access above the diaphragm;
- Use end-tidal CO_2 monitoring to see the return of spontaneous circulation.;
- To assess the gestational age of the fetus;
- Fetal monitoring during resuscitation is not recommended;
- When four minutes have passed since the mother's cardiac arrest began, someone should alert the entire team. If there is no return of spontaneous circulation with the usual resuscitation measures and the uterine fundus is at or above the umbilicus, perimortem caesarean section should be initiated at four minutes and full delivery of the infant within five minutes after CPA. If there are conditions for instrumental termination of birth in this time interval, it is also recommended. These measures are labeled as "four minutes rule" and "five minutes rule" (11). Delivery should take place at the CPR site. In pregnant women, delivery early in the resuscitation process is a key intervention to improve CPR success rates. Cardiac output peaks immediately after delivery as the laboring uterus contracts and blood from the myometrial veins is auto-transfused into the systemic circulation and the vena cava rises, resulting in greater venous return to the heart and increased cardiac output. Although it may seem inappropriate to operate on a hemodynamically unstable patient, cesarean delivery can be lifesaving for both mother and fetus in this condition. But practically, the few available studies show that the "five minutes rule" is difficult to achieve. However, even if labor does not occur within four to five minutes, a perimortem caesarean section can still be helpful. The minimum gestational age for perimortem caesarean section is recommended ≥20 weeks of gestation and the uterus at or above the umbilicus;

- After 15 minutes of unsuccessful resuscitation, direct cardiac massage is initiated if adequate resources and personnel are available;
- The reanimation is continued until all resources are exhausted and then the whole team decides to stop the CPR;
- Factors causing or contributing to cardiac arrest should be treated at the same time (e.g., bleeding, electrolyte abnormalities, tamponade, hypothermia, hypovolemia, hypoxia, hypermagnesemia, myocardial infarction, poisoning, embolism, anaphylaxis, tension pneumothorax, complications of anesthesia, aortic dissection).

Table 1. Antihypertensive agents used for immediate control of blood pressure in pregnancy.

Medicine	Initial dose	Maintenance dose
Labetolol	20mg IV gradually over 2 min. Continuous IV infusion 1-2 mg/min as start or after starting dose 20mg IV	In 10 minutes: 40 mg IV over 2 min. In 20 min: 80 mg IV over 2 min. In 30 min: 80 mg IV over 2 min. In 40 min: 80 mg IV over 2 min. The maximum cumulative dose is 300 mg. If the target BP is not achieved, switch to another agent class.
Hydralazine	5 mg IV gradually over 1-2 minutes	In 20 min: 5 or 10 mg IV over 2 min. In 40 min: 5 to 10 mg IV over 2 min. Cumulative maximum dose is 20-30 mg. If the target BP is not achieved, switch to another agent class.
Nicardipine	Initial dose is 5mg/hour IV by continuous infusion with gradual titration to a maximum of 15mg/hour	Adjust the dose within this range to achieve the target BP.
Nifedipine (fast release)	10mg orally It may be associated with a sudden drop in BP and with abnormalities of the CTG record	In 20 min: 10 or 20mg orally. In 40 min: 10 or 20mg orally. If the target BP is not achieved, switch to another agent class.

IV-intravenous, BP-blood pressure, CTG – cardiotocographic.

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REVIEW ARTICLE *UDK: 618.3:616-036.12*

PREGNANCY AND ACCOMPANYING CHRONIC CONDITIONS

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Introduction

The prevalence of chronic conditions, such as cardiovascular diseases, diabetes mellitus, asthma, mental and malignant diseases, is continually increasing worldwide. It is estimated that in developed countries, half of adults over 20 years old have at least one chronic condition. The simultaneous occurrence of two or more chronic conditions, i.e., multimorbidity, is a growing concern for public health, with prevalence increasing from 25% in 2003 to 32% in 2016. In the general population, there is a correlation between the number of chronic conditions and the rate of hospitalization, the risk of death and the magnitude of attributed healthcare costs.

The impact of multimorbidity on maternal outcomes during pregnancy and postpartum is less understood, but it is considered that chronic diseases, especially cardiovascular diseases, chronic hypertension and diabetes mellitus, are major contributors to increased maternal mortality rates and severe maternal morbidity (1).

The number of women suffering from chronic somatic conditions, who desire to become pregnant, become mothers and have children, is constantly increasing. All accompanying chronic conditions create an unfavorable environment for the development of pregnancy, exacerbating complications that arise during pregnancy, childbirth and the postpartum period. Complications from chronic conditions are a key driver of increased obstetric morbidity and mortality worldwide.

The prevalence of accompanying conditions in pregnant patients is quite high. According to the strictiest estimations, accompanying conditions are diagnosed in 15-20% of the patients, while some reports from various obstetric hospitals indicate that up to 70% of pregnant patients have accompanying conditions. It is estimated that even one in five women enters pregnancy with two or more chronic conditions (2).

The most common accompanying conditions include heart diseases, hypertension, renal disease, diabetes mellitus, gastrointestinal tract diseases and hepatobiliary system diseases. Recently, there has been an increase in pregnant patients with malignant diseases.

When existing risk factors from the mother are present, the gestational period can become complex and challenging. Pregnant individuals with pre-existing medical conditions should be closely monitored to reduce the possibilities of complications during pregnancy.

High rates of negative maternal outcomes in women with multimorbidity would indicate the need for improved preventive efforts to address modified risk factors during the preconception period and patient-centered support during the perinatal period.

This presentation will cover accompanying heart diseases in pregnancy as the most common cause of morbidity and mortality, as well as their anesthetic management.

Accompanying Heart Diseases in Pregnancy

Accompanying heart diseases are the most common cause of non-obstetric morbidity and mortality in pregnant patients, accounting for 26.5% of all pregnancy-related deaths. The mortality and morbidity associated with accompanying heart diseases are highest among women of color and those with a lower socioeconomic status. In the past, rheumatic heart disease was the most common form of heart disease in pregnant women and still prevails in some developing countries. However, in developed countries, congenital heart diseases are the most common type of heart disease complicating pregnancy, largely due to advances in the treatment of congenital heart diseases, allowing affected individuals to reach reproductive maturity and attempt pregnancy.

A large American study showed a significant increase in the number of deliveries by mothers with congenital heart diseases from 6.4 to 9 per 10,000 deliveries from 2000 to 2010. These deliveries had a higher-than-expected rate of medical and obstetric complications. Nevertheless, the primary cause of cardiac death during pregnancy is acquired heart disease, including cardiomyopathy, coronary artery disease and aortic disorders. Additionally, more women are delaying childbirth until the fourth and fifth decades of life, which, combined with other accompanying conditions, complicates pregnancy.

Congenital Heart Diseases in Pregnancy

Advancements in pediatric cardiac surgery have enabled over 85% of children with congenital heart diseases to reach reproductive maturity. The risk of pregnancy for both the mother and the fetus in this population depends on the anatomical and physiological classification of the type of congenital heart disease, as defined by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines from 2018 for the treatment of adults with congenital heart diseases. The risk of cardiovascular complications during pregnancy and the peripartum period depends on the type of underlying defect, the degree and severity of residual hemodynamic lesions, and comorbidities.

According to the Registry for Pregnancy and Cardiac Diseases (ROPAC), among 5,739 pregnancies in 53 countries from 2007 to 2018, congenital heart disease was the most prevalent form of structural heart disease (57%). The number of high-risk pregnancies increased from 0.7% in the period 2007-2010 to 10.9% in the period 2015-2018 (5).

Pregnant Patients with Congenital Heart Diseases: Risk and Physiological Changes

Pregnant patients with congenital heart diseases may face an increased risk during individual pregnancies, but if they survive, the overall risk of pregnancy is generally not cumulative. Thus, consecutive pregnancies generally carry the same, not higher, risk, assuming that cardiovascular status remains stable.

The impact of physiological changes during pregnancy, especially circulatory and respiratory physiology, can have detrimental effects on mothers with congenital heart diseases and their developing fetuses. There are two main hemodynamic changes that can influence this: a decrease in systemic vascular resistance and an increase in cardiac minute volume.

Women with pre-existing heart disease are exposed to an increased risk of thromboembolism during pregnancy. A large study involving 688 pregnancies in women with congenital heart diseases showed an incidence of 2% for thromboembolic events, compared to the expected rate of 0.05-0.10% for uncomplicated pregnancies (6).

For all patients with congenital heart disease, an assessment of the risk of pregnancy and childbirth should be conducted. The guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology for managing congenital cardiovascular diseases during pregnancy recommend the modified classification of the World Health Organization (WHO) as the best predictive model for cardiovascular risk. The modified WHO classification includes risk based on the mother's cardiovascular condition and provides guidance on the frequency of prenatal cardiology and obstetric monitoring.

The risk for pregnancy is classified into four categories. Category 4 includes conditions associated with very high risk for the mother and/or fetus during pregnancy. These conditions are significant pulmonary arterial hypertension of any cause, severe mitral stenosis, severe symptomatic aortic stenosis, bicuspid aortic valve with aortic diameter >50mm, Marfan syndrome with aortic dilation >45mm, severe systemic ventricular systolic dysfunction (left ventricular ejection fraction <30%, NYHA III-IV) and severe maternal coarctation. Pregnancy is contraindicated in these patients.

In addition to the modified WHO classification, there are other scoring systems for risk assessment and predicting adverse cardiac events in pregnant women. These include CARPREG (Cardiac Disease in Pregnancy) and ZAHARA (Pregnancy in women with congenital heart disease II).

Some experts recommend obtaining levels of brain natriuretic peptide (BNP) during pregnancy in women with congenital heart diseases considered at risk for developing heart failure. An elevated level of NT-proBNP (>128pg/mL) in the 20th week of pregnancy can be an independent risk factor for cardiovascular events during pregnancy in women with congenital heart diseases. A negative BNP is useful to exclude heart failure.

The option of terminating the pregnancy should be discussed with women for whom pregnancy poses a significant risk to either the mother or the fetus**.**

Impaired cardiovascular stability of the mother (Category 4), maternal cyanosis and maternal medications, expose the fetus to risks that jeopardize normal intrauterine growth and development, significantly increasing fetal morbidity and mortality. Offspring of women with congenital heart diseases are also at an increased risk of congenital heart defects.

For women with congenital heart diseases, vaginal delivery is recommended, and cesarean section should be reserved for obstetric indications. Successful operation before pregnancy is crucial for reducing risks to both the mother and the fetus. The risks of pregnancy post-operation are mainly determined by the presence, type and degree of cardiac and vascular residues, as well as their consequences.

Given the heterogeneity of these diseases, individual assessment and appropriate counselling by a specialized adult congenital heart disease specialist are recommended for women with congenital heart diseases who are considering pregnancy**.**

Acquired Heart Diseases in Pregnancy

Women with acquired heart diseases are at risk of cardiac complications during pregnancy. Their risk can be assessed by evaluating the severity of their valvular lesions and the degree of ventricular dysfunction. The most common acquired heart diseases in women of reproductive

age include cardiomyopathies, valvular disease, pre-existing coronary artery disease, arrhythmias, prior myocardial infarction, and rarely, patients with a transplanted heart.

In the case of cardiomyopathies, the ventricular dysfunction in these patients can have various etiologies: previous viral infections, HIV infection, peripartum cardiomyopathy, drug-induced cardiomyopathy, or idiopathic causes.

For most of the pregnant women with acquired heart diseases, vaginal delivery is recommended as it poses a lower risk to the heart compared to cesarean section. Cesarean section should be reserved for standard obstetric indications.

Patients with valvular heart disease (VHD) are highlighted as a specific group. Hemodynamic changes during pregnancy, including an increase in heart rate and cardiac output, can result in heart decompensation in women with valvular heart disease (VHD). Generally, stenotic valvular lesions are less well-tolerated during pregnancy compared to regurgitant lesions. The risk of complications varies depending on the type and severity of the underlying VHD.

Whenever possible, women with valvular heart disease (VHD) should undergo a risk assessment and counselling before conception. If already pregnant, a comprehensive risk assessment should be conducted at the first antenatal visit. The most of women with mild forms of VHD will fare well during pregnancy. However, women with mitral stenosis, even in mild cases, face a risk of cardiac complications associated with pregnancy. Those with mechanical heart valves are also at a high risk of cardiac complications related to pregnancy. Women with severe mitral stenosis, symptomatic severe aortic stenosis, and VHD associated with severe left ventricular systolic dysfunction or significant pulmonary hypertension, should be advised to avoid pregnancy due to the high risk of cardiovascular and fetal complications. All patients with moderate or high-risk VHD should be referred to specialized centers for high-risk pregnancy and heart disease.

In general, vaginal delivery with appropriate analgesia/anesthesia is preferred for women with valvular heart disease (VHD). However, in patients with severe valvular lesions (severe aortic stenosis), planned cesarean section is sometimes indicated.

AnestheticTreatment for Pregnant Women with High-risk Cardiovascular Disease

Anesthetic treatment for pregnant women with high-risk cardiovascular disease requires an understanding of the cardiac anatomy and pathophysiology of the individual patient, how the physiological changes associated with pregnancy and childbirth affect the patient, and the hemodynamic changes that can be induced by the choice of analgesic or anesthetic techniques. Understanding the hemodynamic changes during pregnancy and childbirth, allows the anesthesiologist to anticipate decompensation during the birthing period in patients with cardiovascular lesions and to choose appropriate anesthetic monitoring and techniques to minimize this risk. Ideally, an individualized management plan is developed in the period before childbirth by a multidisciplinary team consisting of a gynecologist-obstetrician, cardiologist and anesthesiologist. Interdisciplinary communication and preparation are crucial as peripartum obstetric and cardiac complications may require prompt intervention.

Although the most of pregnant women with cardiovascular diseases experience favorable outcomes, some may undergo a deterioration of cardiopulmonary status before or during childbirth or in the early postpartum period. Plans for emergency situations related to obstetric complications are

developed by a multidisciplinary team, involving the planning for emergency cesarean section, postpartum hemorrhage, and management of cardiopulmonary complications or cardiac arrest. In high-risk patients, scheduling induction rather than waiting for spontaneous labor can ensure that appropriate specialists are readily available, but this decision is multidisciplinary. Induction of labor, if needed, is generally safe. Regarding the mode of delivery, vaginal delivery is generally preferred unless there is an obstetric indication for a cesarean section.

"Cardiac Vaginal Delivery" - In maternal "cardiac delivery" with epidural analgesia, fetal descent during the majority of the second stage is achieved solely through uterine contractions without the aid of maternal bearing down. When the fetal head reaches the pelvic floor, an operative vaginal delivery (either forceps or vacuum extraction) is performed. This avoids the physiological changes associated with maternal pushing (Valsalva maneuver or increased intrathoracic pressure resulting in decreased venous return, reduced preload and decreased cardiac output). However, prolonged passive second stage and instrumented vaginal delivery may increase the risk of neonatal injury, perineal trauma and maternal bleeding. Thus, the appropriateness of "cardiac delivery" remains controversial.

The medications commonly used in the delivery room can have various implications in patients with high-risk cardiovascular diseases. It is noteworthy that oxytocin, which is most commonly used in obstetrics, may have effects on blood pressure. Oxytocin reduces mean arterial pressure and total peripheral vascular resistance, potentially causing a slight increase in pressure in the pulmonary artery. These changes need to be considered, and oxytocin must be administered cautiously in patients with specific cardiovascular lesions, as it may lead to unexpected decompensation when the load is reduced. In these patients, oxytocin is administered as a diluted solution through continuous intravenous (iv) infusion using an infusion pump at rates of 2.5–7.5IU/hour or 7.5–15IU/hour for cesarean deliveries. Importantly, oxytocin should not be administered iv as a bolus in patients with cardiovascular diseases.

Maintaining adequate intravascular volume and avoiding dehydration during delivery is crucial. Allowing moderate amounts of clear fluids to be administered during delivery is recommended. Aggressive fluid administration should be avoided, especially in patients with associated preeclampsia**.**

General principles of anesthetic management for a high-risk cardiac patient include:

- Placement of filters on all ivcatheters in every patient with a known intracardiac or extracardiac shunt to prevent paradoxical air embolism.
- Preparation of vasoactive drugs: Bolus ivdoses of phenylephrine and ephedrine should be immediately available, as well as an infusion of phenylephrine. On the other hand, nitroprusside and nitroglycerin are usually avoided immediately after delivery, as these uterine relaxants may lead to uterine atony and postpartum hemorrhage.
- Monitoring: Continuous pulse oximetry during active labor, continuous ECG recording, and continuous arterial blood pressure monitoring are recommended for high-risk cardiac patients during labor. Other invasive cardiovascular monitoring (central venous pressure, transesophageal echocardiography) may be used in selected patients**.**

Analgesia during childbirth:

Non-neuraxial analgesia is considered essential. If neuraxial analgesia is not an option, the advisability of vaginal delivery may need to be reevaluated. During childbirth, neuraxial analgesia is recommended for most of the women with high-risk cardiovascular diseases, specifically epidural analgesia, epidural with dural puncture, or combined spinal-epidural (CSE) with low doses.

The primary physiological benefit of neuraxial labor analgesia in high-risk cardiac patients is the reduction of peaks in cardiac output during labor, as these increases are largely a result of catecholamine release due to pain and anxiety. Therefore, it is best to place the epidural early in labor. Ideally, the epidural block should be dense enough to minimize each successive pain.

For patients in active labor with intense pain, a combined spinal-epidural (CSE) using intrathecal opioids without a local anesthetic in the intrathecal space may have an advantage over just the epidural technique due to a faster onset of analgesia with minimal hemodynamic effects.

Administration of a test dose with epinephrine is avoided in cardiac patients because a small ivdose of epinephrine can result in catastrophic events (e.g., severe tachyarrhythmias or hypertension with cardiovascular deterioration).

Anesthesia for Cesarean section

Neuraxial anesthesia techniques are preferred for most of the patients undergoing Cesarean section, including those with cardiovascular pathology (9).

For the most of high-risk cardiac patients, a low-dose combined spinal-epidural or slowly titrated epidural anesthetic may be the best choice. Benefits of the low-dose combined spinal-epidural (CSE) technique include a faster onset of neuraxial block, allowing the anesthesiologist to adequately maintain preload and additional afterload, while still achieving the reliability of the intrathecal local anesthetic block. Although there are limited data on deliveries in high-risk cardiac patients with this technique, intrathecal doses of local anesthetics, as opposed to epidural alone, can significantly contribute to good surgical anesthesia. A study involving four patients with high-risk cardiovascular diseases delivered by Cesarean section with CSE showed that CSE was safe and effective. Administration of a low intrathecal dose is followed by slow loading of the epidural catheter with a local anesthetic (e.g., 2% lidocaine without epinephrine) to achieve a surgical level of T6.

Epidural technique for Cesarean section - with or without CSE, the placement of the epidural catheter is followed by titration (3 to 5mL every five minutes) of a substance such as 2% lidocaine. With such titration, along with appropriate monitoring and caution, severe cardiovascular instability is unlikely.

In high-risk cardiac patients, an intra-arterial catheter should be placed before giving epidural anesthesia. Always have a phenylephrine infusion prepared to immediately start titrating phenylephrine to treat hypotension. Other vasopressors should also be ready, although the choice depends on the patient's underlying cardiac abnormality. Moving the uterus to the left immediately after placing the epidural, hydration and rapid fluid overload should be avoided in patients with cardiac weakness. For these patients, reduced crystalloid volumes and slow administration are appropriate during the onset of the block, and the administration of a vasopressor agent may be necessary.

Spinal anesthesia is usually avoided in high-risk patients, primarily due to the rapid onset of sympathectomy with a sudden decrease in systemic vascular resistance and preload, potentially resulting in life-threatening hypotension (severe aortic stenosis, severe mitral stenosis, cyanotic congenital heart disease with right-to-left shunting, severely dilated cardiomyopathies with low ejection fraction, hypertrophic cardiomyopathy).

Some anesthesiologists avoid any neuraxial technique in such highly risky patients. However, carefully and closely monitored epidural anesthesia, or low-dose combined spinal-epidural (CSE) anesthesia for Cesarean section, has been reported to be well-tolerated, even in women with severe aortic stenosis or hypertrophic cardiomyopathy(11).

Occasionally, general anesthesia is required for Cesarean section in patients with high-risk cardiovascular diseases. The pathophysiology and desired hemodynamic goals for the specific cardiovascular lesion of the patient are considered when choosing anesthetic agents. Maintaining the mother's hemodynamic stability is a priority, and for sustaining stability in patients with high-risk cardiovascular diseases, a very slow titration induction is typically indicated. A reasonable approach to induction involves the use of a short-acting hypnotic (etomidate, ketamine, or propofol in divided doses, titrated for effect) with boluses or an infusion of phenylephrine, succinylcholine, and opioids (although opioids are generally avoided in Cesarean sections) for blunting the sympathetic response to laryngoscopy and intubation.

For maintenance of general anesthesia, sevoflurane or desflurane is administered at approximately 1 MAC and nitrous oxide is avoided. Sometimes there is a need for urgent cardiovascular intervention, such as mechanical circulatory support, including veno-arterial extracorporeal membrane oxygenation (ECMO) or insertion of an intra-aortic balloon pump, ventricular assist device, or cardiothoracic surgical procedures.

The intensity of postpartum monitoring is determined based on the patient's underlying cardiovascular disease and any obstetric or cardiac events that occurred during delivery.

Treatment for a birthing woman with high-risk cardiovascular diseases involves a high-risk heart team for pregnancy, consisting of cardiologists, obstetricians and anesthesiologists, working together to develop an individualized treatment plan. Interdisciplinary communication and preparation are crucial because peripartum obstetric and cardiac complications may require emergency intervention.

Anesthetic management for a pregnant woman with high-risk cardiovascular diseases requires a thorough pre-anesthetic evaluation, considerations for monitoring, as well as an assessment of the risks and benefits of neuraxial techniques or general anesthesia. Additionally, methods to minimize the postpartum risk while providing optimal anesthetic care should be implemented.

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ANESTHESIA MANAGEMENT IN PREGNANT PATIENTS FOR NON-OBSTETRIC OPERATIVE INTERVENTIONS AND THE IMPACT ON MOTHER AND FETUS

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Introduction

It has been estimated that each year between 0.5-2.2% of pregnant women receive anesthesia for various surgical interventions of a non-obstetric nature during their pregnancy. The purpose of the operative intervention may be:1.to prolong the pregnancy, 2. it is not related to the pregnancy or 3.to correct the anomalies of the fetus. Therefore, understanding the effects of various anesthetic drugs and techniques on the mother and fetus is essential for safe anesthesia in pregnant women undergoing operative intervention. The operation can be indicated at any stage of pregnancy. The anesthesiologist must provide safe anesthesia for both,the mother and the fetus. For the mother, safety is related to the physiological adaptations associated with pregnancy, which require adjustments to standard anesthesia techniques. Fetal safety refers to the teratogenicity of certain drugs and anesthetics, avoiding fetal asphyxia, and avoiding premature labor and delivery.

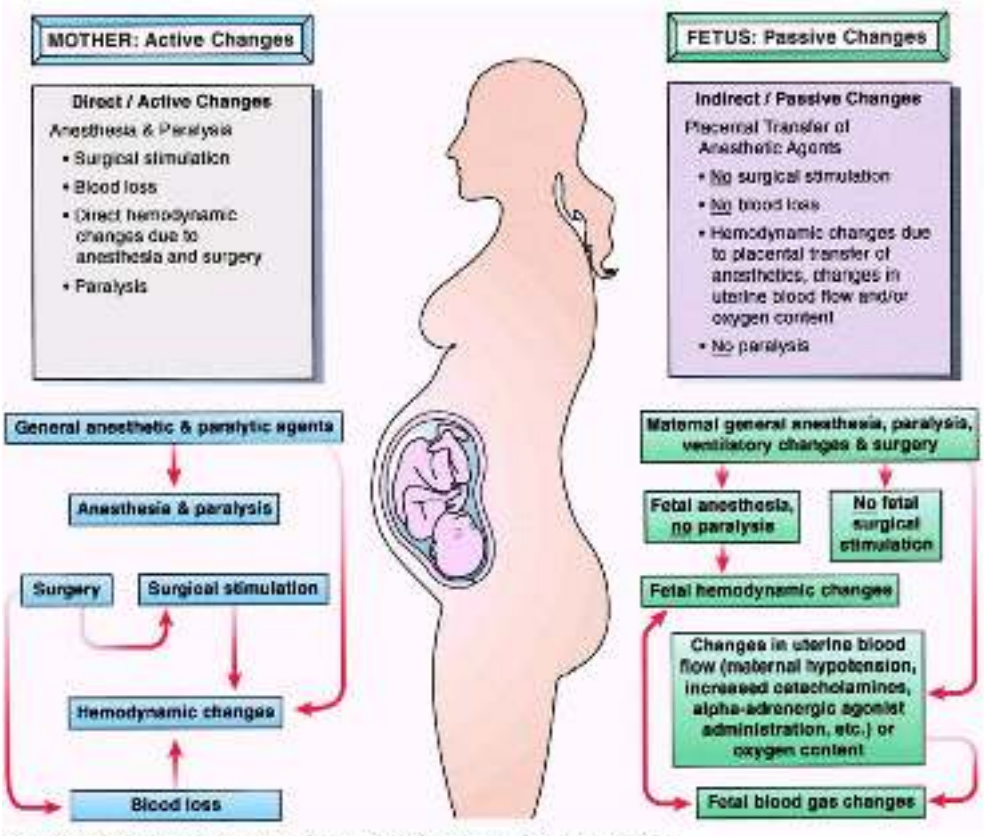


Fig. 1. The effects of anesthetic and paralytic agents and surgery on the mother and fetus.

Maternal safety: Maternal Physiological Adaptations to Pregnancy

A pregnant woman undergoes significant physiological adjustments during pregnancy. Most of these changes are due to the mechanical effects of an enlarged uterus, hormonal changes associated with pregnancy, increased metabolic demands and a low-resistance placental circulation. Minute ventilation and oxygen consumption increase, while residual volume and functional residual capacity decrease. Therefore, oxygen reserves decrease, and pregnant women develop hypoxia and hypercapnia with hypoventilation or apnea more quickly. Airway management by face mask, laryngeal mask, or endotracheal intubation can be technically difficult in pregnant women due to increased anteroposterior chest wall diameter, breast enlargement, laryngeal edema and weight gained affecting the soft tissues of the neck.

Cardiovascular changes - Cardiac output increases gradually starting from the 8th week of gestation and reaching its maximum increase by the end of the 2nd trimester. Both heart rate and stroke volume are increased, resulting in a 50% increase in cardiac output by the end of the second trimester. Myocardial contractility remains unchanged, but systemic vascular resistance is reduced. This is primarily due to progesterone, as well as the presence of low placental resistance. From about mid-pregnancy, women in the supine position are at risk for aortic and vena cava compression by the gravid uterus. Physiological compensation for aortocaval compression may be compromised by anesthetic techniques (spinal, epidural, or general) that prevent the sympathetic nervous system from responding adequately and may result in profound hypotension. Therefore, it is important to avoid this by placing the patient in the left lateral position.

Gastrointestinal Changes - Due to mechanical and hormonal changes, pregnant women are at increased risk for gastric acid aspiration during induction of anesthesia or sedation. Gastroesophageal sphincter tone is reduced, and although gastric motility remains normal during pregnancy, it is significantly impaired by opioid administration, onset of labor, pain, trauma and more. For pregnant women in the second or third trimester, or those with a history of reflux esophagitis, it is necessary to use the so-called “full stomach” techniques.

Fetal Safety- Avoidance of Fetal Asphyxia

During pregnancy, the most important and serious risk for the fetus from the mother’s surgery is intrauterine asphyxia. The greatest challenge for the anesthesiologist is, therefore, to avoid fetal asphyxia by maintaining normal maternal oxygenation and hemodynamics. Maternal oxygenation, carbon dioxide levels, blood pressure and uterine tone are factors that should be controlled during surgery to avoid fetal asphyxia. It is extremely important to avoid hypoxia, hypercarbia, hypocarbia, maternal hypotension and uterine hypertonus during non-obstetric surgery. This is probably much more important than concerns about the teratogenicity of various anesthetic drugs. Mild periods of hypoxemia of short duration are well tolerated. However, prolonged, or severe maternal hypoxemia causes uteroplacental vasoconstriction and decreased uteroplacental perfusion, resulting in fetal hypoxemia, acidosis and ultimately fetal death. Hyperoxia is not dangerous, contrary to what was previously thought. It has been clearly demonstrated that hyperoxia does not result in increased uterine vascular resistance, nor it reduces fetal oxygenation as measured by fetal scalp gas analysis. Maternal hypercarbia directly induces fetal respiratory acidosis. Severe fetal respiratory acidosis causes fetal myocardial depression. Hypercapnia also results in vasoconstriction of uterine arteries and decreased uterine blood flow. Similarly, hypocapnia also results in decreased uterine blood flow and ultimately fetal acidosis. Vasoactive drugs that reduce uterine blood flow, such as α -adrenergic agents, dopamine or epinephrine, are not ideal agents for treating maternal hypotension; although blood pressure

may increase, blood flow to the uterus may remain decreased. For the treatment of maternal hypotension, ephedrine has long been considered the first choice. However, recent data suggest that phenylephrine is equally effective in maintaining normal maternal blood pressure and that phenylephrine produces significantly better fetal acid-base balance, at least in term pregnancies undergoing caesarean section under regional anesthesia. Therefore, it is now considered preferable to treat maternal hypotension with phenylephrine. Several drugs commonly used in anesthesia, such as ketamine or IV local anesthetics, may cause uterine hyperactivity and should be avoided. Maternal oxygen administration will increase fetal oxygenation, however, the fetus is never at risk of hyperoxia, as fetal oxygen tension will not exceed approximately 65mmHg, even with maternal administration of 100% oxygen.

Teratogenicity of Anesthetic Drugs

Medicines can be toxic to the developing embryo and fetus. The first trimester of pregnancy, i.e. the stage of embryonic development and organogenesis is of particular importance because the teratogenic effects of certain drugs affect the normal development of the unborn child at a structural or functional level. A teratogen is a drug or other chemical substance that can affect the normal development of the embryo and cause recognizable congenital defects.

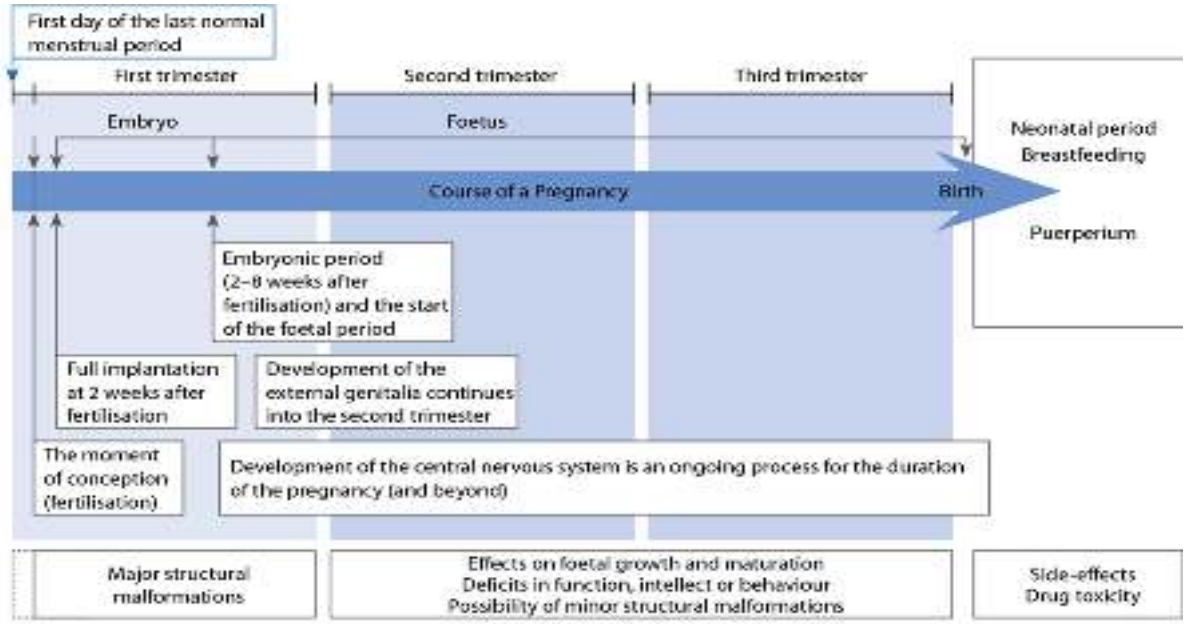


Fig2. The vulnerability of the unborn child and neonate to drug therapy

Anesthetic drugs affect intra- and intercellular exchange and have known effects on cell mitosis and DNA synthesis. Therefore, all anesthetic agents can be potentially teratogenic. The teratogenicity of the drug is determined by the dose administered, the method of administration, the time of exposure of the fetus and the species that is exposed to the drug. The time of exposure to the anesthetic is critical. During the first 15 days of pregnancy, an all-or-nothing phenomenon occurs: the fetus is lost, or the fetus is preserved completely intact. Structural abnormalities may occur during organogenesis (15-56 days). After this period, functional changes may be observed, but structural abnormalities are rare. Because prospective clinical studies are impractical, unethical, and would require large numbers, most of our knowledge

comes from animal studies, accidental exposures, and reports from series of patients who underwent anesthesia while pregnant. Although most of the anesthetics are known as teratogens in certain species, when administered at a sufficiently high dose or when administered directly to the fetus, most of the agents are, however, perfectly safe in the clinical setting. We now know that local anesthetics, volatile anesthetics, induction drugs, muscle relaxants and opioids are not teratogenic when used at clinical concentrations, and when normal maternal physiology is maintained. It is probably best to avoid nitrous oxide during pregnancy, as it is not necessary to use this agent to provide safe and effective anesthesia. Nitrous oxide has known effects on DNA synthesis and has been shown to have teratogenic effects in animals. Nitrous oxide has been shown to inactivate methionine synthetase, which in turn inhibits thymidine and DNA synthesis, inhibits cell division, and potentially disrupts other biochemical pathways. In methylation reactions,to date, there are no clinical data linking these cellular actions to teratogenic outcomes. Laboratory studies of the teratogenicity of inhalation agents in rodents indicate that modern volatile anesthetics at trace and subanesthetic concentrations do not result in adverse reproductive or teratogenic effects. Nitrous oxide is a weak teratogen in rodents when given for long periods. However, coadministration of isoflurane reverses the fetal lethality and teratogenic effects of nitrous oxide without affecting methionine synthetase activity. Large survey studies that have taken into account the results of women who have undergone surgery during pregnancy, do not indicate an increase in congenital anomalies in their offspring, but an increase in the risk of abortions, growth restriction and an increased frequency of small and very low birth weight babies. Birth weight for reasons attributable to the surgery itself, but not to anesthesia. Some smaller retrospective studies have suggested an association with neural tube defects in the first trimester exposure to anesthesia. However, the patient's primary illness, the site of the operation, or the surgical procedure are more likely to increase the risk of abortion than exposure to anesthesia. Although many pregnant women undergo anesthesia and many more are exposed through the anesthetic profession each year, the teratogenic risk of anesthetic agents in humans must be assessed based on incomplete data. Available studies suggest, for a surgical procedure, that administration of nitrous oxide or volatile, opioid, regional, or local anesthetics to pregnant women will have no deleterious effects on embryonic or fetal development and no clinical significance for adverse neonatal outcome. The danger of teratogenic effects from currently available anesthetic or sedative drugs remains only a potential risk. No anesthetic, opioid analgesic, sedative-hypnotic, or anxiolytic appears to be teratogenic or safer than another agent. Long-standing relative contraindications and concerns about the use of benzodiazepines, especially in the first trimester, were later dismissed. And they are used as preoperative medications for women to treat pain or anxiety, because catecholamines that are increased by pain or anxiety can negatively affect blood flow to the uterus as well.

Prevention of Premature Birth - Fetal Monitoring

After surgery performed during pregnancy, the risk of premature birth or abortion is increased, especially if the surgery involves intra-abdominal procedures. Prophylactic tocolytic therapy is controversial, as tocolytic agents have significant side effects and maternal efficacy during non-obstetric surgery has not been proven. Tocographic monitoring during the first hours or days postoperatively is recommended to detect and treat preterm labor as early as possible. Nowadays, it is recommended to routinely use fetal heart rate (FHR) monitoring when feasible. Surgery and anesthesia can affect uterine activity and placental perfusion, and thus fetal oxygenation and fetal heart rate. Fetal heart rate can also be directly affected by drugs that readily cross the placenta, or indirectly by their effect on maternal hemodynamics. Monitoring of the fetus and uterus during surgery is often possible, but in some circumstances access may be difficult. However, such monitoring may be impractical in emergency situations, has not been documented to improve

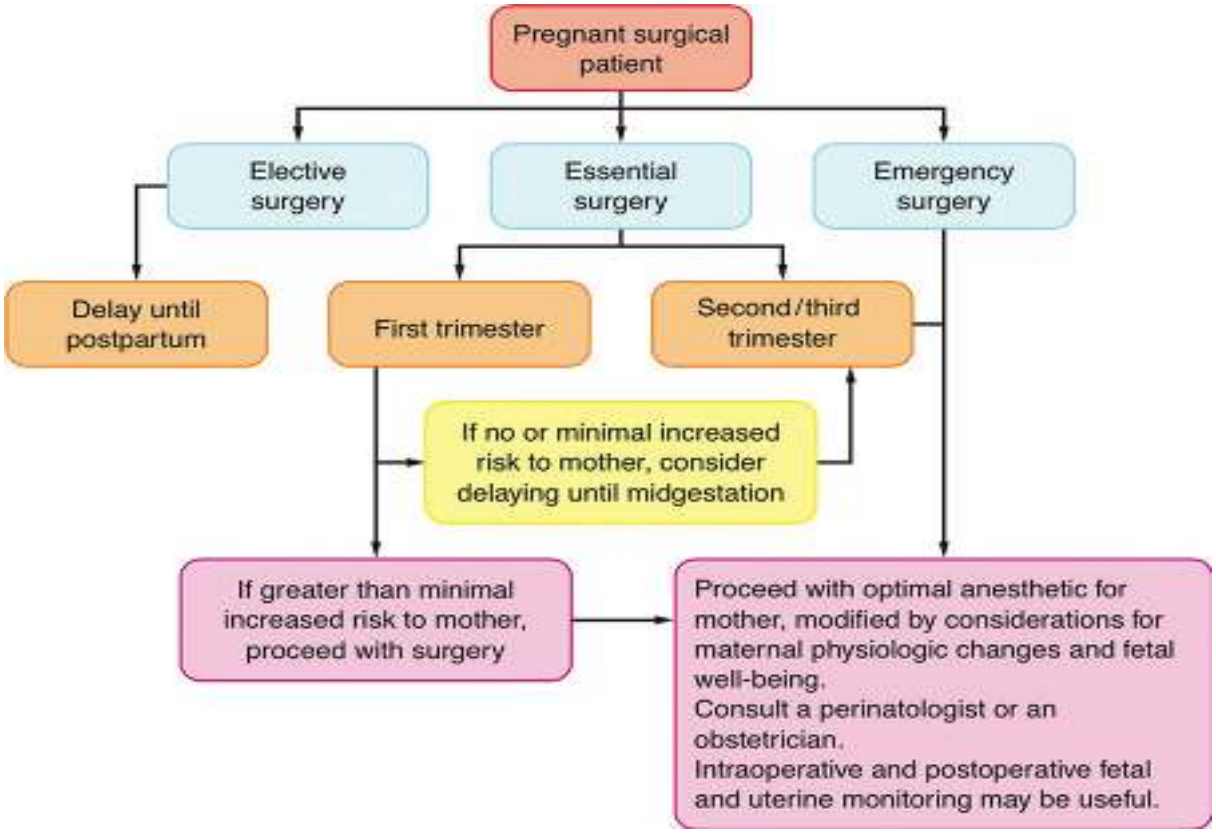
fetal outcome, and requires expertise often not possessed by regular staff. Misinterpretations can lead to unsafe interventions. When used, appropriate personnel trained in basic fetal heart rate interpretation should be immediately available. Unfortunately, there is no evidence to show that the use of intraoperative FHR monitoring improves fetal outcome. The issue remains controversial, but many obstetric textbooks advise monitoring whenever feasible.

Laparoscopy

According to many authors there is a concern for the well-being of the fetus during laparoscopy primarily due to direct trauma to the uterus or fetus and fetal acidosis from absorbed carbon dioxide (CO2). Also, due to increased intra-abdominal pressure, maternal cardiac output, the utero-placental perfusion can be reduced. Animal data have confirmed these suspicions. However, clinical experience, using careful surgical and anesthetic technique is favorable. Reedy et al. compared laparotomy and laparoscopy performed in pregnancy in over 2 million pregnancies in Sweden over a 20-years period. These authors included 2,181 laparoscopies and 1,522 laparotomies with a gestational age between 4 and 20 weeks. They compared 5 fetal parameters (birth weight, gestational duration, growth restriction, infant survival and fetal malformations) for each type of surgery with the overall outcome in the non-operated population. Premature delivery, growth restriction and low birth weight were more common in the operated group compared to the general population. No differences were identified between laparoscopy and laparotomy. Thus, the following guidelines issued by the American Society of Gastrointestinal Endoscopic Surgeons regarding laparoscopic surgery during pregnancy, suggest that whenever possible, surgery should be postponed until the second trimester. Preoperative obstetric consultation should always be obtained.

Other Important Changes

As a result of increased plasma volume, anemia occurs, despite the increase in red blood cell volume. Pregnancy is also associated with benign leukocytosis, causing a hypercoagulable state with an increase in the most of coagulation factors, as well as coagulation and fibrinolysis. Thus, pregnancy is a state of compensated intravascular coagulation. Thrombocytopenia can occur in up to 1% of pregnancies without signaling preeclampsia. The hypercoagulable state puts the pregnant patient at high risk for postoperative thromboembolic complications. The glomerular filtration rate increases by 50% during pregnancy and as a result, creatinine clearance is increased by 50%. Serum creatinine concentrations, therefore, are reduced by almost 1/3. Anesthetic requirements are significantly reduced for both inhaled and intravenous anesthetic agents. Pregnancy is associated with increased sensitivity to inhaled anesthetics with minimal decreases in alveolar concentration of up to 40% reported. Similarly, sensitivity to intravenous agents is also increased. A lower amount of anesthetics given during spinal and epidural anesthesia is required to produce similar dermatomal spread in pregnancy compared to non-pregnant patients. This is due to the hormonal, as well as mechanical effects of the enlarged uterus. Nondepolarizing muscle relaxants have a prolonged duration of action, whereas the duration of action of succinylcholine is not affected by pregnancy.



Practical Approach

These physiological changes in pregnant women require anesthesiologists to adapt their routine anesthetic technique. Ideally, the surgery should be performed during the second trimester. Laparoscopy is possible. Acid aspiration prophylaxis (a combination of H2-blocker, oral sodium citrate 30 mL and metoclopramide) is recommended to reduce gastric contents and increase gastric pH. This clearly results in reduced morbidity and mortality when accidental aspiration occurs. Adequate left lateral tilt positioning of the pregnant woman in supine position (at least 20° left lateral tilt) is required to avoid recumbent hypotensive syndrome. This should be done from the 2nd trimester onwards. The pregnant patient is more prone to hypoxia due to reduced functional residual capacity and increased oxygen consumption. Therefore, careful denitrogenation is recommended before induction of general anesthesia. Rapid sequential induction should be performed using cricoid pressure and a fast-acting muscle relaxant. The drug of choice remains succinylcholine. Rocuronium would be an alternative. However, it has a significantly prolonged duration of action that is difficult to detect during artificial ventilation. All anesthetic agents can be used. The volatile agent is useful in preventing premature uterine activity. It is prudent to avoid nitric oxide. Hypoxemia, hypercarbia and hypocarbia should be avoided, and hypotension should be treated aggressively with intravenous fluids and phenylephrine or ephedrine. Good postoperative analgesia must be provided. Pregnant patients are more prone to thromboembolic complications and appropriate prophylactic measures should be taken, including prophylactic administration of low molecular weight heparins.

The Effect of Anesthetics on the Fetus

Teratogenic studies of various anesthetic agents have been studied mainly in animals. It is very difficult, but also impractical to mirror these results to humans. Fortunately, there are no commonly used anesthetics that are known teratogens when given acutely.

Sedative and Hypnotic Agents

Barbiturates have been used in humans for induction for many years. Although there are conflicting animal reports regarding the teratogenic effect of barbiturates, these agents are safe in pregnant women. Phenothiazineshave also been reported to have no adverse effect for anesthesia for non-obstetric surgery. The association of minor sedatives with teratogenicity is controversial, although retrospective studies have shown diazepam and chlordiazepoxide to be associated with congenital malformations. On the other hand, more recent studies have not found an increased risk of congenital anomalies after diazepam use. No teratogenicity has been observed for midazolam. Recently published literature on women who have attempted suicide during pregnancy by taking large doses of drugs such as diazepam, medazepam, promethazine and meprobamate, has not shown that these drugs are fetotoxic.

Opioids

Geber and Schramm observed the teratogenicity of a wide variety of narcotics administered to pregnant hamsters during critical periods of fetal central nervous system development. Comparative studies using single or multiple doses have shown increased fetal anomalies with diacetylmorphine, thebaine, pentazocine, morphine, hydromorphone as well, such as meperidine. On the other hand, other authors noted that chronic administration of morphine, fentanyl, sufentanil or alfentanil in pregnant rats was not associated with any teratogenic effect. There is also no evidence that these opioids are associated with teratogenicity in humans.

Muscle Relaxants

There is no evidence of a negative effect on the development of the fetus after the use of muscle relaxants.

Local Anesthetics

In a very large study conducted by the Collaborative Perinatal Project and in other studies, no evidence of teratogenicity was found in pregnant rats following administration of benzocaine, procaine, tetracaine, or lidocaine. In contrast, cocaine use has been associated with birth defects in both humans and animals. This could be explained by cocaine-induced vasoconstriction and, hence, fetal tissue hypoxia.

Oxygen and Carbon Dioxide

Hypoxia, as well as hypercarbia, has been associated with teratogenicity in animal species.

Inhalation Anesthetics

Nitrous Oxide

Interest in the teratogenic effect of nitrous oxide increased significantly among anesthesiologists after Nunn and colleagues observed the effect of short-term administration of a nitrous oxide anesthetic on plasma concentrations of methionine, tryptophan, phenylalanine, and

S-adenosylmethionine in humans. Using nitrous oxide intraoperatively and up to 24 hours postoperatively, Scatzel and colleagues observed a significant decrease in plasma methionine concentration after major vascular surgery in humans and recovery that occurred only after cessation of nitrous oxide administration. The main reason for the reduced concentration of methionine in the plasma is related to the inhibition of the enzyme methionine synthetase. Thus, the teratogenic effect of nitric oxide may be related to interference with DNA synthesis by altering folate metabolism. Keeling and his colleagues observed the effect of pretreatment with folic acid on the teratogenic effect of nitrous oxide in rats such that skeletal abnormalities in the group receiving nitrous oxide without pretreatment were five times greater compared to the control group, which had been pretreated with folic acid, where the changes were insignificant. Hence, the authors concluded that the mechanism of teratogenicity after exposure to nitrous oxide may not be related to interference with DNA synthesis, but to a physiological effect of nitrous oxide in reducing uterine blood flow due to increased sympathetic activity. In summary, although there is a relationship between nitrous oxide use and teratogenicity in rats, the exact mechanism is currently unclear. In humans, brief exposure to nitrous oxide during the second trimester was not associated with any adverse effect.

Halogenated Anesthetics

Halothane, enflurane, and isoflurane at physiological minimum alveolar concentrations have not been associated with any teratogenicity in rats, nor has evidence of teratogenicity in humans been observed with these agents. The newer inhaled agents desflurane and sevoflurane are also not associated with any teratogenicity.

Effects on the Fetal Brain: Behavioral Teratogenicity

As with all non-human animal studies, it is difficult to extrapolate the degree of risk from anesthetics to humans undergoing general anesthesia or fetuses exposed in utero to anesthesia due to maternal surgery. Hopefully, in the future, a better understanding of the mechanism of toxicity will also point to strategies to block the harmful effects. While laboratory and eventual clinical trials continue, it is reasonable to assume that general anesthetics are potentially toxic to the developing fetal brain, and their use in obstetric anesthesia should continue to be reserved for emergencies only.

Recommendations to Minimize Abortion or Premature Birth

If an operative intervention is planned, it should be postponed until after delivery. In semi-urgent cases, it is best to postpone the operation until after the first trimester. In emergency cases, the anesthetic chosen should depend on the site and extent of the operation to be performed. If possible, regional anesthesia, spinal, epidural, or caudal block is recommended. However, if necessary, general anesthesia can be applied. Benzodiazepines and opioids can be given preoperatively for premedication, if necessary. A routine antacid should be used before induction, and rapid sequence induction is often chosen. Although there is no general consensus, it is reasonable to use endotracheal intubation for longer or more extensive procedures. Then depolarizing or non-depolarizing muscle relaxants. Anesthesia can be maintained with nitrous oxide, oxygen and halogen anesthetics. Morphine, fentanyl, sufentanil, or alfentanilmay be used as analgesics. Hyperventilation should always be avoided as it may decrease uteroplacental perfusion, as well as shift the maternal hemoglobin dissociation curve to the left. For regional

anesthesia, maintenance of normal blood pressure is absolutely necessary, and routine use of face mask oxygen is recommended. Regardless of whether general or regional anesthesia is chosen, moving to the left lateral position of the operating chair when lying on the back is mandatory from the middle of the second trimester onward. Routine monitoring should include blood pressure, electrocardiogram, oxygen saturation, capnography and temperature. Close communication between the anesthesiologist and obstetrician regarding fetal heart rate monitoring and interpretation of results is essential. Because most of the drugs used for general anesthesia can alter the fetal heart rate, the baseline fetal heart rate should be the main indicator of fetal well-being during general anesthesia. Depending on the location of the surgery, tocodynamometrymay be used to monitor uterine contractions. This is already becoming routine in the postoperative period, when treating pregnant women with premature contractions with tocolytics. Nowadays, laparoscopic surgery during pregnancy is successfully used, but one must have basic knowledge about the physiological changes during pregnancy. During laparoscopic cholecystectomy, women are placed in a head-down position, so these positions can have significant cardiovascular and respiratory effects. Peritoneal insufflation pressure should be kept low because of the possibility of aortocaval compression. Ventilation should be optimal to maintain end-tidal PCO2 at 32-34mmHg. Intra-abdominal pressures were maintained around 15mmHg. Adjusting ventilation to maintain ETCO2 also maintains optimal maternal arterial CO2. Also, cardiac output decreases by about 30% during laparoscopic surgery in pregnant women, and therefore vasopressors (ephedrine) should be given to maintain blood pressure within 20% of baseline.

Conclusion

Elective procedures should be delayed until approximately 6 weeks postpartum, when the physiologic changes of pregnancy have passed, and fetal well-being is no longer a concern. Women of reproductive age should be asked about their last menstrual period, informed of the potential risks, and offered pregnancy testing if their menstrual history is uncertain, or they seek to avoid planned procedures during early pregnancy. Despite the lack of clinical evidence, delaying surgery until the second trimester, when possible, may reduce the risks of teratogenicity and miscarriage. Whenever major surgery is undertaken on a pregnant patient, a perinatologist or obstetrician should be consulted to assist in perioperative management, to diagnose and properly manage possible preterm labor, and to try to avoid preterm labor. Informing the obstetrician or perinatologist about any surgical procedure may be in the patient's best interest.

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REVIEW ARTICLE *UDK: 616.282.1-089.843-089.5-053.31*

COCHLEAR IMPLANTATION AND ANESTHESIA

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In light of the strong trends toward performing cochlear implantation in infants, it is necessary to consider anesthetic issues. Just as anesthetic risk may play an important role in surgical candidacy in the elderly population, anesthesia is of special consideration in infants as well. Even healthy infants are known to be at increased risk for anesthetic complications. For this reason, the most elective surgical procedures are not routinely done within the first two years of life.

The advancement in the technology of cochlear implants has resulted in increasing trend of cochlear implantation in both the children and elderly population. The anesthesiologist is faced with the task of smoothly conducting the surgery without any interference in the stimulation techniques used (1).

The preoperative evaluation is mainly focused on the presence of any congenital anomalies in these patients which may affect anesthetic technique. The reduction of anxiety of the patient, as well as the parents of small children, are important aspects of the preoperative visit. The anesthetic technique chosen should not interfere with the stimulation of the cochlear implant electrode assembly. Postoperative management is mainly focused on prevention of agitation and good analgesia. A close cooperation between the surgeon and the anesthesiologist is essential for a positive outcome in this surgery.

Induction of anesthesia can occur in the standard manner in adults using propofol 2.5mg/kg intravenously with the analgesia given by fentanyl 0.5 - 2μg/kg intravenously for pediatric patients, and 2 - 20μg/kg intravenously for adult patients. Induction in children without intravenous access can be achieved by inhalational induction by oxygen and sevoflurane. Tracheal intubation is achieved after neuromuscular blockade with rocuronium 0.5mg/kg intravenously, with appropriately sized endotracheal tube. Attenuation of hemodynamic response with preoperative remifentanil in a dose of 1mg/kg not only provides stable hemodynamics during induction and intraoperative period enabling a smoother control to provide a bloodless field during surgery, but also decreases the requirement of anesthetic drugs during perioperative period (2).

Anesthesia is usually maintained with oxygen, air and sevoflurane, without intermittent doses of rocuronium. Alternatively, a total intravenous technique involving infusion of propofol can be used to maintain anesthesia. However, the choice of anesthetic technique and drugs is solely the priority of the attending anesthesiologist whether to use experience-based or evidence-based anesthesia based on scientific logical empiricism (3).

The standard monitoring should include heart rate, five lead electrocardiogram, noninvasive blood pressure, pulse oximetry, capnography and neuromuscular monitoring. Tissue oxygenation monitoring is an advance monitoring that give us valuable information about tissue oxygenation during hypotensive anesthesia technique that is the most desirable technique for cochlear implantation inpediatric patients, as well as inthe adult population.

The surgical duration is usually 3 hours with no significant blood loss with proper use of hypotensive technique. There is no requirement of blood transfusion, however sometimes significant blood

loss may occur from large non-collapsible mastoid emissary veins. Adequate blood volume is maintained by infusion of crystalloids compensating for fasting and blood losses.

An important step during the surgery is preservation of facial nerve which may be identified intraoperative by electrical stimulation, thus precluding the use of muscle relaxants. This should be used after the effect of the muscle relaxant used for intubation has weaned off, as evidenced by the response on the train of four stimulation, and during this process the anesthesia can be maintained by propofol infusion in combination with remifentanil, or a combination of remifentanil with sevoflurane.

The two main aspects of electrical stimulation are usually used, that is, the electrically elicited stapedius reflex threshold (ESRT) and electrically elicited compound action potential (ECAP) (4).

ESRT mainly determines the maximum comfort level which is defined as the loudest sound tolerated without pain, while ECAP mainly determines the noise threshold - lowest acoustic stimulus perceived as sound. Anesthesia can affect the ESRT leading to wrong estimationof the maximum comfort level which may produce pain during stimulation. In various studies it has been found that there is a strong correlation between the level of hypnosis and the mean stapedius reflex threshold value (5).

The use of electroencephalograph has been found to be useful in maintaining a sufficient level of hypnosis. In a prospective study including children, it was found that the ESRT increased with increasing concentration of inhalational agent with minimal effect of propofol and nitrous oxide. The ECAP was not found to be affected by either the inhalational agents or the propofol. Thus, it can be concluded that the use of total intravenous anesthesia using propofol and opioid is beneficial in pediatric cochlear implant surgery (6).

Sudden coughing and bucking should be avoided at the end of surgery to prevent dislodgment of the electrode array of the implant. Neuromuscular blockade should be reversed, and spontaneous respiratory efforts are allowed. The child can be extubated in deeper planes and kept in lateral recovery position to prevent sudden agitation. The child should be nursed in post-anesthesia care unit in presence of the parents with proper care of postoperative analgesia.

The major postoperative concern in cochlear implant surgery is the prevention of postoperative nausea and vomiting which is common in ear surgery. The various measures employed are adequate anxiolytics preoperatively, use of total intravenous anesthesia with propofol, avoidance of nitrous oxide, administration of antiemetics like ondansetron 0.1mg/kg intravenously at the end of surgery.Postoperative analgesia can be maintained with parent or nurse-controlled boluses of intravenous paracetamol. It is effective in reducing doses of opioids and thus helps in prevention of opioid-related side effects (7,8).

The incidence of postoperative shivering can also be reduced to a large extent by use of perioperative dexmedetomidine (9).

The patient should be monitored in the post-intensive care unittill the consciousness is regained fully with minimal postoperative nausea and vomiting.

The cochlear implant surgery is considered to be relatively safe and minimal, or no anesthesia-related complications are reported. The complications are mainly surgical including minor complications like mild flap infection, change in taste, minor balance problems and transient facial palsy. The major surgical complications include flap necrosis, device failure, device migration, cerebrospinal leak, meningitis and persistent facial palsy (10,11).

Late postoperative complications requiring reimplantation are less frequent, and thus these patients should be followed for long-term (12). Other less frequent complications include displaced magnet from the receiver pocket by magnetic toys and silicone allergy (13).

Conclusion

The anesthetic technique used may have implications on the method of stimulation of the electrodes of the cochlear implant intraoperative. Moreover, most of these patients are children and it is the responsibility of anesthesiologist to prevent any agitation and smooth induction and emergence from anesthesia. Close cooperation between the anesthesiologist and surgeon is essential for a positive outcome.

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BLOOD LOSS AND FLUID REPLACEMENT IN PEDIATRIC PATIENTS

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Abstract

While strategies for the management of hemorrhage, transfusion and blood loss replacement in adults are well established, there aren't any concrete, evidence-based recommendations for pediatrics.

Promoting hemodynamic stability, preserving organ perfusion, minimizing transfusion-related injury, avoiding over-transfusion, and avoiding the deadly triad of coagulopathy, acidosis, and hypothermia are among the objectives of bleeding therapy in pediatric patients. At the beginning of treatment, crystalloid or colloid solutions may be used until blood products are available. Preventing dilutional coagulopathy requires caution. Monitoring end-organ perfusion and maintaining a healthy blood pressure are essential. Red blood cell transfusion should be matched with "yellow" blood product transfusion in the form of a 1:1:1:1 volume ratio of PBRC: fresh frozen plasma (FFP): cryoprecipitate: platelets form, in order to prevent coagulopathy and preserve sufficient oxygen supply to tissues.

Hemolytic transfusion reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO) and transfusion-related immunomodulation (TRIM) are only few of the hazards connected with blood transfusion.

Rapid and appropriate access for blood product transfusions is essential. To calculate the maximum permitted blood loss, a weight-based estimated blood volume (EBV) is used. A tried-and-true strategy for managing intraoperative hemorrhage should be used, including blood preservation techniques, balanced transfusion ratios and adjunct medicines. Transfusion decisions may be influenced by point-of-care and laboratory tests, such as thromboelastography.

Transfusion-related laboratory abnormalities should be watched for and treated as appropriate. Children's platelet transfusion thresholds are unclear; however, maintaining a platelet count of 50,000/L while bleeding continues is seen as sufficient in adults. When EBV loss surpasses 50%, fresh frozen plasma (FFP) and platelet transfusions should be taken into consideration. Electrolyte levels, particularly those of calcium, magnesium and potassium, need to be monitored.

As a result, controlling severe bleeding and transfusion in pediatric patients necessitates specialized approaches, such as meticulous preoperative planning, goal-directed therapy and monitoring of laboratory derangements. PBM program implementation can improve patients' outcomes and lower transfusion-related hazards.

***Key Words**: blood loss, fluid replacement, pediatric patients.*

Introduction

A multimodal and multidisciplinary strategy is necessary for the control of bleeding and fluid replacement in pediatric patients. Interventions start before surgery to identify patients who might have a higher risk of bleeding. This may involve identifying any underlying coagulation disorders (inherited or acquired), stopping the use of specific antithrombotic drugs, or identifying and treating anemia before undergoing any major surgical procedures. The proper use of blood products is receiving increased focus, and recommendations are shifting to a more evidence-based individualized approach (1-4).

It is crucial to stay up to date on the most recent research in this dynamic area of medicine where there are numerous treatment choices available along with surgical procedures of varying complexity. However, there is comparatively little high-quality research in pediatric patients to support evidence-based guidelines when compared to adult practice. This document updates recommendations, suggestions and assertions from a comprehensive literature search to address the whole spectrum of treatment and retains clinical practice recommendations from the existing guidelines (1-6).

Material and Methods:

The key words "pediatric patients," "blood loss "and" fluid replacement" were used in the key word searches strategies of the Medline, IBSS databases, Pubmed, CINAHL, and reference lists of the primary articles that were found during the initial search. To make this method robust and sensitive enough to cover all of the requested keywords, further searches were conducted. Personal and college libraries were also searched for texts on the topic. Guidelines, case reports, editorials and commentaries were included in the search result as well.

Fluid Replacement

The introduction of intravenous (IV) fluids is necessary for children having surgery to address the fluid need resulting from perioperative deficiencies (fasting, hemorrhage and third space losses; gastrointestinal, renal, or cutaneous losses). In a typical person with normal intracellular fluid (ICF) and extracellular fluid (ECF) volumes for a 24-hours period, maintenance therapy represents the fluids and electrolyte requirements due to predicted physiological losses from breathing, sweating and urine output. In order to counteract the effects of anesthetics, proper tissue perfusion must also be maintained, which requires fluid (7). In order to maintain or restore the child's normal physiological condition, including normovolemia, normal tissue perfusion, and normal metabolic activity, normal electrolytes, and normal acid-base balance, intraoperative fluid administration is required (8). There has been a lot of studies done on perioperative fluid administration, specifically on the type of fluid supplied (crystalloids or colloids) and the composition (isotonic vs. hypotonic) (9). Children who have had trauma or major surgery may experience intraoperative blood loss.The most frequent cause of cardiac arrest in children under anesthesia is hypovolemia brought on by blood loss (10). The major objectives of intraoperative management of a bleeding child are to prevent hypotension, maintain appropriate tissue perfusion and oxygenation, and maintain hemostasis. On the other hand, autologous blood transfusions and their constituent parts are linked to higher rates of morbidity and mortality, due to transfusion-associated circulatory overload (TACO) and transfusion-associated acute lung injury (TRALI) (6,11).

Guidelines for Perioperative Pediatric Fluid Therapy

Guidelines by various societies (APA), NICE and guidelines from Association of the Scientific Medical Societies of Germany have been proposed for calculating the volume of fluid to be administered during surgery (8,12-14).

The recommendations state that, in order to minimize patient's discomfort, dehydration and ketoacidosis, preoperative fasting periods for children should be as brief as feasible. Based on the liberalization of fasting guidelines for pediatric patients, which now allow clear fluids for up to 1–2 hours, the amount of IV fluids required to be covered for preoperative fluid deficit may be decreased. However, despite the 2-hours recommendation for fasting, there are several circumstances where a child may be fasting for more than 6 hours (14).

Fluid Maintenance Therapy and itsPhases

The Holliday and Segar 4-2-1 formula is used to calculate the maintenance fluid requirements (15), Table 1. The maintenance fluid administration of isotonic fluids based on the Holliday and Segar formula is advised by both APA (12) and NICE (13) guidelines. However, according to NICE guidelines, fluid intake should be limited by 50–80% due to the danger of water retention caused by non–osmotic ADH secretion (13). The German recommendations include starting with an initial infusion of balanced electrolyte solution containing 1-2.5% dextrose at a rate of 10ml/kg/h and then adjusting the rate as needed (8).

Table 1. The Holliday and Segar formula.

Weight (kg)	Hourly	Weekly
< 10kg	4ml/kg/h	100ml/kg/day
10– 20kg	40ml + 2ml/kg for every kg>10kg	1000ml + 50ml/kg/day for every kg>10
<20kg	60ml + 1ml/kg for every kg>20kg	1500ml + 20ml/kg/day for every kg>20

There are four specific physiology-driven time periods for children that require IV fluids. The phase of resuscitation is when the IV fluids are required during the acute presentation window, in order to restore appropriate tissue perfusion, and stop or lessen end-organ damage. It is crucial to assess intravascular repletion and the trajectory of fluid gains vs losses in critically ill children throughout the titration phase, which occurs when IV fluids are switched from boluses to maintenance. A precise homeostatic balance between needs and losses should be achieved during the maintenance phase, which takes into account the fluids given during the first two stabilization periods. The convalescent phase, which follows the cessation of exogenous fluid delivery and the patient's return to intrinsic fluid management, is the last stage. A fixed protocoled dose cannot be applied to all patients, and the fluid dose during these four phases of fluid treatment must be modified based on the individual physiological requirements of each patient (1,8,12-14).

Replacement Fluid Therapy

The APA guidelines state that blood or isotonic solutions and colloids, depending on the child's hematocrit, should be used to replace intraoperative losses (12).

It is difficult to quantify the third space loss, but it is generally estimated to be:

- 2ml/kg/h for superficial surgery minimal trauma,
- 4–7ml/kg/h for moderate trauma, and
- 5–10ml/kg/h for severe trauma surgery.

The rate of fluid delivery is not included in the NICE guidelines; only replacement of ongoing losses with isotonic saline is (13). Sumplemann et al. advise giving repeat dosage infusions of 10–20ml/kg of balanced, isotonic electrolyte solutions without glucose to patients with circulatory instability until the desired effect is attained (8). A necessary condition for proper venous return, cardiac output and sufficient tissue perfusion is a normal blood volume. Interstitial fluid moves toward intravascular space as blood volume falls. Stabilizing the circulatory system by infusing a balanced salt solution to maintain extracellular fluid volume and blood volume is the first step (14).

Colloids such albumin, gelatin and hydroxyethyl starches, are used as repeat dose infusions if the volume of crystalloids is too high in order to prevent interstitial fluid excess, which can cause hemodilution and a reduction in the oxygen supply. The entire dose, however, should not be more than 10 to 20ml per kilogram (not to exceed a 50ml/kg dose) (12-14).

Which Type of Isotonic Solution is Preferred?

A variety of IV fluids are commercially available for use on newborns and kids. The main differences between these solutions are the kind of electrolyte composition, the addition of a buffer, and whether or not they contain glucose.

There are many other kinds of isotonic solutions that can be administered, but the most popular ones are normal saline (NS), Ringer lactate (RL) and PlasmalyteTM (acetate). RL has a somewhat hypotonic osmolality of 273mOsmol/kg compared to normal saline's 286mOsmol/kg. These solutions contain a very high concentration of chlorine (156mmol/L) and administering significant amounts of them can lead to chloride overload, which can restrict renal blood flow and the renin-angiotensin-aldosterone system, resulting in hyperchloremic acidosis (16). Additionally, lactate can still be used for diagnosis as a marker of tissue perfusion because acetate, which is present in the solutions, is quickly metabolized by the liver in comparison to lactate. For intraoperative infusion, balanced electrolyte solutions are advised (17,18).The key action statements of APAare that isotonic solutions with suitable potassium chloride (KCl) and dextrose should be administered to patients aged 28 days to 18 years who need maintenance IVFs because they greatly lower the risk of hyponatremia (1A level ofevidence) (1,12).

Table 2. Composition of commonly used maintenance intra venous fluids (1).

Fluid	Glucose g/dL	Sodium	Chloride	Potassium mEq/L	Calcium	Magnesium	Buffer	Osmolarity mOsm/L
Human plasma	0.07 -0.11	135-145	95-105	3.5-5.3	4.4-5.2	1.6-2.4	23-30 bicarbonate	308
Hypotonic solution								
0.25%NaCl	5	34	34	0	0	0	0	78
0.45%NaCl	5	77	77	0	0	0	0	154
Isotonic solution								
0.9%NaCl	5	154	154	0	0	0	0	308
Lactated Ringer	5	130	109	4	3	0	28 lactate	273
PlasmaLyte	0	140	98	5	0	3	27 acetate and 23 gluconate	294

Role of Colloids

There is significant debate over, and little research on the use of colloids intra operatively in pediatric patients (19,20). The majority research investigations that have demonstrated renal failure in sepsis patients, were conducted on adult patients. However, using moderate and high dosages of HES 130 has not been associated with renal failure in pediatric animal trials or in children having major heart surgery. When given to children during the perioperative period, intravascular volume expansion with low molecular weight 6% HES, did not seem to affect renal function, blood loss, or transfusion, according to a meta-analysis (21).

To evaluate their impact on children, the authors advised conducting high-quality RCTs due to the poor quality of the evidence.

Blood Loss and Need for Transfusion

Through research and practical experience in specific circumstances, the treatment of major bleeding and massive transfusion has been described in adults. Tourniquet use, damage control resuscitation techniques, balanced transfusion ratios and anti-fibrinolytic medication have all been demonstrated to have significant effects on reducing trauma-related death (22). There are number of regimens for managing large hemorrhage in children, many of which have been derived from the trauma literature and procedures for adults (23). Children are not miniature people (24).Pediatric strategies should focus on preventing the well-described lethal triad (coagulopathy, acidosis and hypothermia) associated with massive transfusion, as well as patients' or procedural risk factor awareness, system and provider readiness for potential hemorrhage in high-risk situations and intraoperative goal-directed care. During the perioperative phase, blood transfusions are frequently necessary, especially when children are having surgery, but it is particularly common during trauma, liver transplant, cardiac surgery, major spinal surgery, cranial vault surgery, neurosurgical procedures (arteriovenous malformations, Vein of Galen), and minimally invasive procedures where direct bleeding control can be challenging.

Inherited bleeding disorders and other patient-related factors can potentially increase the chance of hemorrhaging (24). Assessment of the necessity for and value of blood transfusion is thus a crucial component of anesthesia management. It's also crucial to realize that giving blood to kids entails serious risks for morbidity and mortality due to acute lung injury from transfusions, circulatory overload and hemolytic transfusion responses (25). These have led to the implementation of patients' blood management (PBM) programs, which offer evidence-based treatment and enhance outcomes by using the best possible transfusion therapy. Although these programs have been used successfully in the adult population, they have not yet gained much attraction with newborns, young children and babies (11,26). For neonates, babies, and children as well as adults, many practice guidelines and recommendations for perioperative blood management have been published (27,28,29). Patients' blood management (PBM) is the timely implementation of scientifically supported medical and surgical principles intended to preserve hemoglobin concentration, maximize hemostasis, and reduce blood loss in order to enhance patients' outcomes (5). The establishment of a multidisciplinary PBM program inside a facility can assist in addressing the system demands and strain brought on by a patient suffering from a major hemorrhage in a way that is both effective and safe. This program should specify the protocols to be followed, the transfusion triggers to be used to start a large-scale transfusion event, and the quantity/ratio of blood products delivered throughout the event. This lessens needless transfusions, while enabling safe and effective optimization of blood product consumption. The patient's morbidity and mortality may go down, and the institution's medical expenses might go down consequently (8). According to the PBM programs, infants and children may require stringent hemoglobin thresholds (the objective is 7g/dL for patients who are hemodynamically stable). A restrictive Hb trigger (7.0g/dL) was shown to be equally safe and efficacious as a liberal Hb trigger (9.5g/dL) in a randomized controlled trial of stable critically sick children (33). This has not been generalized to unstable individuals, and children with cardiorespiratory impairment and/or anemia symptoms may require a higher threshold. If necessary, red blood cell transfusions should be single donor, irradiated, fresh and leucocyte depleted.

The requirement of blood transfusion depends on many factors like age, quantity of blood loss, the baseline hemoglobin concentration and different blood physiology. Neonates and infants have higher blood volume per weight (Table 2) but are less tolerant of the loss. In addition, the metabolic rate and baseline oxygen demands are greater than in adults. Preoperative iron deficiency anemia is more prevalent in this population and increases the risk of blood transfusion requirement intra operatively. Neonatal hemoglobin (Hb) is more than 70% fetal Hb in term neonates compared to 90% in preterm implying decreased oxygen delivery to the tissues (14).

Table 3. Normal blood volume in neonates and children.

Age	Blood volume
Preterm neonate	90 - 100ml/kg
Full term neonate - 3 months	80 – 90ml/kg
Above 3 months	70 – 80ml/kg
Above 2 years	70ml/kg

To minimize swelling, edema and hemodilution in a bleeding child, the intraoperative goal should be to maintain normovolemia while avoiding hypervolemia. Initial fluid replacement for blood loss can be accomplished by giving crystalloids or colloids in a 2:1 ratio to the predicted blood loss. The preferable fluids are Ringers Lactate (273mOsm) and Plasmalyte (294mOsm), which are associated with less severe acidosis than isotonic saline. It may be necessary to provide colloids in a 1:1 ratio in the event of fast blood loss and hemodynamic instability (2,14).

The maximum permitted blood loss (MABL), which is determined by following formula determines when to give children blood:

MABL= EBV (H0 - H1)/H0

(EBV = estimated blood volume; H0 = starting Hct; H1 = lowest acceptable Hct).

Age, Hb level and concomitant illness states, determine whether blood transfusions are necessary (30).

On the other hand, massive hemorrhage in children is defined as blood loss that exceeds one circulating blood volume (CBV) in a 24-hours period, blood loss that equals 50% of CBV in a 3-hours period, or transfusion at a rate of 10% of total blood volume (TBV) every 10 minutes (5). According to this definition, the healthcare professional must figure out the patient's weight-based estimated circulation blood volume (EBV) Table 2.

Less is known about massive transfusion. Warfare literature offers one potential definition. Greater than 40ml/kg of blood transfused within the first 24 hours after an accident in a pediatric patient is regarded as a major transfusion and is linked to a higher risk of in-hospital death (31,32).

Goal-directed therapy in management of hemorrhage aims to:

1. Promote hemodynamic stability as indicated by vital signs,

2. To ensure oxygen supply and end organ perfusion,

3. To lessen the negative effects and risks of transfusion,

4. To prevent over-transfusion by using laboratory and point-of-care diagnostics, as well as the appropriate usage of blood components,

5. To avoid the fatal triple threat of hypothermia, acidosis and coagulopathy.

However, initial therapy may need boluses of crystalloid or colloid solutions until blood products are available. Care must be taken since excessive amounts may cause dilutional coagulopathy. Temporizing measures, such as vasopressor support, may be necessary to maintain a healthy blood pressure after a major bleeding (5,24,32). Appropriate blood pressure targets differ by age and tend to rise as people get older. In preterm infants and teenagers, it is advised to keep mean systolic blood pressure (SBP) at an average of 55 mm Hg and 110 mm Hg, respectively (31). Monitoring end organ perfusion can be done with the aid of lactate, base deficit monitoring, and urine output. Non-invasive monitoring of cerebral oxygenation using near infrared spectroscopy (NIRS) has also been linked to increases in brain tissue oxygen tension (24).

Red blood cell transfusion should be balanced with "yellow" blood product transfusion in the form of a 1:1:1:1 volume ratio of PBRC: fresh frozen plasma (FFP): platelets: cryoprecipitate to prevent coagulopathy and maintain adequate oxygen delivery to tissues when massive hemorrhage necessitates massive transfusion. When EBV loss exceeds 50% of total blood volume, transfusion of fresh frozen plasma (FFP), platelets, and cryoprecipitate should be taken into consideration. If possible, laboratory testing such as thromboelastography (TEG or ROTEM) and point-of-care tests such as thromboelastography should be used to guide and direct the delivery of blood products (1,2,5,24,34).

On the other hand United Kingdom Transfusion service recommend red cell:FFP transfusion ratios to be based on volume (mL) rather than "units" when used. After the patient has been

stabilized with "damage control resuscitation" and transfusions based on clinical indicators, the proper treatment aims (based on speedy return laboratory or near-patient Hb 80 g/L, fibrinogen > 1.0 g/L, PT ratio 1.5, and platelet count > 75 109/L are the results of testing.

When managing a hemorrhage, a number of risk factors and adverse effects should be taken into account. In addition to non-hemolytic events including transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), and transfusion related immunomodulation (TRIM), transfusion of blood products can result in hemolytic transfusion reactions.

Additionally, banked blood products can result in citrate toxicity and aberrant electrolyte levels such hyper- and hypokalemia, hypocalcemia, and hypomagnesemia (5,24). It is advised that blood cleaning or the use of "fresh" red blood cells obtained within 7 days of transfusion lower the risk of hyperkalemia in children under 1 year old or 10 kilos (5). Due to dilution, red cell lysis, and blood preservation components, blood transfusion causes lab derangements. If available, electrolyte and coagulation testing should be used to look for anomalies. If testing is not possible, however, some anomalies (such as acidosis and hypocalcemia) may be treated empirically. Calcium can be replaced with calcium gluconate (30-100 mg/kg) or calcium chloride (20 mg/kg) (5), and sodium bicarbonate (1 mEq/kg) can help with acidosis (31). Calcium chloride, if there is line infiltration, might result in tissue necrosis. It should only be managed through centralized access. A safer drug for peripheral delivery is calcium gluconate. Children's minimal platelet count transfusion thresholds have not been established, although in the adult population, a platelet count of $50x10^9$ platelets/L is now regarded as sufficient with persistent bleeding (5). The platelet count will rise by $50\text{-}100x10^9$ platelets/L following a transfusion of 5–10 ml/kg of platelets. The pediatric population has also noticed this. For transfusion, FFP should be administered at a dose of 10-15 ml/kg. This can support fibrinogen levels, which can affect coagulation when they are between 150 and 200 mg/dL (24). It's important to keep fibrinogen levels stable. To maximize hemostasis during heavy transfusion, maintain fibrinogen > 150 mg/dL. The best sources of fibrinogen are cryoprecipitate and fibrinogen concentrate (5).

Autologous blood can be drawn from the operating room using cell salvage procedures for processing and transfusion. It might be challenging to gather sufficient numbers of salvageable cells from babies for transfusion. Overall, patients >10 kg and with >40% bood loss may benefit from cell salvage the mos. The use of cell salvage during tumor surgery or in situations where blood cell lysis occurs is debatable. It is also acknowledged that in many places, this management approach might not be appropriate (5).

Both adults and children have been investigated on the adjunctive use of antifibrinolytic treatment to reduce surgical bleeding (2,35). One of the most widely used antifibrinolytics is tranexamic acid (TXA). According to the PED-TRAX trial, TXA is linked to lower mortality in children who have been injured and that "the timely administration of TXA to injured patients is associated with a survival advantage and this advantage seems to extend to the injured pediatric population" (36). A loading dose of 10 to 30 mg/kg (maximum 2 grams) administered over 15 minutes, followed by an infusion of 5 to 10 mg/kg/h, is the optimal TXA therapeutic dosage range (24,37). These dosages have been demonstrated to increase effect while minimizing negative side effects, such as seizures. TXA has been used safely in pediatrics, although it should not be administered to kids who have consumption coagulopathy or active thromboembolic illness. Patients with acquired thrombotic disease and renal impairment are generally contraindicated (37). Patients with genetic or acquired platelet function problems may benefit from pharmacological treatment with an anti-fibrinolytic, DDAVP, or rFVIIa.

Indication for Red Blood Cell transfusion for the critically ill child Table 3. (1,2,4,28-30,38).

- If the Hb concentration is less than 5 g/dL in children who are critically ill or who are at risk for critical illness, an RBC transfusion is advised (1C recommendation).
- We cannot propose a specific RBC transfusion decision-making method for critically sick children or those at risk for critical illness upon physiologic metrics and biomarkers.
- We advise against giving RBC transfusions to children who are critically ill or who are at risk for critical illness, who are hemodynamically stable and have a Hb concentration > 7 g/dL (1B recommendations).
- There is inadequate evidence to make a recommendation about transfusion thresholds for critically ill children with an Hb concentration between 5 and 7 g/dL, according to a weak recommendation, low quality pediatric evidence (2C).
- If the child is with respiratory failure. It is not advisable to give transfusion if Hb is <5 g/dL and not to give if it is >7 g/dL. However, it is reasonable to consider transfusion based on clinical condition when Hb is between 5 – 7 g /dL.
- When in shock or septic shock it is not recommended to administer RBC if Hb is > 7 g/dL.
- Exception is child with brain injury. They should have transfusion if Hb falls between 7 – 10 g/dL.

Table 4. Summary of BCSH recommendations for neonatal transfusion

Postnatal age	Suggested transfusion threshold of Hb g/dL		
	Mechanically ventilated	On oxygen/CPAP	No oxygen
First 24h	<120	<120	<100
Week 1	<120	<100	<100
Week 2	<100	<95	<75-85
Week 3	<100	<85	<75-85

European Society of Anesthesia recommends following triggers for intraoperative transfusions and volume control during active bleeding:

- Maintaining a target hemoglobin concentration of 7 to 9 g/dL (1B)
- To give an individualized strategy to identifying individuals who may benefit from transfusion, advise central venous oxygen saturation or arterial-venous oxygen difference surrogates for the oxygen delivery to consumption ratio in patients who have a superior vena cava catheter in place (1C).
- Recommend repeated measurements of a combination of tissue perfusion, tissue oxygenation, and the dynamics of blood loss during acute bleeding using haematocrit/haemoglobin, serum lactate, and base deficit (1C).
- Extending these analyses by measuring cardiac output, dynamic variables of volume status (stroke volume variation and pulse pressure change), CO_2 gap, central venous oxygen saturation, or any combination of these (1C).

- Replacing extracellular fluid losses with isotonic crystalloids as soon as possible and according to a set protocol (1B).
- Compared to crystalloids, iso-oncotic colloids require less volume to accomplish macro- and micro-haemodynamic stabilization and induce less tissue edema(C).
- Colloids can worsen dilutional coagulopathy in patients with severe bleeding by having extra effects on fibrin polymerization and platelet aggregation(C).
- For crystalloids and as a foundational solute for iso-oncotic preparations, we advise the use of balanced solutions(2C).
- In order to aid transfusion in neonates and kids having cardiac and noncardiac surgery, viscoelastic hemostatic assay (VHA) guided therapies is recommended (2C).

In a recent RCT, an individualised strategy based on a central venous oxygen saturation threshold of 70% allowed for a more restrictive RBC transfusion strategy with no incidence on postoperative morbidity or 6-month mortality (2). Furthermore, a retrospective study in critically ill patients found that when A–V O_2 difference is greater than 3.7 ml, it could provide a more personalized approach in identifying patients who might benefit from transfusion, as indicated by lower mortality compared with those who received transfusion when A–V O_2 diff was lower.

Indication for platelet transfusion

Indication for platelet transfusion are differing depending of pediatric patient's age and the typical platelet dose is 5–10 mL/kg, as tolerated.

Patients < 4 month of age

- Infants with low platelet production or platelet count of 20–30,000/μL (20–30 x 109/L);
- Platelet count <50,000/μL (50 x 109/L) with bleeding or before a non-neurologic invasive procedure or minor surgery.
- Platelet count <100,000/μL (100 x 109/L) in a sick premature infant or before a neurologic invasive procedure or surgery, cardiovascular surgery, or other major surgery;
- Qualitative platelet defect with bleeding, prior to an invasive procedure or surgery.
- Platelet count 80,000-100,000/μL (80-100 x 109/L) before or during an ECMO procedure, or with unexplained severe bleeding.

Notably, there is no obvious link between the seriousness of thrombocytopenia and significant bleeding incidents such intracranial hemorrhage (ICH) (37).

Patients > 4 month of age

- Patients with hypo proliferative thrombocytopenia should get prophylaxis if platelate count is <10,000μL ($10x10^9$/L).
- If an invasive surgery cannot be delayed, patients with a platelet count of at least 50,000/μL (50 x 109/L) should receive prophylaxis.

- Prior to some ophthalmologic and neurosurgical procedures, a platelet count of 100,000/μL (100 x 109/L) is advised.
- For ECMO procedures, or in cases of unexplained severe bleeding during the surgery, a platelet count of 80,000/μL (80–100 x 109/L) is advised.

By getting a platelet count 10–60 minutes after each transfusion, the response to platelet transfusions should be kept in track. Platelet refractoriness is shown by low post-transfusion platelet count increments (CCI 7.5 x 109/L) after two or more consecutive transfusions of ABO-compatible platelets (35).

Patients with genetic or acquired platelet function problems may benefit from pharmacological treatment with an anti-fibrinolytic, desmopressin acetate, or rFVIIa.

Table 5. Summary for suggested transfusion thresholds for platelet transfusion

Platelet <20 -30 x 10^9 /L	In the absence of bleeding
Platelet <50 x 10^9 /L	Bleeding, current coagulopathy, planed surgery or exchange transfusion
Platelet <100 x 10^9 /L	Major bleeding, major surgery

Indication for transfusion of FFP

- For exchange transfusion for reconstitution of RBCs.
- Multiple or singular coagulation factor deficiencies.
- Support in disseminated intravascular coagulation (DIC) treatment.
- Vitamin K deficiency or liver disease.
- While awaiting plasma exchange in thrombotic thrombocytopenic purpura (TTP).
- Clinical evidence of coagulopaty in bleeding patients.
- Replacement therapy when a specific factor concentrate is not available for congenital antithrombin deficiency, protein C deficiency, or protein S deficiency.
- To replace clotting factors as part of a massive transfusion protocol (for instance, in cases of severe trauma, surgical bleeding, fetomaternal hemorrhage, or ECMO).
- Reversal of warfarin in patients with ongoing bleeding or those who urgently require an invasive treatment, albeit safety and effectiveness in pediatric patients have not been shown.

As tolerated, a plasma dosage of 10-15 mL/kg is usually given. Any component or pool's total administration time cannot go beyond 4 hours. In the absence of consumption (DIC), a plasma dosage of 10-15 mL/kg is anticipated to result in a 15-20% increase in clotting factors (38).

Indications for transfusion of cryoprecipitate

- Dysfibrinogenemia or hypofibrinogenemia (fibrinogen 100–150 mg/dL) brought on by a lack of synthesis (liver illness), consumption (DIC), dilution (large transfusion) or dilution with bleeding, or occurring prior to surgery when fibrinogen concentrate is unavailable or not required.

- Von Willebrand disease with bleeding, before an invasive procedure or preoperatively, when factor concentrate containing von Willebrand factor is not available and dezmopressin is ineffective or contraindicated (a fibrinogen concentrate is approved in the US for treatment of congenital fibrinogen deficiency).

Note: desmopressin is contraindicated for children < 2 years of age.

- If a specific clotting factor concentrate is not immediately accessible and desmopressin is ineffective or contraindicated, hemophilia A with bleeding or before an invasive surgery.
- When an FDA-approved Factor Xlll concentrate is not immediately available, replacement therapy is used for the following situations:factor XIII deficiency with bleeding.
- Making fibrin sealant (if pathogen-inactivated fibrin sealant is not readily available).

In the absence of consumption, the recommended dosage of cryoprecipitate is 1-2 units/10 kg, which is predicted to increase fibrinogen by 60-100 mg/dL (38).

Conclusion

It is evident from a review of these papers that there is no solid agreement on the precise indications for transfusion of pediatric patients. To treat perioperative bleeding in pediatric patients, institutional protocols based on recommendations must be devised while taking into account the local resources available. It is necessary to check the patient's valemic condition and replace blood in a target-oriented manner. Massive bleeding requires consideration of the danger of coagulopathy and prompt achievement of hemostasis. The care of critically ill children requires fluid resuscitation. Fluid administration that is appropriate and timely is essential for the best results and recommendations are shifting to a more evidence-based individualized approach

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REVIEW ARTICLE *UDK: 616.24-085.816.2-053.31*

MECHANICAL VENTILATION IN NEWBORNS

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Abstract

Mechanical ventilation is a commonly used therapy in neonatal intensive care centers and is associated with increased mortality and morbidity.The goals of mechanical ventilation are to enable adequate gas exchange including adequate oxygen delivery and adequate ventilation to remove CO2, to reduce the work of breathing and to minimize the risk of lung injury.Indications for mechanical ventilation are respiratory failure, pulmonary insufficiency, severe apnea and bradycardia, congenital heart disease, diseases of the central nervous system and surgical interventions.The use of mechanical ventilation in newborns is a real challenge due to certain characteristics of the newborn, such as non-compliant lungs, fast irregular breathing rate, short inspiratory time and limited muscle strength.Basic knowledge of the respiratory physiology and pathophysiology of the existing diseases that can lead to respiratory failure is necessary in choosing the optimal ventilation mode and adjusting proper ventilator parameters.This ensures adequate gas exchange and minimal damage to the lungs.Neonatal mechanical ventilation is a very demanding, yet, still developing field. In this text we discuss various models and modalities of ventilation commonly used in neonatology.

Key Words: *mechanical ventilation, newborn, respiratory failure.*

Introduction

Mechanical ventilation is one of the most common therapies in neonatal intensive care units. The primary goal of mechanical ventilation is to ensure adequate gas exchange such asadequate oxygenation and removal of carbon dioxide (CO2).Despite the development of non-invasive ventilation modes, mechanical ventilation remainsa main treatment in the intensive care units.

In a 2010 cohort study, itwas reported that 74% of infants born before 28thgestational week were intubated and received surfactant during hospitalization(1).

Indications for mechanical ventilation include respiratory failure, pulmonary insufficiency, severe apnea and bradycardia, congenital heart disease, central nervous system disorders and surgical interventions.However, mechanical ventilation can also be the cause for lung injury (VILI-Ventilator induced lung injury). In order to reduce the risk of VILI, basic knowledge of respiratory physiology and understanding the pathophysiology of the existing disease leading to respiratory weakness is necessary, along with the selection of the optimal mode of ventilation and appropriate ventilator parameters (3).

Historically, pressure ventilation has been the most commonly used method of ventilation(4). However, recent research suggests that volume-targeted ventilation is the best mode of ventilation

for newborns.The improved technology in the field of advanced respirators has allowed the development of ventilation modes that mimic the physiological aspects of spontaneous breathing innewborn in order to reduce VILI.

Basic principles

The primary goal of mechanical ventilation is to achieve satisfactory oxygenation and ventilation. Oxygenation (PaO2) depends on the fraction of inspired oxygen (FiO2) and mean airway pressure (MAP). Ventilation (CO2 clearance) depends on the minute volume [minute volume (MV) = respiratory volume (VT) x number of respirations (RR)].

Mechanical ventilators enable control of oxygenation and ventilation by adjusting certain parameters. Oxygenation can be improved by increasing mean airway pressure (MAP), extendinginspiratory time (Ti) and adjusting FiO2.Increasing peak inspiratory pressure (PIP) or positive end-expiratory pressure (PEEP) raises MAP, thereby enhancing oxygenation.

Ventilation facilitates CO2 removal from the lungs.A higher minute volume leads to increased CO2 removal and consequently reduced PaCO2.This can be achieved by increasing the respiratory rate or increasing the tidal volume.

↑ PaO2 ↑ FiO2, ↑ Ti

↑ MAP (PIP/PEEP)

↑ ventilation ↑ TV

(↑ PaCO2) ↑ RR

Standard modes of ventilation

Standard ventilation modesinclude pressure-controlled, volume-controlled and hybrid ventilation. In pressure-controlled ventilation, the ventilator delivers gas flow until the set pressure is reached while in volume-controlled ventilation the ventilator delivers already set volume (5). In pressure-controlled ventilation, there is a variable respiratory volume (Vt) while the pressure (PIP) remains constant (6).

Pressure-controlled Ventilation

Pressure-controlled ventilation is the most commonly used method for respiratory failure in newborns. An appropriate peak inspiratory pressure (PIP) is set that overcomes the resistance of the airways to achieve the delivery of a specific gas volume (Vt) into the alveoli. The gas volume entering the alveoli depends on the compliance of the lungs, inspiratory pressure, inspiratory time, flow, and synchronization of the ventilator with the newborn's spontaneous respirations (7). Changes in compliance alter the achieved Vt at the same PIP, and can lead to hypoventilation or hyperventilation, thus atelectasis or hyperinflation. In conditions like respiratory distress syndrome (RDS) where surfactant is deficient, the lungs are stiff, poorly expandable and compliance is low. Applying surfactant improves compliance by expanding previously atelectatic lungs. In the case of lungs with areas of hyperinflation, such as bronchopulmonary dysplasia

(BPD), they easily expand having a high compliance. Monitoring the gas analysis and following ventilator parameters and curves is necessary for proper adjustment of the already set pressure in order to avoid hypoventilation or hyperventilation.

Volume-controlled Ventilation

Modern ventilators are equipped with microprocessors capable of measuring and delivering low gasvolumes which is very important for premature newborns. Usually, respiratory volume is set between 4-5ml/kg. In volume-controlled ventilation, the ventilator automatically adjusts the peak inspiratory pressure (PIP), achieving the already given respiratory volume based on changes in compliance and resistance in the airways. This reduces the risk of hypoventilation and hyperventilation, thereby minimizing the risk of ventilator-induced lung injury (VILI). Therefore, this invasive ventilation mode is the greatest for premature newborns. In comparison to pressure-controlled ventilation, the use of volume-targeted ventilation shows a reduction in mortality, lower cases of bronchopulmonary dysplasia, less days on mechanical ventilation, less cases of pneumothorax, hypocarbia and severe intraventricular hemorrhage (8). It is crucial to note that volume controlled ventilation relies on precise measurement of the flow and it is not a choice in the presence of a significant leak (>50%) around the endotracheal tube.

Hybrid Ventilation Modes

Hybrid ventilation modes are combination of different modes aimed to create ventilation that is more physiological, thus reducing the risk of lung injury.

Other ventilation modes

The fast technological development and appearance of new and advanced ventilation modes for newborns allows various options for mechanical ventilation to be chosen from. Despite the existence of different types of ventilators, the basic principles apply to all. The most commonly used ventilation modes in the treatment of newborns are pressure-controlled (assist-control [A.C.] and synchronized intermittent mechanical ventilation [SIMV]), volume controlledand high-frequency ventilation. Muscle relaxants are usually not used in newborns while on mechanical ventilation, allowing them to have their own respirations. Therefore, synchronized ventilation models are often used, where the ventilator coordinatesthe delivered respirations with the spontaneous breaths of the newborn. Those spontaneous respirations are detected by the flow sensor located between the endotracheal tube and the Y-connector. The sensor detects minimal changes in flow initiated by spontaneous inspiratory respirations, triggering the ventilator to provide support during inhalation. This enables synchronization of the newborns breathing with the ventilator in achieving the pre-set pressure or volume. The sensitivity of the flow sensor can be adjusted if necessary. Sometimes, fluid in the ventilator system can mimic changes in flow, causing auto-triggeringas in spontaneous breathing.

Basic Synchronized Ventilation Modes

Three basic synchronized ventilation modes are assist/control (AC), synchronized intermittent mandatory ventilation (SIMV) and pressure support ventilation (PSV).

Assist/control (AC)

In AC ventilation, the newborn triggers and initiates the inspiratory phase but the ventilator completes it, thereby reducing the work of breathing. In AC ventilation, pressures (PIP and PEEP)

and inspiratory time are controlled. During weaning, PIP needs to decrease as the respiratory frequency is primarily controlled by the newborn. Inspiratory time is fixed, which results in very short expiratory time at high breathing frequencies, leading to air trapping (autoPEEP).

Synchronized Intermittent Mandatory Ventilation (SIMV)

SIMV is a ventilation mode where the ventilator delivers predetermined respiratory volume and respiratory frequency which is synchronized with the newborns inspirations and strong enough to trigger the ventilator. Spontaneous respirations overcoming respiratory frequency are supported only by PEEP. Lowering the pre-set frequency reduces ventilator support for spontaneous respirations. This increases the work of breathing and results in unsuccessful weaning.

Both synchronized modes (AC, SIMV) can have an additional mode of volume-guaranteed ventilation.

Pressure Support Ventilation (PSV)

PSV is a mode of spontaneous breathing where the patient triggers respiration and the ventilator provides inspiratory support with a pre-set inspiratory pressure (pressure support). The inspiratory phase ends when the inspiratory flow decreases to a previously set threshold, usually 10-15% of the peak flow. At this point, the gas flow stops, and passive expiration begins. The patient determines the respiratory frequency, respiratory volume and inspiratory time. PSV reduces the work of breathing and allows synchronization between the patient and the ventilator, avoiding prolonged inspiration. However, this can lead to very short inspiratory time (Ti) and a rapid respiratory frequency in newborns in their first few days of life. Short Ti results in a relatively low mean airway pressure (MAP), therefore adequate PEEP must be used to prevent atelectasis (9). This ventilation mode is very useful in assessing the newborn weaning which should be stopped if there is apnea even when minimal backup respiratory frequency is set to be delivered by the ventilator.

High-Frequency Ventilation (HFV)

HFV is a special type of ventilation where a rapid respiratory frequency and respiratory volumes smaller than the anatomical dead space are set, reducing the possibility of lung injury by reducing PIP. The advantage of this ventilation compared to standard ventilation modes is the ability to provide adequate alveolar ventilation and arterial oxygenation at low PIP and small respiratory volumes, thereby preventing barotrauma (10).

Variables set in HFV include frequency (Hz), mean airway pressure (MAP), amplitude, inspiratory time, and FiO2. Increasing MAP causes greater lung recruitment, allowing better oxygenation. Increasing FiO2 increases the diffusion gradient, thus improving oxygenation. CO2 removal is achieved through high-frequency oscillations of small volumes in and out. CO2 removal is determined by amplitude and frequency. Increasing the amplitude reduces PaCO2, while increasing the frequency increases PaCO2.

HFV is used in severe lung conditions where standard ventilation modes are inadequate due to the need for high PIP and FiO2, which potentially leads to barotrauma. When transitioning a newborn from standard ventilation to HFV, it is recommended to increase MAP by 2-3cmH2O above the previous value. Other parameters are adjusted based on oxygen requirements and appropriate lung expansion, with the diaphragm positioned at the 8-9th posterior rib as diagnosed on X-ray.

Table 1. HFOV parameter adjustments.

	Condition			
	Poor oxygenation	**Over oxygenation**	**Under ventilation**	**Over ventilation**
1st choice	↑↑ FiO_2	↑↑ FiO_2	↑↑ Amplitude	↑↑ Amplitude
2nd choice	↑↑ MAP (1–2 cmH_20) if CXR shows high diaphragm position	↑↑ MAP (1–2 cmH_20) if CXR shows low diaphragm position	↑↑ Frequency (1–2 Hz) if Amplitude maximal, or if Air Leak present	↑↑ Frequency (1–2 Hz) if Amplitude minimal

NAVA (Neurally Adjusted Ventilatory Assist)

NAVA is a ventilation mode that utilizes an electrical signal from the newborn's diaphragm to synchronize the ventilator with spontaneous respirations.

Ventilator parameter settings [NICE (The National Institute for Health and Care Excellence) Guidance - https://www.nice.org.uk/guidance/ng124]:

Preterm infants with Respiratory Distress Syndrome

- PC-AC with VG → Rate 40-50, Ti 0.3, PEEP 5, VT 4ml/kg (Pmax 28)
- Pressure limit: 20-22cmH2O for newborns and 25-28 cmH2O for babies
- To avoid hypocarbia (pCO2 < 4.5)
- Gas analysis in the first hour, and VT adjustment based on the results.

Terminal infants with a pulmonary disease

- PC-AC with or without VG → Rate 50, Ti 0.4-0.45, PEEP 5-6, set PIP to achieve VT 4-5ml/kg
- HFOV if high pressure is needed (PIP > 28-30)

The minute volume at the beginning of ventilation should be set at 0.15-0.35ml/kg. If the delivered respiratory volume is too high or too low, the ventilator should alarm. The gas analyses should also be checked.To enable synchronization and measurement of respiratory volume, the proper functioning of the flow sensor with an alarm is essential.

NICE recommends the use of SIMV with PLV (pressure-limited ventilation) if VG or HFOV is not suitable. With PC-AC, more frequent respirations are set at higher pressure which can damage the lungs. SIMV with PLV provides greater control over the number of respirations set with high pressure, thereby minimizing lung damage.

Mismatch between ventilation and perfusion due to atelectasis and hypoventilation causes hypoxemia. Depending on the current oxygenation, an appropriate PEEP is set. The use of high PEEP can lead to hyperinflation of the lungs, pneumothorax, reduced venous return and increased PaCO2. Low PEEP can lead to hypo-inflation, lung collapse and an increased need for FiO2. It is recommended to start with a PEEP of 5-6cmH2O. If FiO2 needs to get higher than 30% or there is inadequate lung expansion with the diaphragm positioned at the 8-9th posterior rib diagnosed on X-ray, PEEP need to be increased to 8cmH2O.

Ventilator settings should be set according to the individual needs of each patient.

Weaning

The decision to wean from the ventilator is based on gas analyses and saturation levels. Initially, FiO2 is reduced to 30% while SpO2 ranges from 91% to 95%. Depending on the PaCO2 levels, both Vt and respiratory frequency can be decreased. With improved oxygenation, PEEP is also reduced. Extubatingshould be performed when the newborn exhibits good spontaneous respirations, minimal pressure support (PIP < 18) and favorable gas analyses.

Conclusion

There is no ideal mode of mechanical ventilation for newborns. A great understanding of the physiology and pathophysiology of newborns,along with knowledge fordifferent ventilation modes, is essential in their treatment using mechanical ventilation. It is crucial to monitor the dynamics of changes in ventilation and adjust parameters or ventilation modes accordingly. This approach minimizes the risk of lung injury.

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REVIEW ARTICLE *UDK: 616-089.5-053.31*

ANESTHESIA FOR NEWBORNS AND INFANTS

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Abstract

One of the most difficult andthe most challenging assignments for anesthesiologist is providing safe and effective treatment for newborns and infants during operation.

When performing endotracheal intubation, we must consider specific anatomical differences of this age: larger head, flexible longer and larger epiglottis, voluminous tongue and high larynx position. The data from the literature suggest that the safest position for intubation is "neutral position" of the body with light head flexion towards the chest. However, some pediatric anesthesiologists are preferring the "sniffing position" that is reached by setting a soft roll under the shoulders (1). All newborns with body weight<1kg should be intubated with 2.5 cuffless endotracheal tube, and newborns with body weight >2.5kg with 3.0 cuffless endotracheal tube. Current protocols are suggesting the routine use of video-laryngoscopy for elective intubation of all children <1year and body weight <10kg (2).Due to small compliance of the neonatal myocardium, the minute volume at this age is more dependent of the hearth rate. The newborns have less ability to compensate the blood loss because of the less efficient vasoconstriction.

Children at this age have decreased ability to metabolize and eliminate drugs. The renal and hepatic function reaches the adult levels approximately after 6 months, and in preterm babies even later. Glomerular filtration rate in the 25th week of gestation is only 10% of adult levels, while at birth reaches only 35%. Drugs have larger volume of distribution due to higher percentage of total body water and extracellular water content (2). The nerve routes are completely myelinated all the way to the thalamus by the end of the 30th week of gestation, so all the babies, even premature newborns, are feeling pain at birth. Therefore, all newborns and infants are requiring careful pain treatment for all painful procedures (1).

Conclusion: It is very important to have good knowledge of the dynamic process of the development of the physiological functions and the specific pharmacodynamics of drugs in the early life of the newborns. The safe treatment of this highly vulnerable age population requires experience, continuous education and excellent manual skills.

Key Words: *anatomical differences, infants, newborn, pediatric anesthesia.*

1. Introduction

One of the most difficult and the most challenging assignment for anesthesiologist is providing safe and effective anesthesiology treatment for newborns and infants during operation. At the same time,this part of our clinical practice frequently is reason for worry and uncertainty even for experienced practitioners. The reason for this is the fact that newborns are not "small adults" and protocols and dosage of drugs for anesthesia cannot simply be transferred to this age group. The main characteristicof this age is the dynamic process of adaptation to extra-uterine life in the form of physiological development changes of different organs. In this process of adaptation, the respiratory and the cardiovascular system are susceptible to the biggest changes. Anesthesiology strategy must be made individually through tight understanding of these physiological processes.

2. Respiratory System

The breathing activity starts with sporadic movements of the diaphragm by the end of the 1st trimester and is gaining stability during late pregnancy. At term the breathing activity reaches 30-60% of the normal values. One very important characteristic of the neonatal age is the presence of "Hypoxic respiratory depression", a reflex that can persist up to 6 months after birth. The initial stimulation of the respiration during hypoxia is quickly converted to respiratory depression to levels of ventilation below the normal oxygenation level. Immaturity of the respiratory control is also manifested with the presence of apneas and periodic breathing. Laryngeal and pharyngeal protective reflexes (laryngospasm, glottic spasm, expiratory reflex, coughing, sneezing, apneas and spasmodic breathing) are present in early life but with certain degree of hyperactivity. There are not enough scientific data regarding the development dynamic of these reflexes after the birth. It is understood that the process of maturation of central synapses leads to disbalance of the excitatory and inhibitory control of the central nervous system. The presence of the "Trigeminus-cardiac reflex" is presented with severe bradycardia and prolonged apneas after the stimulation of the stretch receptors of trigeminus nerve. In newborns,it is essential to select the right size and the correct form of the face maskand to avoid excessive pressure on the face. The "Hering-Beuer reflex" results in the depression of the inspiratory activity and prolongation of respiratory cycle after overdistension of the lungs caused by high inspiratory volume and increase in the inspiratory muscle activity after severe deflation of the lungs.

The supraglottic airways in newborns are narrow and soft and can easily collapse during forced inhalation (1). Epiglottis of the newborn is bigger and has a different shape compared to adults (narrow and longer) and has higher position with more vertical presentation. The tonsils and adenoids are disproportionally big and determine the size of upper airways. Their size is continuously increasing until school age and the involution doesn't start until adolescence. The length of the trachea at birth has 40% of the adult value, but at the same time it reaches only 10-15% of the internal lumen compared to adults. The tracheal diameter is the best correlated with the age, but the length of the trachea correlates with the height of the baby. Cartilaginous rings are soft at birth and gain solidity later.

The main objective of all anesthesiology techniques is to maintain open upper airways and to provide adequate gas exchange. The obstruction of the airways in newborns most often originates from the supraglottic segment and the pharyngeal tissues. Short periods of airway obstruction will lead to the development of severe hypoxemia, bradycardia and if not corrected to cardiac arrest. The positioning of the head and the neck is playing a vital role in prevention, and also the treatment of airway obstruction. Opposite to school children where in supine position and a light extension of the head is suggested, at this age it is the safest to maintain neutral position

of the head and neck, with light flexion towards the chest. The simple method to de-obstruct the upper airway is the "chin lift and jaw trust" maneuver. "Lateral position"is considered the safest for all children from 2-12 years that receive any form of analgesia-sedation and are breathing spontaneously (2).

Alveolarizationis the process of the formation of new alveoli and starts at the beginning of the 1st trimester. This process is followed by parallel forming of capillary vessels, the production of surfactant and progressive thinning of the interstitial tissue and alveolar walls.To the purpose of easy and efficient passing try the narrow and rigid birth canal, the rib cage of the newborns is more flexible and with lower degree of calcification. But at the same time the lungs consist of high percentage of immature alveoli that contain less elastin. The combination of soft and flexible rib cage and solid and relatively inelastic lungs parenchyma, leads to higher closing volume of the lower airways and is creating conditions for collapsing and interruption of ventilation. This is happening in the periods of the decreased minute ventilation. It takes a long period for recruitment of the collapsed alveoli to re-open and again take part in the gas exchange. During spontaneous ventilation, babies are dynamically compensating for this immaturity of the tissues by maintaining a higher respiratory rate and shortened expiratory pauses. This creates conditions for diffuse air movement and increased resistance during exhalation, which is helpful in maintaining open alveoli during all phases of the respiratory cycle.

The main determinant of the diffusion capacity of the lungs is the ventilation/perfusion relation (V/Q). While in adults, V/Q relation is mainly dependent on the gravitation force, in newborns ventilation is directed to the non-dependent parts of the lungs. For this reason, the V/Q relation at this age is unfavorable for efficient gas exchange. As the child is approaching school age the V/Q is becoming more efficient. The newborns also have lower and relatively instable value of the functional residual capacity (FRC). There are developed defense mechanisms at this age for maintaining adequate value of FRC, such as: post-inspiratory activity of the diaphragm and inter-costal muscles, higher respiratory rate, and short exhalation phase (auto PEEP) and adduction of the larynx during forced exhalation (functional PEEP). General anesthesia (GA) and deep sedation are lowering the effectiveness of these defense mechanisms. The literature shows that in the most children < 3years old, atelectasis will develop after the induction in GA and giving muscle relaxant (1). The use of positive pressure (PEEP) and recruitment maneuvers is helpful in re-opening of the collapsed alveoli and recovering of the FRC. Volatile anesthetics decrease the activity of the respiratory muscle activity, and consequently lower the FRC. This effect is higher in young newborns that have high compliance of the chest wall. Propofol given to spontaneously breathing children is causing dose-dependent reduction of FRC, decreased V/Q and non-homogenous ventilation. Midazolam given as premedication is causing decreased lung compliance and decreases also the FRC value. Ketamine, even in high doses,doesn't have clinically relevant effect on the FRC and V/Q relation, but we should always be careful of the unpredictable influence on the respiratory rate and the depth of breathing. Opioids have the potential to cause activation of the intercostal and abdominal muscles, which can lead to clinically significant rigidity of the chest wall. This phenomenon is less present in small children. However, we should be always aware of the possibility of difficult face mask ventilation in newborns after administration of opioids. Babies in the first months of life have higher rate of oxygen consumption in accordance with body mass and body surface area compared to adults (6ml/kg/h vs 3ml/kg/h) (3). Higher alveolar ventilation, that has almost double value compared to adults, is effectively compensating for the high oxygen consumption. Increased alveolar ventilation offers advantage for the anesthesiologist and provides fast and predictable inhalator induction in GA due to fast absorption of volatile anesthetics. On the other hand, the standard practice of administration of high levels of oxygen (FiO_2) during the induction in anesthesia and reanimation, can lead to de-recruitment of alveoli, atelectasis and inhomogeneous ventilation with unstable V/Q relation. The data are showing that prolonged periods of FiO_2>80% during

GA and postoperatively can result in low breathing volumes that can persist up to 24 hours after extubating the newborn (2). At the same time, we need to be aware of the rapid desaturation that can happen after short apneas even after period of adequate pre-oxygenation with 100% FiO_2.

Small babies have very soft supraglottic airways that are susceptible to obstruction. They have big tongue, voluminous tonsils and adenoids, developed fatty tissue in the cheeks and bigger and horizontal epiglottis. For that reason, they are considered to be "obligatory nasal breathers". Great care should be taken to maintain open nasal cavities and airways for the whole period of hospitalization, pre and postoperatively.The positioning of the infants on the operational table and endotracheal intubation are in the center of every anesthesiologic plan and require certain knowledge and experience. To the purpose of easy passing, try the rigid birth canal the bones of the skull have lower degree of calcification and are considered soft and flexible. Therefore, during the positioning of the head on the operational table in supine position, we need to provide soft surface and adequate fixation of the head and the neck in the neutral position. The newborns have small body surface area which makes the correction of the head and body position very difficult once the site of operation is covered with sterile sheets. It is very important before the sterilization of the operational site to secure and fixate: all the iv lines, endotracheal tube, nasogastric tube, the lines of the hemodynamic monitoring.

The latest reports from the literature are suggesting that the use of video-laryngoscopy for all routine elective endotracheal intubations for newborns < 1 year and body weight < 10kg, will increase the safety and will decrease the rate of unsuccessful intubations (2,3). The experience is showing that the safest position for face mask ventilation and for endotracheal intubation after birth and in the 1st year of life, is the "neutral position" of the head, while the baby is in supine position. Some anesthesiologists prefer light flexion of the head towards the chest wall in early age, as it provides better route for placing the ET. Some pediatric anesthesiologistson the other hand prefer the "sniffing position" that is accomplished by putting a soft roll under the shoulders of the newborn, as well as small flat pillow under the head. All newborns with body weight <1kg should be intubated with 2.5 cuffless endotracheal tube, and newborns with body weight >2.5kg with 3.0 cuffless endotracheal tube. In terms of the correct depth of the ET at this age, there are several orientation formulas for the calculation of the distance to which the tube should be fixated. The famous "7-8-9 formula of Tochen" is calculating the adequate ET tube depth by adding 6cm to the current weight of the child in kilograms. The safest and the most reliable method to determine the correct position and the depth of the ET after intubation in all age groups is, of course, the bilateral auscultation of the lungs and careful monitoring of the end-tidal CO_2 curve during mechanical ventilation. During the mechanical ventilation at this age even small variations of the minute volume can lead either to atelectotrauma, or overdistension and volume trauma of the lung parenchyma. After careful tunning of the respiratory rate, we need to limit the upper value of the tidal volume (6-8ml/kg) and choose the lowest safe margin for FiO_2 in order to avoid oxygen toxicity. Permissive hypercapnia ($PaCO_2$ 45-55mmHg) will contribute to decreased possibility of lung trauma. The current recommendations are suggesting that peripheral saturation (SAT) should be maintained between SAT 89-95% for all newborns, while high value in the operation room should be limited on SAT – 95%, as it will prevent all the possibility of oxygen toxicity (2,3).

3. Cardiovascular System

The circulatory system undergoes dramatic changes in the period of adaptation from the fetal circulation to the extrauterine life. Certain perinatal complications (meconium aspiration, asphyxia and septicemia) can prevent or postpone this transition of circulation and potentially

lead to "persistent fetal circulation" that can result with increased pulmonary vascular resistance and raised BP. Clinically this condition is manifested as moderate to severe hypoxemia, right ventricle dilatation and circulatory collapse. Because of the high risk of perioperative complications in this group of newborns, it is recommended that all elective operations should be postponed until this hearth condition is treated (2).

Myocardium of the newborn has smaller compliance and lower ventricle filling pressures. Hearth myocytes after birth are less elongated and have agreater percentage of non-contractile elements, whereas the contractile elements have irregular organization. Based on the findings from animal studies, the Sarco-plasmatic reticulum (SR) and the T-tubular system are immature at birth. Myocardium contraction is less efficient and more dependent on calcium levels, and for this reason, it is very important to monitor and maintain adequate circulatory level of calcium in the first 4 weeks of life. The neonatal myocardium in early life is less responsive to changes in preload which is described as flattening of the Starlings curve. When filling volumes of the ventricles are increased, the pressure on the ventricle wall increases up to the levels when the coronary circulationsdecrease (3). For these reasons the minute volume (MV) in newborns is highly dependent on the hearth rate. This should always be kept in mind, and the mandatory part of all perioperative protocols is continuous monitoring and control of the hearth rate of the newborn.Autonomic control of the circulation is present at birth but is still immature. The data from the literature show that immediately after birth the responses of the autonomic nerve system are limited and the sympathetic component is more reactive. However, quickly after birth (in the first couple of weeks) the parasympathetic becomes dominant component, and this ratio is maintained until school age. Consequently, we can see that instead of acceleration of the hearth rate, every stimulation of the circulation results in a paradox deceleration of the hearth rate and further decrease of the MV. The administration of anesthetics in the circulation is compromising and reducing the autonomic nerve system responses to changes in the blood volume and makes newborns even more vulnerable to bleeding and fluid loss. Due to unstable sensitivity of the baroreceptors, the vascular resistance cannot adequately respond to fall in the BP either with increase in hearth rate or vasoconstriction. Decrease of blood volume of 10% at this age can lead to fall in mean arterial pressure (MAP) for 15-30% (3). At the same time newborns have high circulating blood volume (90-100ml/kg) compared to adults, which means that term newborn with body weight of 3.8kg has blood volume of 320ml. Recommendations suggest that blood transfusion should be initiated when approximately 20% of blood volume is lost, or after loss of 50-75ml of blood. It is also recommended that strategies should be adopted in the direction of monitoring of the blood loss and timely substitution (2). At all stages of the treatment of hypovolemia we should take into account the developmental physiology of the neonatal myocardium and the circulatory system. At this age the myocardium cannot adequately respond to increased preload, and excessive administration of fluids in the circulation can lead to increased filling volume of the right ventricle and even heart failure. The modalities of treatment of hypovolemia in newborns and infants consist of administration of crystalloids (to restore adequate blood volume) and inotropes and vasoconstrictors (to improve minute volume and the hearth rate). Administration of catecholamines has the effect of rise in the MAP and improved perfusion of the coronary circulation and other vital organs. The developmental changes are making myocytes highly vulnerable to high doses ofcatecholamines. It has been confirmed that high doses can lead to decrease in the levels of adenosine triphosphate (ATP) and low energetic depos in the cells and even structural damage of the hearth muscle. Modern recommendations suggest that the use ofcatecholamines in newborns is necessary in the treatment of hypovolemia and shock, but with special care to the administered dose, and we should always be aware of their potential to cause cell damage and decreased energy levels of the hearth (3).

4. Pharmacotherapy

There are limited data regarding the metabolism of different drugs and anesthetics in newborns and infants. The volume of distribution at this age is significantly higher due to a higher percentage of total body water (75-80% of body weight compared to 60% in adults), as well as extracellular fluid content. Consequently, in newborns a higher initial dose of the drug is required for therapeutic concentration in the serum to be reached. We should always keep in mind that it is not possible to simply transfer the protocols and the dosage of the drugs according to body weight. Main routes for elimination of anesthetics and their metabolites are hepato-biliary, renal system and lungs. All these systems are undergoing process of adaptation and maturation in early life. Renal and hepatic function usually reach adult levels of activity in terms of metabolism and elimination of drugs around 6th month of life (4). Glomerular filtration rate (GFR) at term is relatively small and is doubled after 2 weeks of life. At the end of 25th week of gestation, GFR has the activity of 10% of adult values, while at term GFR reaches around 35%. At the end of the 1st year, the GFR has the activity of around 90% and it not reaches full adult activity until the end of the 2nd year of life. . Hepatic route of metabolism and elimination through the activity of P450 isoenzymes is present at birth and reaches approximately 85% of the adult values by the end of 44th week of gestation. The ability for bonding to the plasmatic proteins, albumin and α1 glycoproteins is reduced due to lower circulatory concentration of these proteins in the serum. As a result, we can see higher concentration of free "unbound" fraction of the drugs in the circulation, which is increasing the danger of unwanted effects and complications. The values of proteins in the circulation is stabilized in the 6th month of life.

Minimal alveolar concentration (MAC) is used to express the potency of volatile anesthetics. MAC of all volatile anesthetics is lower in preterm babies but is significantly higher in all other term newborns (3). High values of MAC are maintained until the 6th month and are then starting to decrease, but MAC doesn't reach adult values until adolescence. For example, MAC of Sevoflurane after birth is 3.2% and this high value is stable in the first 6 months of life.

Intravenous anesthetics are a fundamental part of the anesthesia plan in newborns. After the introduction of secure iv line, we need to establish a clear plan regarding the types of drugs and their doses and dosage intervals respectively. The administration of anesthetics should be adapted to the specific developmental physiology of renal and hepatic systems, as well as the levels of circulatory proteins.The pharmacodynamics of opioids is probably the best understood at this age, probably because of the most frequent use (4). All newborns, as well as premature babies, are experiencing pain that if left untreated can lead to serious stress response in form of: metabolic acidosis, hyper or hypoglycemia, cardiovascular instability or electrocytes abnormality. Therefore, all infants have the need for active treatment of pain (1). Morphine is still the most frequently used opioid worldwide, but the data are showing that there is high dependency from the renal route of elimination, and when administered in clinically significant doses we can expect prolonged half-life in circulation and pronounced hypotension. Synthetic opioid fentanyl has less effects on the cardiocirculatory system and is safe solution for the treatment of surgical pain at this age. Propofol has broad use as secure drug for intravenous induction of anesthesia mainly due to positive pharmacodynamic profile. The drug is highly liposoluble and when administered in doses sufficient for the induction in anesthesia, it has prolonged redistribution and longer elimination times from the plasma. Consequently, we can expect the effects of accumulation of the drug and prolonged activity. High doses can lead to deep hypotension and circulatory instability. Although hypotension is transitory, reversible and self-limited, it is important to note that it is more frequent in newborns compared to adolescent and adult population. The use of depolarized muscle relaxant (Succinylcholine) in infants is reserved for providing fast muscle relaxation for endotracheal intubation. Due to high volume of distribution, the dose needed for intubation is higher (2mg/kg) compared to adults (1mg/kg).

Despite the high dose, the effect of muscle relaxation is not prolonged because of the fast plasmatic clearance through the activity of plasma esterase enzymes. The response in terms of the length of muscle relaxation of non-depolarizing muscle relaxants is much less predictable and highly variable. All agents from this group have a large volume of distribution and decreased plasmatic clearance. At the same time the neuro-muscular bonds in newborns have increased sensitivity to the presence of these drugs. This is making the clinical use of non-depolarizing muscle relaxants very unpredictable. Historically, the most used drug from this group was pancuronium, mainly because of its capability to decrease vagal activity and increase the hearth rate. But the prolonged muscle relaxation has limited its clinical use. Vecuronium and rocuronium exert less effecton the vagal activity but are also producing much shorter periods of muscle relaxation. It should be emphasized that the length of muscle relaxation in newborns and infants is longer compared to adults and can surpass 60 minutes. All guidelines for pediatric anesthesia are strongly limiting the use of muscle relaxants in the operation room, where the complete equipment for endotracheal intubation and mechanical ventilation is present and ready for use (2,4).

5. Conclusion

Newborns and infants cannot be treated as "small adults". Therefore, the protocols and anesthetic treatment regarding the plan of perioperative care and dosage of anesthetics and other drugs cannot be simply mirrored from adults to this age group of patients. The perioperative treatment of newborns requires significant knowledge of the dynamic process of postnatal adaptation of different organ systems because these physiological changes are carrying significant specific to the creation of the anesthetic plan for every individual patient at this age. Only by careful planning and strictly following the established anesthetic plan, we can be sure to provide safe and effective care to this highly vulnerable population. Also, the recommendations suggest that the most experienced anesthesiologist in pediatric anesthesia should always perform all techniques in newborn babies. This strategy has been proven to minimize the risk of potentially fatal incidents.

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ANALGOSEDATION IN PEDIATRIC POPULATION

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Introduction

Almost all interventions and medical procedures cause great distress such as anxiety, fear and pain in children and their families. Achieving the optimal combination of adequate analgesic and sedation is a major challenge in this patients' population due to the wide spectrum of age, size and developmental stage.[1]

Under dosing increases the risk of physical and psychological stress that can have long-term consequences. Excessive sedation, on the other hand, increases the risk of side effects of analgesic and sedative agents, prolonged respiratory support, prolonged hospital stays or hospital admission. Both, insufficient analgosedation and overdose, put pediatric, especially critically ill patients at high risk of developing complications such as delirium, withdrawal syndrome, neuromuscular atrophy and weakness, post-traumatic stress and poor rehabilitation.

Optimal analgesia and sedation depend on continuous assessment with validated tools to help titrate analgesic agents.[2]

Many procedural procedures, such as endoscopy, computed tomography, bronchoscopy and magnetic resonance imaging are performed for the diagnostics and therapy of diseases. Also, everyday medical care involves blood sampling from venipuncture, nasogastric tube and urinary catheter placement, lumbar puncture, bone marrow aspiration etc.

All these invasive and inevitable investigation methods often represent a severe burden for children and can only be carried under anesthesia or sedation. Therefore, analgosedation is carrying great significance in the diagnostics and treatment in children to avoid psychological trauma and to optimize the results of the examination. [3]

Analgosedation can principally only be carried out by trained personnel who are capable of independently dealing with any complications that might occur. Prerequisites for dealing with complications are a good background knowledge on the pharmacokinetics and pharmacodynamics of the medications applied, the safe performance of basic and advanced cardiac life support in children, and the appropriate equipment. Complications rarely occur during sedation for diagnostic and therapeutic measures when a competent team takes care of the children based on predefined guidelines.

Pharmacodynamics and pharmacokinetics of analgesic and sedative agents

Clearance, metabolism and duration of drug effect, can be affected by dysfunction or insufficiency of the end organ (hepatic, renal, cardiac). The key factors affecting pharmacokinetics (PK)

and pharmacodynamics (PD) can be divided into two elements: Patients' factors and factors resulting of the Pediatric Intensive Care Unit (PICU).[4], [5]

Patients'Factors

These factors include change in the redistribution of body fluids that affects the volume distribution of the drug, altered protein binding that may affect plasma drug concentration, and end-organ dysfunction that may alter drug absorption, metabolism and excretion. Other factors are natural age-related physiology that can affect drug absorption, metabolism, and excretion and inflammatory conditions that alter drug-metabolizing enzymes, as well as affecting drug absorption, efficacy and clearance.[6], [7]

PICU factors

Non-pharmacological interventions such as the use of continuous renal replacement therapy (CRRT), extra-corporeal membrane oxygenation (ECMO) and therapeutic hypothermia are belonging to PICU factors, all of which affect the extent of volume of distribution, metabolism, absorption and clearance.[8]

Analgesia

Effective, titrated treatment of acute, procedural and chronic pain, especially in PICU is essential tool for good patient's outcome.

The goal of analgesic therapy is to provide comfort, to reduce the physiological response to stress, to reduce adverse events associated with analgesics, such as respiratory depression, risk of dependence, hemodynamic instability and end-organ injury.

In the critically ill pediatric patient, this balance is delicate and, if failed, can predispose children to inappropriate pain management.[9]

Pain Assessment

In order to titrate analgesic therapy for adequate pain management, and monitor for signs of drug toxicity, or adverse effects, gold standard for monitoring the effectiveness of pain medication is patients' self-assessment scales. The premise of these scales is assigning a numeric value to the perception of pain, such as designating 0 as"nopain" and 10 as "worstpain".

Self-assessment is a good tool to detect the presence of pain, as well as the perceived intensity of pain. However, pain self-assessment can be challenging in some pediatric patients because of their limited ability to communicate (PICU patients) or comprehend as a result of age or disability.

Physiological indicators as tachycardia, rise in blood pressure, tachypnea, pupil dilation, increased muscle tone, sweating, etc. are unreliable signs because they lack pain sensitivity and specificity. Behavioral signs of a child in pain, either verbal (vocalized description of intensity, quality, location with concomitant moaning or crying) or non-verbal (facial expression, body posture/repositioning, decreased activity) were also shown to be uncertain signs.[10]

In children <3 years, the standard for pain assessment is the use of behavioral observational pain scales using subjective and objective indicators that interpret facial expression and physiological and motor responses, often including the opinions of family members.

Children aged 4 to 8 years are usually able to self-report pain, so their subjective information is complemented by the application of an appropriate pain tool.

Older children (8 years and older) are usually able to self-assess their pain using more validated methods such as the verbal rating scale (VRS), numerical rating scale (NRS), and visual analog scale (VAS), similar to adults (11).[11]

Not all pain scales require self-assessment and interpretation of verbal cues. The Wong-Baker FACES scale and the Bieri Faces Pain Scale Revised (FPS-R) are suitable for children of any age and developmental stage and rely on nonverbal cues.

Each scale has its limitations. The observational scales as Neonatal Pain, Agitation, and Sedation Scale (N-PASS), Nonverbal Pain Scale (NVPS), and Face, Legs, Activity, Cry and Comfort (FLACC) scale cannot measure pain intensity or quality.

Table 1.FLACC Scale

	0	1	2
Face	Relaxed face, no particular Expression or smile.	Occasional grimace or scowl, retiring, disinterested.	Frequent to constant scowl, quavering chin,clenching jaw.
Legs	Normal position or relaxed.	Uncomfortable, restless, tense.	Kicking or legs pulled up.
Activity	Lying down quietly, normal position, moves easily.	Wriggling,shifting back And forth,tense.	Arched, rigid body or jerking.
Cry	No cry (awake or asleep).	Moans of whines, occasional compliant.	Crying consistently, screams or sobs, frequent complaints.
Consolability	Pleased, relaxed, not require consoling.	Reassured by occasional touching, clasping, or being talked to, distractible.	Inconsolable, difficult to comfort.
Total score 0=Relaxed and comfortable, 1–3=Mild discomfort, 4–6=Moderate pain, 7–10=Severe discomfort or pain or both. Adapted from Merkel SI *et al.*22			

Table 2. Comparison of Pain Assessment Instruments.

FLACC	Children, all ages	Acute, surgical	Observational	Behavioral,physiological
FPS-R	≥4years	Acute, surgical	Self	Pictorial
N-PASS	Neonates	Acute, surgical	Observational	Behavioral,physiological
NVPS	Children,all ages	Acute, surgical	Observational	Behavioral,physiological
NRS	≥6years	Acute, surgical, chronic	Self	Numeric
VAS	≥6years	Acute, surgical, chronic	Self	Numeric
Wong-Baker FACES	≥4years	Acute, surgical	Self	Pictorial

FLACC = Face, Legs, Activity, Cry, and Consolability scale; FPS-R = Faces Pain Scale Revised; N-PASS = Neonatal Pain, Agitation, andSedation Scale; NRS = numeric rating scale; NVPS = Nonverbal Pain Scale; VAS = visual analog scale.

Pain Treatment

Non-pharmacologicalTreatment

Non-pharmacological interventions include a range of so-called age-appropriate redirection techniques. Redirection techniques for infants include pacifiers, swaddling, rocking and holding.

For older children, diversion techniques may vary but include using familiar toys, video games and television.

Other non-pharmacological interventions may include music or art therapy, a quiet environment with low stimulation and cognitive behavioral therapy.

The use of non-pharmacological therapies should always be considered and intertwined with pharmacological therapy.[12]

Pharmacological Pain Treatment

Pain assessment and identification of its underlying causes must lead to the choice of analgesic drug which must be of adequate power, and targeted to properly pain treatment.

Acute pain is the most frequent form of pain in PICU, but complex patients with prolonged stay in intensive care unit may present with persistent, chronic forms of pain, for which it may be necessary a multidrug combination.

The therapeutically schedule had to be daily reassessed according to the analgesic requirements.

WHO's pain ladder, a step grading pain therapy still remains a valid method in treating pain by choosing drugs secondary to pain intensity.

Table 3. Analgesic drugs.

Drug	Intravenous bolus	Intravenous infusion	Per os
Morphine	Neonates - 25mcg/kg, Infants-children - 30-100mcg/kg.	Neonates - 5-10mcg/kg/h, Infants-children - 10-50mcg/kg/h.	Neonates - 80mcg/kg 4-6 hourly, Infants – children - 200-500mcg/kg/ 4 hourly.
Fentanyl	Neonates - 0.5-1mcg/kg, Infants-children - 1-2mcg/kg.	Neonates - 0.5-3mcg/kg/h. Infants-children - 1-5mcg/kg/h.	
Remifentanil		Neonates - 0.01-30.1mcg/kg/min, Infants-children - 0.02-1 mcg/kg/min.	
Paracetamol	Neonates - 7.5-10mg/kg 6-8 hourly max 30mg/kg/day, Infants (⊠ 10kg) 15mg/kg 6-8 hourly max 60mg/kg/day, Children- (⊠ 50 kg) 1g 6-8 hourly max 4g/day.		Neonates - 10-15mg/kg 8-12 hourly max 30mg/kg/day, Infants - 15mg/kg 4-6 hourly max 60mg/kg/day, Children – 15mg/kg 4-6hourly max 90mg/kg/day.
Ibuprofen Above 3 months			5-10mg/kg 6-8 hourly max 40mg/kg/day.

Recommendations:

- For children assessed as having mild pain paracetamol and non-steroidalanti-inflammatory drugs (NSAIDs) should be considered as the first options.
- For the treatment of severe pain, administration of opiates delivered by continuous intravenous infusions is recommended because of more accurate control of the dose and more steady plasma concentration.[13]
- Enteral route, when gastrointestinal motility and function are recovered, is also highly recommended.
- An iv analgesic drug may be administrated during oral route administration of analgesic treatment as adjuvant or rescue therapy.
- Paracetamol and nonsteroidal anti-inflammatory drugs in children above three months of age, and only paracetamol in neonates, are recommended for treating mild pain.
- Adding nonsteroidal anti-inflammatory drugsor paracetamol to opioids is useful to limit the total opioid dose required.

- Fentanyl is indicated in presence of cardiocirculatory instability, and in neonates with persistent pulmonary hypertension.

Loco-regional techniques must always be considered in cases of localized pain, such as procedures, surgery, trauma or burns. Ultrasound guided peripheral nerves block sare strongly recommended also in infants within 6 months of age even if there is scarce evidence that ultrasound technique is more reliable than traditional land marking.[14]

- Epidural analgesia is effective for acute pain after surgery or trauma to the chest and abdomen.

- Use of EMLA in severe premature infants, mostly in repeated applications during the same day, carries the real risk of developing methemoglobinemia.

Sedation

The sedation targets are reduction of distress, fear, agitation, improvement of patient-ventilator synchrony and decrease in self-removing of invasive devices. Sedation cannot be implemented without an adequate analgesic treatment, since persistent not treated pain undermined the sedation strategy. Since standard sedation protocols suitable for all patients do not exist, one should be able to tailor sedative plan for each patient using minimal effective doses.[15]

Sedation is a particular challenge for anesthesiologists, nevertheless the pediatric patient is assigned for procedural sedation, or the patient is on mechanical ventilation in PICU.

The optimal condition for a patient who is breathing independently is that he wakes up easily, or is conscious, feels comfortable and breathes in synchronizing with the ventilator - the Goldilocks zone (not too deep and not too shallow). Balancing sedation to synchronize the patient with the ventilator is matter of mastering.

Balancing the depth of sedation is important because insufficient sedation can lead to dislocation of intravascular access and catheters, unplanned extubation, and potential injury to staff or the patient. Excessive sedation, on the other hand, can lead to unstable hemodynamics, respiratory depression, and possible extubation failure. Also, prolonged intubation poses an increased risk for muscle hypotonia, delirium, cognitive impairment, decreased tolerance and withdrawal syndrome.[16]

Table 4. Levels of sedation.

Level of sedation	Stimulus response	Airway	Ventilation	Hemodynamics
Minimal ("anxiolysis")	Verbal and tactile	Unaffected	Unaffected	Maintained
Moderate ("conscioussedation")	Verbal and tactile	Unaffected	Unaffected	Maintained
Deep	Noxious tactile	Affected	Affected	Maintained
Generalanesthesia	None	Affected	Affected	Impaired

Sedation Assessment

- State Behavioral Scale (SBS),
- COMFORT behavior scale,
- COMFORT-B scale,
- Richmond Agitation Sedation Scale (RASS).

State Behavioral Scale (SBS)

SBS monitors 8 parameters in mechanically ventilated children[17]:

1. Respiratory drive,
2. Response to ventilation,
3. Coughing,
4. Best response to stimulation,
5. Attention to the care provider,
6. Care tolerance,
7. It can be comforted,
8. Ability to move after comfort.

COMFORT Behavior Scale

The COMFORT behavioral scale is an observational scale that measures eight parameters to determine the level of distress of a critically ill child.[18]

Unlike the SBS, the COMFORT scale contains two physiological parameters and six behavioral dimensions:

1. Pulse,
2. Mean arterial pressure,
3. Alertness,
4. Calmness,
5. Respiratory response,
6. Movement,

7. Muscle tone,
8. Facial expression.

COMFORT BScale

The COMFORT-B scale eliminates both physiological parameters but adds excessive sedation and insufficient sedation. A limitation of this scale, however, is that scores of 10-23 are not predictive of adequate depth of sedation. The COMFORT-B scale is commonly used in conjunction with other observational scales. [19]

Richmond Agitation Sedation Scale (RASS)

The RASS is an agitation and sedation scale that has been validated for both adults and children (intubated and non-intubated) in the critical care setting.

The RASS is a 10-points scale ranging from 5 (unreactive) to +4 (combative) with 0 indicating readiness for increased attention and calmness.

For infants and children with cognitive or developmental limitations and for whom the level of alertness is difficult to assess, the original RASS is adapted to replace eye contact with eye opening when the RASS is -1 to -3.[20]

An important limitation of all these rating scales is their inability to be used for children with neuromuscular blockade.

Table 5. Initial Doses of Opioids and Sedatives in Children.

	Intermittent dose	Continuous intravenous infusion
Chloral hydrate	PO: 0.5–5mcg/kg	N/A
Clonidine	PO: 0.5–5mcg/kg	N/A
Dexmedetomidine	IN: 1–4mcg/kg IV: 0.5–1mcg/kg	0.2–0.7mcg/kg/hr
Etomidate	IV: 0.1–0.3mg/kg	N/A
Fentanyl	IN: 1–2mcg/kg IV: 0.5–3mcg/kg	0.5–2mcg/kg/hr
Hydromorphone	IV: 0.01–0.02mg/kg	0.003–0.005mg/kg/hr
Ketamine	IM: 5–10mg/kg	0.3–0.6mg/kg/hr
	IN: 3–5mg/kg	(5–10mcg/kg/min)
	IV: 0.5–3mg/kg	
	PO: 5–8mg/kg	

Lorazepam	IV: 0.05–0.1mg/kg PO: 0.05mg/kg	0.05mg/kg/hr
Midazolam	IM: 0.05–0.15mg/kg	0.03–0.12mg/kg/hr
	IN: 0.2–0.3mg/kg	
	IV: 0.05–0.1mg/kg	
	PO: 0.25–0.5mg/kg	
Morphine	IV: 0.03–0.2mg/kg	0.01–0.04mg/kg/hr
Pentobarbital	IM: 2–6mg/kg IV: 1–2mg/kg PO/PR: 1.5–6mg/kg	0.5–1mg/kg/hr
Propofol	IV: 0.5–2mg/kg	1.2–4.8mg/kg/hr (20–80mcg/kg/min)

Conclusion

Providing safe, effective and appropriate analgesia and sedation in children is challenging, complex and stressful intervention requiring experienced and well-trained personnel. However, the provision of analgesia and adequate level of sedation is frequently necessary to optimize the healing environment. Challenges with analgosedation in children include understanding of the pharmacokinetics and pharmacodynamics in pediatric patients, as well as how obesity and other illnesses contribute to medication pharmacokinetics. Analgesics and sedatives carry a high risk to imbalance the child homeostasis.

Appropriate analgosedation in children is hard to achieve. Over- or under-treatment are both harmful. Frequently, the reasons are lack of knowledge in pharmacological profiles of drugs and an insufficient applications of assessment tools.

Optimal analgesia and sedation are dependent on the implementation of validated tools to guide the titration of analgosedative agents, and screen for withdrawal and delirium. Optimal sedation should minimize physical and chemical restraints, encourage safe liberal activity, promote restorative sleep, and reduce the incidence of PICU-acquired complications (PACs).

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"DEVELOPMENTAL HEMOSTASIS" AND PEDIATRIC SURGERY

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Hemostasis can be defined as a physiological process that stops bleeding after injury of blood vessels. It is a complex and highly regulated process to localize the blood clot only to the site of injury. The hemostatic system in the human body is based on the components of Virchow's triad:

1. vascular injury,
2. change in blood coagulability,
3. disturbance of blood flow (stasis).

If the third component (blood flow) is excluded, hemostasis can be defined as an inter-reaction between the blood vessel wall, blood cell components and plasma proteins that maintain the hemostatic balance. The final outcome of hemostasis is coagulation of blood at the site of vascular injury(1,3).

Hemostasis can be divided into primary, secondary and tertiary hemostasis. These three independent mechanisms combine to maintain hemostatic balance.

Before primary hemostasis begins at the site of blood vessel injury, a local contraction occurs in order to reduce blood loss from the site of the damaged blood vessel. It is the result of nerve reflexes and local myogenic spasm, most likely caused by the painful impulse at the site of blood vessel injury and surrounding tissue. This spasm of the damaged blood vessel extends several centimeters along it. The greater damage of blood vessel produces the greater contraction of the blood vessel. When a blood vessel is cut sharply, it bleeds more than in crushed tissue. The local spasm of the damaged blood vessel can last several minutes or even hours. It has been shown that in patients with bruised lower legs, there is a strong vasoconstriction of the large blood vessels of the lower legs, such as the anterior tibial artery, as a compensatory mechanism to prevent lethal blood loss (1,2,3).

Primary hemostasis is a process aimed at the formation of a platelet plug, that plugs the site of injury, through the cellular interaction of platelets with the sub-endothelium of the injured blood vessel. Small injuries to blood vessels that occur every day are closed with platelet plugs, and larger injuries to blood vessels with blood coagulum (plugs). Platelets together with erythrocytes and leukocytes are the cellular part of the blood. Platelets are created by the megakaryocytes in the bone marrow, more precisely as the buds of the megakaryocyte are separated from it and released into the blood. The platelet does not have a nucleus, but its cytoplasm has:

1.**Actin and myosin molecules** that enable the contraction of Tr.

2. Remains of endoplasmic reticulum and Golgi apparatus that synthesize various enzymes and store a large amount of calcium.

3. ***Enzymatic systems*** that synthesize prostaglandins.

4. Protein-***factor of fibrin stabilization***.

5. ***Growth factor*** that enables the growth of vascular endothelial cells, vascular smooth muscle cells and fibroblasts.

6. ***Glycoprotein in the cell wall of the Tr.*** which enables the adhesion of the Tr. to the endothelial cells of the blood vessel and the collagen from the deep parts of the blood vessel. 7. **Phospholipid** - which can activate the "intrinsic" system.

8. Protein ***enzyme adenyl-cyclase*** stimulates the creation of C-AMP (enables platelet activity).

9. The half-life of Tr is 8-12 days. It is degraded by macrophages in the spleen.

10. Thrombus takes an irregular shape and sticks to the collagen from the endothelium of the damaged part of the blood vessel, and at the same time it secretes thromboxane A, which increases the adhesion of other thrombin to the platelet plug. The platelet plug does not close the lumen of the blood vessel, but the blood coagulum can close it (1,2,3,4,5,6).

Secondary hemostasis depends on the activation of coagulation proteins sequentially, which is regulated by many feedback mechanisms. The formation of a coagulation plug - coagulum at the place of the damaged part of the blood vessel begins, and it is created in 15 to 20 seconds if the injury to the blood vessel is large, and 1-2 minutes if the injury to the blood vessel is small. If the opening of the blood vessel is not too large, in 3-6 minutes the coagulum fills the cut part, and in 30-60 minutes it retracts and can almost close the blood vessel. In the created blood coagulum, fibroblast threads penetrate, which make a fibroblast network in which Tr, blood cells, plasma are trapped, so that later this structure can be organized and passed into connective tissue (7-10 days), i.e., complete healing of the blood vessel. When it comes to heavy bleeding, a hematoma is created in the tissues, which itself produced enzymes that break it down (2,3,4,5,6).

Stages of Blood Coagulation

In the blood and tissues there are about 40 substances that act on blood clotting, namely substances that enable blood pro-coagulation and substances that inhibit blood anticoagulation. Basically, these two systems are in balance, but with greater dominance of anticoagulation. But when a blood vessel is injured, pro-coagulation prevails over anticoagulation and the formation of a coagulum occurs.

The first stage of blood coagulation, when a blood vessel breaks or when blood is damaged, is to create a prothrombin activator (substance complex).

At the ***second stage***, the prothrombin activator enables the conversion of prothrombin into thrombin.

In the ***third phase***, thrombin acts as an enzyme and converts fibrinogen in the coagulum into fibrin threads (in which Tr, blood cells and plasma are trapped) in a period of 10 to 15 seconds from the injury of the blood vessel (3,4,5,6).

The Conversion of Prothrombin to Thrombin

When a blood vessel is injured, a prothrombin activator is immediately created, which will allow prothrombin to pass into thrombin, and thrombin to lead to the polymerization of fibrinogen molecules into a fibrin network. Prothrombin (factor II) is a plasma protein, alpha 2 - globulin with a concentration of 0.15g/l, with a molecular mass of 68,700. It is created in the liver, and its reserves in the liver are used up in 24 hours if no new ones are created. It is unstable and breaks down into smaller parts - thrombin, which has molecular weight of 33,700. Vitamin K is needed for synthesis of prothrombin – (f-or II) in the liver, as well as for factor VII, IX, X, protein C and protein S. Deficiency of vitamin K and the existence of liver disease, obstruction of bile ducts, increase the possibility of bleeding, because Vit.K is created in the intestines by intestinal bacteria or comes from food and is resorbed from the intestines with the help of fats and bilirubin. In such patients, 4-8 hours Vit. K is given preoperatively. So, if there are even the smallest number of intact hepatocytes, coagulation factors (VII, IX, X) and prothrombin can be created.

Updated Classification of Vitamin K-Dependent Clotting Factors or Protein Defects:

1. Conditions associated only with bleeding (FX deficiency),
2. Conditions associated with both bleeding and thrombosis (FII, FVII, and FIX),
3. Conditions associated only with thrombosis (protein C and protein S),
4. Conditions with no association with either bleeding or thrombosis (protein Z) (5,6).

The Conversion of Fibrinogen to Fibrin

Fibrinogen is a plasma protein with a large molecular weight of 340,000 in a concentration of 1-7g/l. It is synthesized in the liver, so as for prothrombin, liver diseases reduce its synthesis. The large molecular mass prevents it from leaving the blood bed, but with pathologically increased capillary permeability, it exits into the interstitium and can lead to coagulation of the interstitial fluid. Fibrinogen in the presence of thrombin, which is a protein enzyme with proteolytic properties, allows fibrinogen to be broken down into fibrin threads that form a fibrin network and solidify the blood coagulum, which is still unstable at the beginning, but under the action of a fibrin stabilization factor (which is secreted mostly from the Platelets) becomes firmer. In that fibrin network there is Tr, Er, Le and plasma. After a few minutes of the formation of the blood coagulum, it begins to retract (30-60minutes) and serum that does not contain fibrinogen and most of the coagulation factors comes out of it. To retrace it, platelets are also needed, from which the pro-coagulation substances are released (1,3,5,6).

Generation of Prothrombin Activator

The creation of prothrombin activator is by two mechanisms: an extrinsic mechanism and an intrinsic mechanism of blood coagulation.

An **extrinsic mechanism** of blood clotting begins with the generation of prothrombin activator when blood comes into contact with a damaged vessel wall or with tissue outside the vessel and tissue thromboplastin is released. This mechanism includes three stages:

1. Release of tissue ***thromboplastin (factor III)*** from the damaged tissue.

2. Activation of factor X to create ***activated factor X***, through coupling of tissue glycoprotein with factor ***VII-proconvertin*** which act enzymatically on factor X.

3. Activated factor X in the presence of Ca++, ***factor V (proaccelerin)*** creates the activated prothrombin which allows prothrombin in the presence of ***Ca++ (factor IV)*** to pass into thrombin.

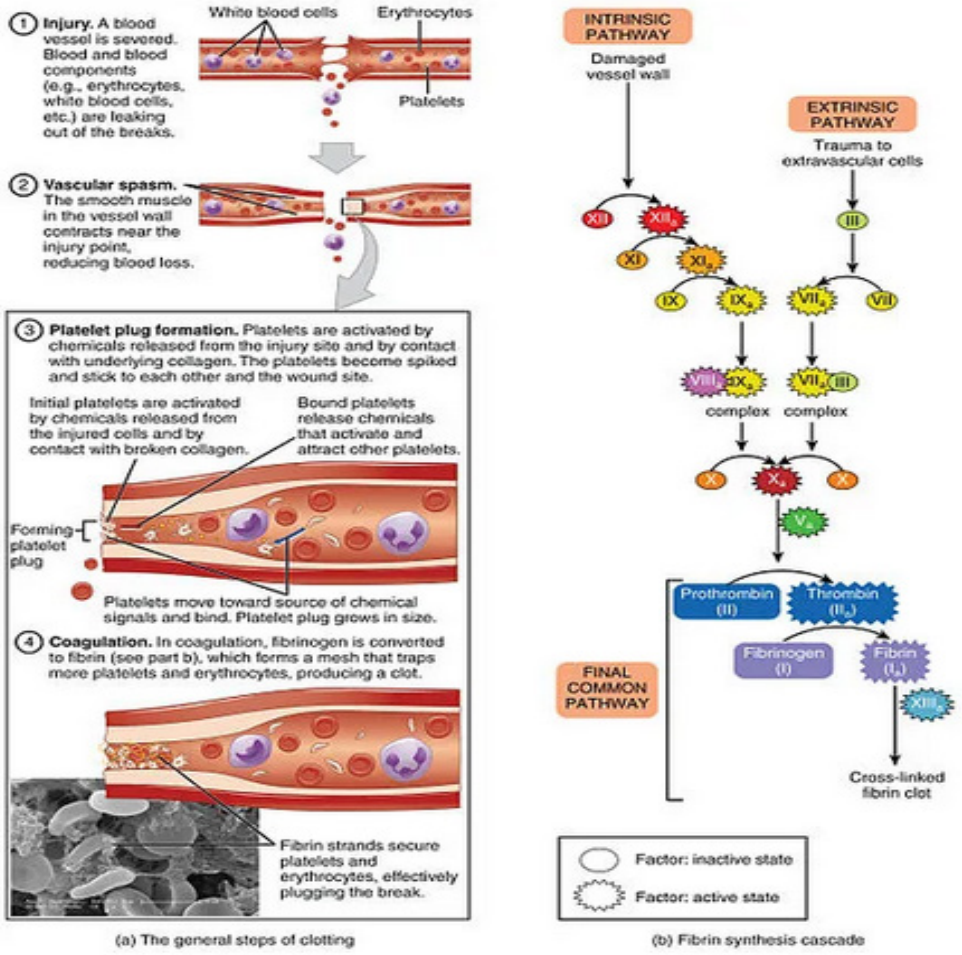

Table1. Intrinsic and extrinsic mechanism of blood clotting.

An **internal mechanism** of blood clotting begins with the creation of a prothrombin activator when the blood, that is, factor XII and Tr come into contact with the collagen from the damaged blood vessel wall. This mechanism includes:

1. Activation of factor XII (Haegeman factor) and release of platelet phospholipids.

2. Activation of factor XI by activated factor XII which acts as an enzyme.

3. Activation of factor IX by activated factor XI acting as an enzyme.

4. Activation of factor X by factor VIII, factor IX and Ca ++.

5. Activated factor X together with factor V and Ca ++ initiate the prothrombin activator which allows prothrombin to pass into thrombin, and thrombin to act as an enzyme in the reaction for fibrinogen to pass into fibrin threads.

6. The role of Ca ++ in all cascade processes of the internal and external coagulation mechanism.

The internal mechanism of coagulation is much slower than the external one. It takes 2-6 minutes to cause coagulation (3,5,6).

Tertiary hemostasis describes fibrinolysis, namely the lysis of the blood clot that was created during damage to the blood vessel wall and thereby restores the normal integrity of the blood vessel. Fibrinolysis occurs under the action of fibrinolysin (plasmin), which is a proteolytic enzyme derived from profibrinolysin, which is found in the plasma as euglobulin which when activated passes into plasmin (fibrinolysin). It is actually found in the blood coagulum as plasminogen together with other plasma proteins. It will not turn into fibrinolysin (plasmin) if it is not activated with the help of 1. thrombin, 2. activated factor XII, 3. lysosomal enzymes from the damaged tissue, 4. factors from the blood vessel endothelium. Activated fibrinolysin begins to act 1-2 days after the formation of the blood coagulum in order to lyse the fibrin threads, factor V, VIII, XII and prothrombin from it. Natural activators of fibrinolysin are urokinase, streptokinase, and its natural inhibitor is alpha 2-antiplasmin(3,4,5,6).

What is the Importance of the Fibrinolytic System?

The fibrinolytic system enables dissolution of blood clots and the cleaning of blood that has come out of the tissues from the damaged blood vessels. The coagulum in the small blood vessels is more easily fibrinolyzed and allows the patency of the blood vessels. Larger coagulum of large blood vessels is more difficult to lyse and the blood vessel remains most often obstructed.

Hemostasis is a complex mechanism depending on a very delicate balance of hemostasis and pro-coagulant and anticoagulant factors. These factors are essential for maintaining the fluidity of blood in intact blood vessels and promoting effective blood clotting in vascular injury. They are also essential for limiting clotting at the site of injury and avoiding its spread to other uninjured parts of the blood vessels(3,4,5,6).

Evaluation of Hemostasis in Neonates and Children

Hemostatic balance is different in newborns and children compared to adults, that is, hemostasis is in continuous evolution. Maturation begins early intra-uterine, until complete maturation for some factors and puberty.The neonatal hemostatic system is remarkably different from that of adults.Among other differences, neonates show hyporeactive platelets and decreased levels of coagulation factors, which translate into prolonged coagulation times (PT and PTT). Because preterm infants have a high incidence of bleeding, especially intraventricular hemorrhage, neonatologists often administer blood products (i.e., platelets and FFP) to nonbleeding infants with low platelet counts or prolonged coagulation times in an attempt to overcome these "deficiencies"and reduce the risk of bleeding. However, it is becoming increasingly clear that both platelet hyporeactivity and decreased levels of coagulation factors are effectively offset by other factors in neonatal blood that promote hemostasis (i.e., high vWF levels, high hematocrit and MCV, decreased levels ofnatural anticoagulants), resulting in a well-balanced neonatal hemostatic system, perhaps slightly biased towards a prothrombotic phenotype. Although life-saving in the presence of active major bleeding, administration of platelets and/or FFP to nonbleeding neonates (based on laboratory tests) not only failed to reduce bleeding, but was associated with

increased neonatal morbidity and mortality, especially when platelets are given. Such evaluation of hemostasis is especially important in the first few months of postnatal life.At birth, plasma coagulation proteins have been shown to be about half of adult values. They are even lower in premature babies than in full-term newborns and increase postnatally, so that after a few months they reach the values of coagulation proteins as in adults, and for some coagulation factors, even until puberty(7,8,9,10).

Developmental Hemostasis

Children cannot be considered miniature adults in terms of hemostatic balance. There is a big difference between pediatric and adult hemostatic systems. In the 1980s, Maureen Andrews introduced the term "developmental hemostasis" to describe the changes that occur in the coagulation system, progressively, from the beginning of intra-uterine fetal life, postnatal, pediatric life to adulthood, and then in geriatric systems (8,10). Maternal coagulation factors do not cross the placenta, and the fetus begins the synthesis of coagulation proteins from the fifth week of intrauterine life, its blood can coagulate as early as 11 weeks of pregnancy. At gestational age between 19 - 23, reference values for coagulation factors are ten to thirty percent of adult values, progressively increasing to levels between 10% - 50% at gestational age between 30-38 weeks. The importance of hemostasis development is to prevent misdiagnosis and treatment of hemostatic problems in infants and children, and to explain the pathophysiological basis of hemorrhagic and thrombotic complications of all ages (1,2,8,9,10,11).

Difficulties in Interpreting the Hemostatic System in Infants and Children

There are limited data on the physiology of hemostasis in neonates and children when compared to the available data on the hemostatic system in adults. Many factors increase this limitation in neonates and children, since more reference ranges are needed that go with the age-related evolution of the hemostatic system, which in turn requires many patients to establish normative data, despite the difficulty of blood sampling in pediatric age groups(11,12).

Sampling Problems

Sampling in neonates and young infants relative to adults is a problematic process, which is a key point to consider. Heparin-contaminated blood samples are often obtained from central vascular catheters or pre-used heparinized syringes. All of these give incorrect results. Moreover, neonatal polycythemia (which is common), during collection of blood in the tube can affect the result due to the influence of the citrate-to-blood ratio (9:1) (11,12,13).

Defining Reference Values

Lack of use of appropriate reference values remains the most common obstacle in the interpretation of pediatric coagulation tests. One problem in defining age-dependent reference values is that functional levels of coagulation proteins change with the age of children. These changes are reflected in the results of some coagulation tests, such as activated partial thromboplastin time (APTT). Other tests are less affected by age-related changes in hemostatic factors, such as thromboelastography. Use of the international normalized ratio (INR) minimizes variation in prothrombin time (PT) results. Thrombin time in newborns is prolonged due to the absence of calcium during its derivation, as fibrinogen is present in a "fetal form" at birth, and to polymerize, it needs calcium. Another problem is that reference values are age-dependent and are dependent on each analyzer-reagent in many clinical laboratories. The same happens with aPTT interpretation. Many laboratories with their own reference values can lead to unnecessary

referrals to hematologists, multiple searches, wrong diagnoses, cancellations of operations or excessive treatments of the child. Accordingly, ISTH, "The Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis" (2012) recommended to define, depending on age, reference values for each laboratory according to their technical conditions (13,14,15).

New Diagnostic Tests

Knowing the basics of developmental hemostasis in children and the large number of pediatric clinical studies, there was a need to introduce a new Endogenous Thrombin potential (ETP) analysis, which measures, in vitro, the overall ability of the hemostatic system to generate thrombin (16).

Age-related Changes in the Hemostatic System

At birth, there is a transient increase in the number of platelets, so that by the end of the first year it reaches the values as in adults (20). Although platelet functions are depressed in the neonatal period, bleeding time and platelet clotting time (PFA-100) were found to be paradoxically shortened in neonates by the end of the first month of life. Von Willebrand factor (factor 8) in newborns has been shown to be elevated and it decreases reaching adult levels after the first year (14,15,16,17).

Changes in Coagulation Proteins

Coagulation proteins in the fetus begin to be synthesized intrauterine in the 5th gestational week, and blood begins to coagulate from the 11th gestational week. Already, from 19-23 gestational weeks, the values of gestational coagulation factors are represented by 10-30% in relation to of adults, to progressively increase from 10-50% between 30-38 weeks of gestation. Gestational coagulation factors synthesized during fetal life are unable to cross the placenta, nor can maternal coagulation factors cross the placental barrier.

By **the10th week** of intrauterine life, coagulation proteins have measurable concentrations in plasma, gradually increasing with the progression of pregnancy. It has been shown in many studies that Vit. K-dependent factors: **Prothrombin (FII), FVII, FIX and FX** at birth have physiologically low values, below 30% of the adult values (while they do not have clinical manifestations of bleeding), especially they gradually increase to reach the adult level. The last to reach adult levels is **FVII**, which may not reach adult levels until age of 16. Levels of **FXI, FXII and contact factors (pre-kallikrein and high-molecular-weight kininogen)** gradually increase to adult values sometime around the 6th month after birth. Low values of contact factors are the cause of prolonged aPTT in the first months of life. A high basal metabolic rate in infants and children may accentuate the low level of plasma proteins by accelerating their clearance rate. Levels of **fibrinogen, FV, FVIII, FXIII and von Willebrand- factor (vWF)** are not decreased at birth. On the contrary, plasma levels of FVIII may rise and be higher than adult levels, requiring adjustment of the lower limit of normal. Also, vWF levels are elevated at birth and for the first 3 months of life. Regarding fibrinogen levels, not only is the fibrinogen is low at birth, but it has also been shown to exist in a "fetal form", in cord blood. This "fetal form" of fibrinogen has a high sialic acid and phosphorus content relative to adult fibrinogen. Sialic acid directly in fibrinogen binds to Ca+2 leading to a reduction of repulsion between fibrinogen chains and facilitation of fibrin polymerization. Prolonged thrombin time (TT) in neonates may be attributed to different polymerization of fetal fibrinogen than adult fibrinogen, leading to the notion that infants have **"dysfunctional fibrinogen"** (1,7,8,9,10,11).

Natural Anticoagulants

1**. Factors on the surface of the endothelium**- The smooth surface of the endothelium (monomolecular layer of adsorbed proteins) of the blood vessels prevents the contact activation of F XII, Tr and contact proteins, and thus the chain of activation of the internal coagulation system.

2. Thrombin is inhibited by many anticoagulants present in cord blood, such **as antithrombin, α2-macroglobulin, dermatan sulfate as an anticoagulant and heparin cofactor II** [38]. In neonates, **α2-macroglobulin** appears as a more potent inhibitor of thrombin than in adults, which accounts for the low levels of antithrombin in neonates. Despite the greater potency of neonatal α2-macroglobulin, thrombin inhibition is still slower in neonates than in adults (7).

3. Fibrin threads that create the network of the coagulum act as anticoagulants, on the principle of binding thrombin to the very threads of the blood coagulum, and thus prevent the expansion of the coagulum.

4. **Antithrombin III** is an alpha globulin that binds thrombin that remained unbound to fibrin threads and blocks the action of thrombin on fibrinogen for 12-20 minutes.It inactivates thrombin. In the first three months after birth, the concentration of antithrombin is 50% lower compared to adults who had recurrent thrombosis in heterozygous anti-thrombin deficiency. Its concentrations gradually increase during the first 6 months after birth. In neonates and infants, there are no data on thrombotic manifestations despite the low levels of antithrombin.
5. **Heparin** is a conjugated polysaccharide with a strong negative charge, by itself it has little or no anticoagulant effect, however, when bound to antithrombin III, it increases the anticoagulant power by a thousand times by removing thrombin. This **antithrombin-heparin cofactor** also removes from circulation the following coagulation factors XII, XI, IX, X. Heparin is secreted by basophilic cells in the blood and fat cells that are located pericapillary in the connective tissue of the entire organism, especially around the capillaries in the lungs and liver. The number of mast cells in these organs acts in some way protectively because in the venous slow current of blood come very small coagulum, and such coagulum from human antithrombin-heparin prevent the growth of these coagulum. Thrombin is inhibited by many anticoagulants present in cord blood, such as antithrombin, α2-macroglobulin, dermatan sulfate as an anticoagulant and heparin cofactor II (1,3,7).

Protein C, Protein S and Thrombomodulin

At birth, plasma concentrations of protein C and protein S are very low. Protein C levels remain low during the first 6 months of life. The low level of protein S is compensated with the increase of its functional activity. Protein S is present in an active form due to the absence of C4 binding protein in newborns. In addition, increased levels of α2-macroglobulin facilitate the interaction of protein S with activated protein C in the plasma of the newborn. Whereas plasma **thrombomodulin** levels increase in early childhood, and leveling off to adult-like values is reached in adolescence (1,2,7).

Conclusions

Understanding of developmental hemostasis is of crucial importance for achieving a diagnosis of bleeding and thrombotic disorders in infants and children, as well as avoiding hematological and non-hematological complications. Correct age-appropriate sampling techniques, specific reference to analyzers and reagents are crucial to avoid misdiagnosis and overtreatment. Finally, new assays should be developed, taking into account the basis of developmental hemostasis.

Points for Clinical Practice

1. Proper sampling is a necessity in pediatric coagulation studies.Attention to details, repeatability of sampling, are all important to avoid erroneous results.

2. Age-appropriate reference values are crucial for accurate diagnosis and treatment of coagulation disorders in infants and children, such as sudden changes in hemostatic protein concentrations during the first few months of life.

3. Each laboratory should establish its own specific reference values depending on its technical conditions.

4. Adult plasma products or drugs may have adverse effects on the neonate due to the multiple non-hemostatic functions of hemostatic proteins.

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ANESTHESIA FOR NON-CARDIAC SURGERY IN CHILDREN WITH CONGENITAL HEART DEFECTS

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Abstract

Congenital heart defects are the most common form of birth defects and occur in over 1% of newborns. Patients with congenital heart disease undergoing noncardiac surgery have increased perioperative morbidity and mortality. The purpose of this lecture is to teach anesthesiologists, who do not usually deal with cardiac anesthesia in children with congenital heart defects, to provide reliable and safe perioperative care for these patients. The anesthesiologist is required to have basic and advanced knowledge of the heart defect and its pathophysiological characteristics. In the preoperative preparation, an exhaustive anamnesis and status is required, as well as contact of the anesthesiologist with the child's primary pediatric cardiologist. Prevention of endocarditis should always be considered. The administration of anesthesia is in accordance with the pathophysiological characteristics of the congenital heart defect, and the underlying surgical disease for which the child is operated. Certain patients need to be sent to a specialized center, where, in addition to basic surgery, they also have teams to care for these patients. The anesthesiologist needs to know the anatomy and physiology of the congenital heart defect, and correctly to assess the current condition of the patient, in order to provide safe perioperative care in these patients.

Key Words: *anesthesia, congenital heart defects, non-cardiac surgery.*

Introduction

Congenital heart defects (CHD) are the most common form of heart defects and occur in over 1% of newborns. The prognosis, especially in patients with complicated CHD, has improved significantly in recent decades. Not only diagnostics, but also treatment, such as surgery, interventional procedures and intensive care medicine, have made significant progress in the last few decades. That's why it is expected that an increasing number of patients with palliative or corrective operations of CHD will need non-cardiac surgery.

Regarding the risks, there are studies that confirm that the risk of perioperative cardiac arrest is higher in children with CHD, but on the other hand, the frequency of perioperative complications in non-cardiac surgery in patients with CHD who do not have pulmonary hypertension, congestive heart failure or cyanosis are low, same as in patients who do not have CHD. The purpose of this lecture is that anesthesiologists who do not usually deal with cardiac anesthesia in CHD, can safely and reliably manage the perioperative care of patients with CHD, having a basic and advanced knowledge of CHD and its pathophysiological characteristics.

Special Aspects of the Medical Examination and Anamnesis in Patients with VSM

The anesthesiologist, who examines the patient with CHD and informs the parents and the child about the perioperative anesthetic care, must have at least a basic knowledge of CHD and its pathophysiological characteristics. Parents are usually very well informed about their children's CHD and know their medical history well, including therapy and surgeries that the patients have undergone. That is why an interview with the parents gives us a lot of information. But in addition, of course, the last examination by a cardiologist or cardiac surgeon must be checked, in order to understand the real status of the patient and the anatomy of their circulatory system.

In 30% of children with CHD there are also other extracardiac anomalies, and this is significantly more than the prevalence in children without CHD. The presence of these extracardiac malformations significantly increases the perioperative risk. Therefore, a detailed history and examination, especially in younger patients, is particularly important. In addition to this, it is necessary to assess the degree of heart failure. The questions are asked depending on the age of the child: Does the baby sweat while drinking from a bottle? Is it gaining weight? Does it have respiratory infectionsfrequently? Does the child tire easily when playing? In this way, the content of the questions changes according to the age of the child. The NYHA (New York Heart Association) functional classification is also useful in assessing the patient's abilities (Table1).

Table 1. Functional classification New York Heart Association (NYHA).

NYHA Class	Symptoms
I	There is no restriction on physical activity. Ordinary physical activity does not cause excessive fatigue, palpitations, dyspnea.
II	Mild restriction of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitations, or dyspnea.
III	Significant limitation of physical activity. Comfortable at rest. Little activity causes fatigue, palpitations, or dyspnea.
IV	Any physical activity causes discomfort. Symptoms at rest. If any physical activity is undertaken, the discomfort increases.

It is also very important to assess the possibility of a difficult airway. Laryngotracheal stenosis can cause a difficult airway. It is important to ask how long mechanical ventilation lasted after heart surgery and whether there are symptoms of possible stenosis. Certain syndromes are also associated with both difficult airway and CHD.

Prevention of Endocarditis

Infective endocarditis is a life-threatening disease and is difficult to treat, so it can have serious consequences for patients. For this reason, liberal antibiotic treatment has been recommended and implemented for all patients with CHD for a long time. However, it is now recommended that only defined patients at high risk of endocarditis receive antibiotic treatment. Table 2 shows patients at risk for endocarditis who should receive prophylaxis, and Table 3 provides an example of antibiotic prophylaxis.

Table 2. Patients at risk for endocarditis.

Heart valve operations (mechanical or biological valve)	
Previous endocarditis	
Congenital heart defect (CHD)	Uncorrected cyanotic CHD
	During the first 6 months after palliative or corrective surgeries using prosthetic material or catheter intervention
	Corrected VSM with residual damage to the prosthetic material
Heart transplant patients who develop cardiac valvulopathy	

Table 3. Example of antibiotic prophylaxis for endocarditis for non-cardiac surgery in high-risk patients.

Method of application	**Antibiotic**	**Dose**	
		Young child	**Older child**
Oral (PO)	Amoxicillin	50mg/kg PO	2gr PO
Intravenous IV (when oral not possible)	Cephazolin	50mg/kg IV	2gr IV
In penicillin allergies, oral PO	Clindamycin	20mg/kg PO	600mg PO
In penicillin allergies,IV	Clindamycin	20mg/kg IV	600mg IV

Laboratory Tests

Patients with cyanotic CHD have very high Hb/Hct as a consequence of chronic hypoxia. Hb>20gr/dL or Hct>65% leads to a high risk for thromboembolic complications. Hyperviscosity can be aggravated by too long preoperative fasting or vomiting, or insufficient intraoperative fluid replacement. For this reason, the patients with cyanotic CHD should receive adequate fluid replacement.Also, during intraoperative bleeding, the target hematocrit is always higher than in other children (about 40-45%), because the chronic hypoxia must be compensated in this way. Chronic congestion of the liver can reduce the production of coagulation factors, for example in patients with Fontan circulation.Preoperatively, serum electrolytes should be checked in patients receiving diuretics. The EKG will show us the rhythm of the patient and the workload of the heart. A chest X-ray shows the position of the heart, size, possible atelectasis, acute respiratory infections, and the position of the hemidiaphragms.

Premedication in Patients with CHD for Non-cardiac Surgery

Premedication is especially important for patients with CHD, because hemodynamic balance can be disturbed due to stress, fear due to separation from parents, or induction of anesthesia. Some patients with CHD have had multiple heart surgeries and therefore some of them have unpleasant memories and impressions. Premedication is a solution to this problem. However, excessive sedation must be avoided, which may result in an increase in PaCO2 due to respiratory suppression with subsequent hypoxia. This is especially important in patients with pulmonary hypertension.

Oral application of Midazolam 0.5mg/kgTT 15-30 minutes before entering the operating room is commonly used for premedication. Oral premedication with midazolam is also safe and effective in children with cyanotic CHD. If we have set up an intravenous route, intravenous application of Midazolam 0.05-0.1mg/kgTT and Ketamine 1mg/kgTT can be used, but still after giving the drugs i.v., monitoring of the child is required and the possibility of possible oxygen therapy if it is necessary. Ketamine can be given both orally and intramuscularly. Dexmedetomidine intranasal 1mcg/kgTT 45-60minutes before intervention can also be used.

Intraoperative Management of Patients with CHD

All used drugs and methods of induction of anesthesia can be used in patients with CHD, but of course in a certain dose and combination. We should always think about systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR). Inhalation anesthesia and inhalation induction of anesthesia can be used in these patients, but caution should be exercised with higher doses in patients with poor cardiac reserve. All intravenous anesthetics can be used, but be careful with propofol, which strongly reduces SVR. Ketamine is the drug of choice in patients with weak cardiac reserve, but it must not be used in high doses, because it has a negative inotropic effect. High-dose opioid anesthesia is suitable for these patients, but the problem of postoperative respiratory depression and patient extubation remains.

The amount of intraoperative monitoring will depend on the severity of the CHD, but also on the degree of risk of the operation itself. Routine monitoring consisting of ECG, noninvasive arterial pressure, SpO2, and temperature is sufficient for the most interventions. But if we have high-risk operations and/or complex heart defects, it is necessary to place a central venous catheter, an arterial catheter, as well as measurement of diuresis and NIRS.

Congenital heart defects with left-right shunt are present in 50% of these children. Examples are atrial septal defect, ventricular septal defect, A-V channel. Here the blood from the left heart, instead of going completely through the aorta in the systemic circulation, partially, through the existing communication, returns to the right heart and burdens the pulmonary circulation. Use of 100% O2 should be avoided in these patients, as it is a potent vasodilator of the pulmonary vessels and may lead to pulmonary congestion.

The existence of a right-left shunt means that the blood from the right side of the heart passes partially into the left heart through the existence of communication. We have this in the Tetralogy of Fallot. After induction of anesthesia, as a result of a drop in SVR due to the existence of a VSD, the normally left-to-right shunt now becomes right-to-left, as the pressure in the right ventricle becomes higher than the pressure in the left ventricle. The patient becomes cyanotic after induction of anesthesia. This is treated by giving a fluid bolus and increasing SVR with phenylephrine and reducing infundibular spasm with B blockers. Another important aspect in

these patients is that pulseoximetry is higher than real, as saturation decreases, and end-tidal CO2 is different from arterial CO2. Therefore, taking gas analyzes in these patients is mandatory.

A mean pulmonary arterial pressure greater than 25mmHg at rest and 35mmHg during activity is pulmonary hypertension. The high pulmonary flow that occurs with an unrestricted left-to-right shunt will lead to congestive heart failure and pulmonary hypertension. Initially, pulmonary hypertension is reactive and responds to hypothermia, stress, pain, acidosis and hypercarbia, hypoxia and increased intrathoracic pressure, but later it becomes fixed. Prevention of these trigger factors should be the goal of anesthetic management. A crisis of pulmonary hypertension can occur in the case of shallow anesthesia and airway instrumentation. Its termination requires deepening of anesthesia, administration of 100% O2, good CO2 elimination, and ventricular support with inotropic support.

Patients with single-chamber pathology go through several stages of palliative operations. B-T shunt is performed in newborn age, then Glenn operation and finally Fontan operation. Children with B-T shunt and Glenn have a normal saturation of about 70-85%. In patients with Fontan surgery, the venous inflow into the heart is directed directly into the pulmonary artery, and the entire heart, as a single chamber, works only to pump blood through the aorta into the systemic circulation. Venous blood flow will depend on the gradient between central venous pressure and pulmonary vascular resistance. Therefore, these patients need easy lung ventilation, without the use of high PEEP and high respiratory pressures, as well as improvement of the preload with a sufficient amount of fluids. These patients are volume dependent. Mechanical ventilation negatively affects these patients, so it is necessary to plan their early extubation.

Risks Classification

Children with BSM who have noncardiac surgery are at increased risk for morbidity and mortality. The most important factors affecting the risk are the complexity of the congenital heart defect, the physiological status of the child, the type of surgery and the age of the child. To enable a practical and structured approach to dealing with these patients, the risk for surgery is classified into three groups, shown in Table 4.

Table 4. Risk classification of children with congenital heart defects for non-cardiac surgery.

High risk	**Medium risk**	**Low risk**
Physiologically poorly compensated or presence of major complications	Physiologically normal or well compensated	Physiologically normal or well compensated
a) Heart failure		
b) Pulmonary hypertension		
c) Arrhythmias		
d) Cyanosis		

Complex lesions (univentricular heart, cardiomyopathy, aortic stenosis)	Simple lesions	Simple lesions
Major surgery (intraperitoneal, intrathoracic, anticipated major blood loss)	Major surgery (intraperitoneal, intrathoracic, anticipated major blood loss)	Minor surgery
Under 2 years of age	Under 2 years of age	Over 2 years of age
Emergency surgery	Emergency surgery	Elective surgery
Preoperative hospital stay more than 10 days	Preoperative hospital stay more than 10 days	Preoperative hospital stay less than 10 days
ASA status IV or V	ASA status IV or V	ASA status I-III

Conclusion

Children with congenital heart defects presenting for noncardiac surgery are at increased risk for perioperative morbidity. High-risk children require transfer to a specialized center, where there is specialized cardiosurgical intensive care and cardiology. Children with intermediate risk, depending on the circumstances, can be operatedatthe local center, but with specialist support from a specialized center or possible transfer. Low-risk children can be operated at the local hospital. All anesthesiologists responsible for children with congenital heart defects need to understand the anatomy, physiology and risk factors associated with the perioperative morbidity, perform a good preoperative assessment, and know the impact of anesthetics and mechanical ventilation in this patients' population.

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REVIEW ARTICLE *UDK: 618.6-083.98*

NEWBORNS RESUSCITATION

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Abstract

Most of the newborns adapt well to extra-uterine life, but some of them need stabilization or resuscitation. Expressed as a percentage, 85% breathe on their own, 10% after stimulation, and about 5% require positive pressure ventilation. The incidence of intubations varies between 0.4% and 2%, about 0.3% require cardiac compressions, and only 0.05% receive adrenaline. There are known risk factors, antepartum and intrapartum, which are the most common reasons for forced stabilization or resuscitation.

The protocols (European Resuscitation Council) have precise recommendations for each segment of resuscitation, starting with standards for personnel, equipment, environment; handling of the umbilical cord after birth; initial examination and assessment (tone, breathing, heart rate); and life support. The protocols have details that differ between full-term and premature newborns.

Resuscitation in the narrower sense of the word implies undertaking one or more of the four basic procedures (ABCD):

I. Initial stabilization steps (warming, airway aspiration if necessary, drying, stimulation),

II. Ventilation,

III. Heart compressions,

IV. Administer epinephrine and/or volume replacement.

It is of crucial importance to respect the "Golden Minute" rule, i.e., taking initial measures, re-evaluation and starting ventilation, if necessary, within 60 seconds.

After recovery of vital signs and adequate ventilation and circulation, the newborn should be transferred to an intensive care unit under appropriate monitoring and care. Induced therapeutic hypothermia should be an option following a properly prescribed implementation protocol. Failure to establish ROSC in neonates after 10-20 minutes of intensive resuscitation is associated with a high risk of mortality and a high risk of neurological damage in survivors. Refraining from applying resuscitation measures is reasonable in cases with a certain poor prognosis (gestational week <22 weeks and/or bw<350g; anencephaly; major chromosomal abnormalities), a decision for which with prior consultation and discussion with the parents is preferred.

Key words: *newborn resuscitation, newborn life-support, resuscitation guidelines.*

Introduction

Newborn resuscitation is a critical medical procedure aimed at reviving newborns who experience breathing difficulties or have trouble adapting to life outside the womb. As medical professionals, it is crucial to stay informed about the latest guidelines and the best practices in newborn resuscitation to ensure the best possible outcomes for these vulnerable patients. In this article, we will present the fundamental principles and techniques of newborn resuscitation while emphasizing the importance of continuous education and adherence to current guidelines. They apply primarily to newly born infants undergoing transition from intrauterine to extrauterine life, but the recommendations are also applicable to neonates who have completed perinatal transition and require resuscitation during the first few weeks to months following birth.

The European Resuscitation Council (ERC) Guidelines provide a comprehensive framework for healthcare providers to manage newborn resuscitation and support the transition of infants at birth.

Newborn Resuscitation and Support of Transition of Infants at Birth

Up to 85% of the newborns breathe spontaneously without intervention; a further 10% respond after drying, stimulation and airway opening maneuvers; approximately 5% receive positive pressure ventilation. Intubation rates vary between 0.4% and 2%. Fewer than 0.3% of the infants receive chest compressions and only 0.05% receive adrenaline.

Number of risk factors has been identified as increasing the likelihood of requiring help with stabilization, or resuscitation. Antepartum risk factors could be fetal (intrauterine growth restriction, <37 weeks gestation, serious congenital abnormality) and maternal (infections, gestational diabetes, pregnancy-induced hypertension, pre-eclampsia, high BMI, short stature). Intrapartum factors include evidence of fetal compromise (non-reassuring CTG etc.), meconium- stained amniotic fluid, forceps or vacuum delivery, significant bleeding, emergency C-section, general anesthesia.

Developing a comprehensive algorithm for newborn's life support is essential to guide healthcare professionals in providing immediate and effective care to infants in distress. This algorithm provides a step-by-step guide for healthcare professionals in providing life support for newborns. It covers assessment, initial steps and advanced interventions in accordance with the European Resuscitation Council Guidelines.

Initial Assessment and Identification

Immediate Assessment

Place the newborn on a warm, dry surface. Ensure a clear airway by gently suctioning the mouth and nose if needed. Assess breathing, heart rate, muscle tone, reflex irritability and color using the Apgar score.

Thermal Control Recommendations

The newborn infant's head and body should be immediately covered with a warm and dry towel to prevent further heat loss. Its body temperature should be monitored regularly after birth, in

order to avoid hypothermia or hyperthermia and it should be maintained between 36.5^{0}C and 37.5^{0}C. In case resuscitation is required, the newborn should be placed on a warm surface. As far as premature babies are concerned, recommendations include increased room temperature, warm blankets, head cap and thermal mattress.

Classification according to Initial Assessment

Based on the initial assessment, the infant can usually be placed into one of three groups:

- **Satisfactory transition** (good tone, vigorous breathing or crying, heart rate>100min) – does not require support, only maintenance of the body temperature;
- **Incomplete transition** (reduced tone, breathing inadequately (or apneic), heart rate <100 min) – it requires maintaining the airway, lung inflation and ventilation, as well as continuously assessment of the changes in heart rate and breathing;
- **Poor/failed transition** (floppy, pale, breathing inadequately or apneic, heart rate <60 min or undetectable) – the cord should be clamped immediately, continue with ventilation and asses the changes in heart rate and breathing.

Newborn Life Support

Airway

Ensuring an open airway, aerating and ventilating the lungs, is usually all that is necessary. For this purpose, the newborn should be placed on his back, with the head in a neutral position. In floppy infants, pulling the jaw forwards (jaw lift) may be essential in opening and/or maintaining the airway and reducing mask leak. If having difficulty providing both jaw lift and ventilation, an oropharyngeal on nasopharyngeal airway should be used. Attention should be paid to airway obstruction from meconium, mucus blood cloths or vernix and aspirate if necessary.

Breathing & circulation

If the newborn is apneic, gasping or not breathing effectively, aim to start positive pressure ventilation as soon as possible - ideally within 60 seconds of birth. Give five "inflations" via face mask maintaining the inflation pressure for up to 2-3 seconds. Provide initial inflation pressures of 30cm H2O for term infants commencing with air. Start with 25cm H2O for preterm infants <32 weeks using 21-30% inspired oxygen (21% inspired oxygen for term infants). The heart rate should be checked (whether it increases or there is no response), as well as chest movements. If the heart rate rises and the chest rises, it means that ventilation is effective and, in that case, it should be continued with ventilation 30/min until the newborn starts to breathe adequately. If there is no response in terms of increased heart rate or adequate breathing, rechecking of the newborn's position, as well as ventilation techniques and/or ensuring a safe airway with a laryngeal mask or endotracheal intubation should be undertaken.

Table 1 – Approximate oral tracheal tube size by gestation (for approximate nasotracheal tube length add 1 cm).

Gestational age (weeks)	Length at lips (cm)	Internal diameter (mm)
23–24	5.5	2.5
25–26	6.0	2.5
27–29	6.5	2.5
30–32	7.0	3.0
33–34	7.5	3.0
35–37	8.0	3.5
38–40	8.5	3.5
41–43	9.0	4.0

For this purpose, it is recommended to use a video laryngoscope, and to check the position of the tube by all available methods (auscultation, etCO2 appearance, evidence of adequate ventilation through demonstrating adequate expired tidal volume (about 5-8mL/kg), visible evidence of chest rise or chest X-ray). As for the fraction of inspired oxygen, the following recommendations are given:

Term and late preterm infants 35 weeks - In infants receiving respiratory support at birth, begin with air (21%).

Preterm infants <35 weeks - Resuscitation should be initiated in air or a low inspired oxygen concentration based on gestational age:

- 32 weeks 21%,
- 28-31 weeks 21-30%,
- <28 weeks 30%.

In infants <32 weeks gestation the target should be to avoid an oxygen saturation below 80% and/or bradycardia at 5 minutes of age. Both are associated with poor outcome.

Regarding mechanical ventilation, CPAP (in preterm infants with spontaneous breathing) and use of PEEP of 5-6cmH2O are recommended. If even after 30 seconds of ventilation the heart rate is not adequate (<60/min or absent), chest compressions should be applied. It is recommended to use a synchronous technique, providing three compressions to one ventilation at about 15 cycles every 30 seconds and to use a two-handed technique for compressions if possible. The response should be re-evaluated every 30 seconds. If there is no response, vascular access and drugs should be considered. If peripheral venous access cannot be established, umbilical venous access or intraosseous can be used. Central venous access is sometimes required.

Drugs

Although medications are rarely needed, they should be considered when there is no adequate response to ventilation and chest compressions. The recommendations are as follows:

1. **Adrenaline**

- When effective ventilation and chest compressions have failed to increase the heart rate above 60/min;

- Intravenous or intraosseous is the preferred route - at a dose of 10-30micrograms/kg (0.1-0.3 mL/kg of 1:10,000 adrenaline [1000 micrograms in 10 mL]);

- Intra-tracheally if intubated and no other access available - at a dose of 50-100micrograms/kg;

- Subsequent doses every 3-5minutes if heart rate remains< 60/min.

2. **Glucose**

- In a prolonged resuscitation to reduce likelihood of hypoglycemia;

- Intravenous or intraosseous: 250mg/kg bolus (2.5mL/kg of 10% glucose solution).

3. **Volume replacement**

- With suspected blood loss or shock unresponsive to other resuscitative measures;

- Intravenous or intraosseous: 10mL/kg of group O Rh-negative blood or isotonic crystalloid.

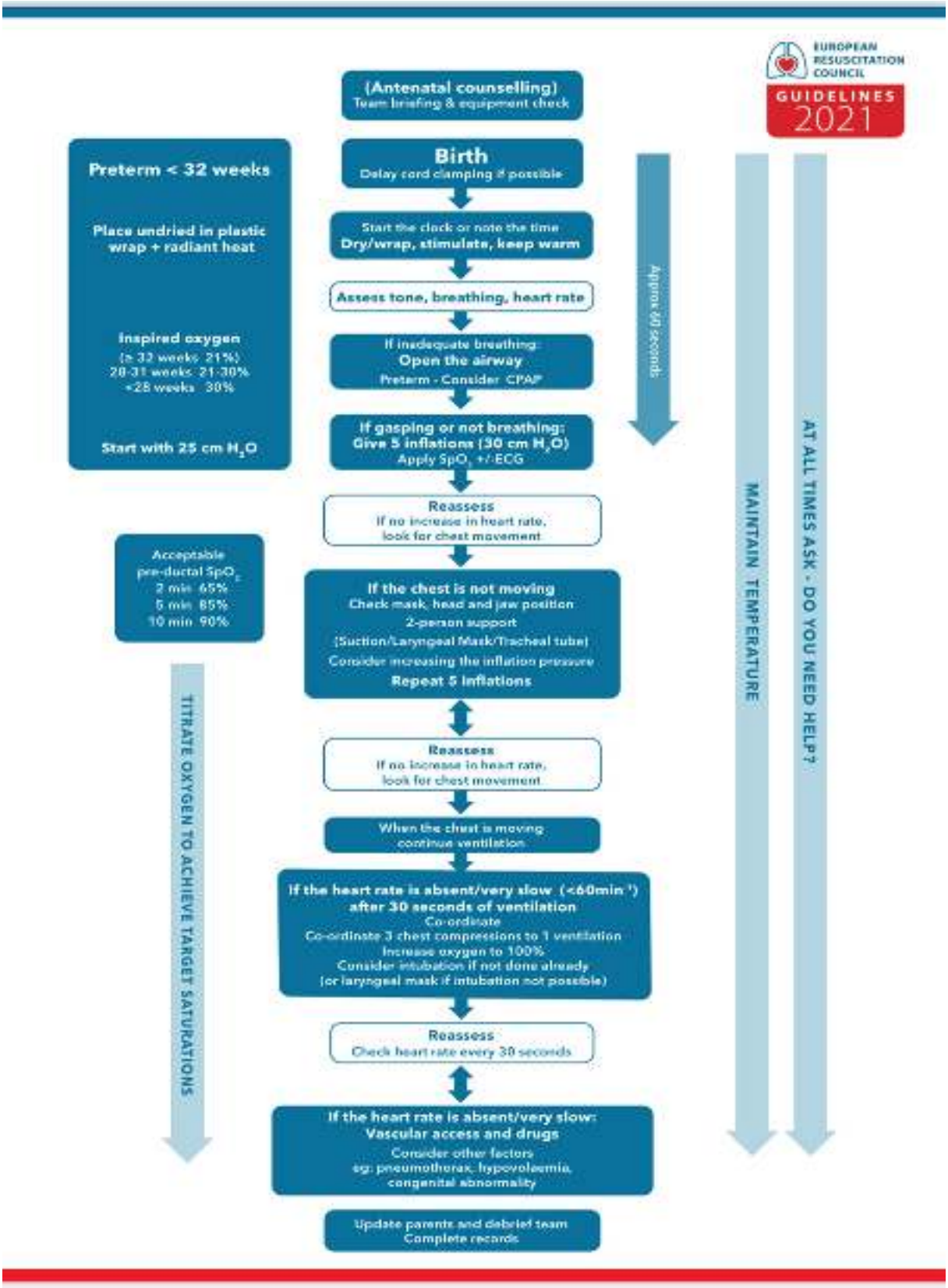
4. **Sodium bicarbonate**

- May be considered in a prolonged unresponsive resuscitation with adequate ventilation to reverse intracardiac acidosis;

- Intravenous or intraosseous: 1-2mmol/kg sodium bicarbonate (2-4 mL/kg of 4.2% solution) by slow intravenous injection.

5. **Naloxone** - In situations of persistent apnea

- Intramuscular - an initial 200 microgram dose may help in thefew infants who, despite resuscitation, remain apneic with good cardiac output when the mother is known to have received opioids in labor. Effects may be transient, so continued monitoring of respiration is important.


EUROPEAN RESUSCITATION COUNCIL
GUIDELINES 2021
(Antenatal counselling)
Team briefing & equipment check
Birth
Delay cord clamping if possible
Start the clock or note the time
Dry/wrap, stimulate, keep warm
Assess tone, breathing, heart rate
If inadequate breathing:
Open the airway
Preterm - Consider CPAP
If gasping or not breathing:
Give 5 inflations (30 cm H2O)
Apply SpO2 +/-ECG
Reassess
If no increase in heart rate, look for chest movement
If the chest is not moving
Check mask, head and jaw position
2-person support
(Suction/Laryngeal Mask/Tracheal tube)
Consider increasing the inflation pressure
Repeat 5 inflations
Reassess
If no increase in heart rate, look for chest movement
When the chest is moving continue ventilation
If the heart rate is absent/very slow (<60min-1) after 30 seconds of ventilation
Co-ordinate
Co-ordinate 3 chest compressions to 1 ventilation
Increase oxygen to 100%
Consider intubation if not done already
(or laryngeal mask if intubation not possible)
Reassess
Check heart rate every 30 seconds
If the heart rate is absent/very slow:
Vascular access and drugs
Consider other factors
eg: pneumothorax, hypovolaemia, congenital abnormality
Update parents and debrief team
Complete records
Preterm < 32 weeks
Place undried in plastic wrap + radiant heat
Inspired oxygen
(≥ 32 weeks 21%)
28-31 weeks 21-30%
<28 weeks 30%
Start with 25 cm H2O
Acceptable pre-ductal SpO2
2 min 65%
5 min 85%
10 min 90%
Approx 60 seconds
MAINTAIN TEMPERATURE
AT ALL TIMES ASK - DO YOU NEED HELP?
TITRATE OXYGEN TO ACHIEVE TARGET SATURATIONS

Post-resuscitation Care

When the newborn infant responds positively to resuscitation, post-resuscitation care follows. It should be placed in an intensive care unit with continuous monitoring of vital parameters. Among other things, it is important to monitor closely the following parameters:

- Blood glucose level – in order to avoid hypo/hyperglycemia,
- Body temperature - consider inducing hypothermia to 33-34^{0}C in situations where there is clinical and/or biochemical evidence of significant risk of moderate or severe HIE (hypoxic-ischemic encephalopathy).

When to withold the resuscitation?

In situations where there is an extremely high mortality rate (>90%), resuscitation is not recommended, but it is always indicated in conditions associated with at least 50% survival rate. In conditions where there is low survival (<50%) and a high rate of morbidity, and where the anticipated burden of medical treatment for the child is high, parental wishes regarding resuscitation should be sought and usually supported.

When to discontinue the resuscitation?

If the heart rate of a newborn term infant remains undetectable for more than 20 minutes after birth despite the provision of all recommended steps of resuscitation and exclusion of reversible causes, consider stopping resuscitation.

Conclusion

Newborn resuscitation demands a systematic and evidence-based approach outlined in the latest guidelines to optimize outcomes. Healthcare providers must stay updated with these guidelines, employing proper assessment techniques, effective positive pressure ventilation and appropriate interventions. Mastery of the skills, techniques and decision-making processes involved in newborn resuscitation is crucial for medical professionals to ensure the best possible outcomes for neonates in distress. By adhering to and implementing these guidelines, medical professionals can provide effective and timely interventions during this critical transitional period, ultimately improving neonatal survival rates.

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DRUG INTERACTIONS

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Abstract

Drug interactions can be described as the pharmacological influence of one drug on another drug, when administered in combination. Drug interaction can cause an increased or decreased effect of the drug, but it can also lead to a toxic effect. In daily practice in operating rooms and intensive care units, anesthesiologists routinely combine drugs. Interactions are usually divided according to the mechanism of occurrence and the most frequent are pharmacokinetic and pharmacodynamic. In pharmacokinetic interactions, the interactions are at the level of absorption, distribution, metabolism, or elimination processes. Such interactions are predictable, but their extent cannot be predicted. Pharmacodynamic interactions refer to antagonistic or synergistic action between drugs. It remains a challenge to teach clinicians how to combine these drugs in order to achieve and maintain optimal anesthetic and vital conditions, while minimizing side effects. A good understanding and knowledge of drug interactions can improve the ability to titrate multiple drugs more effectively.

Key Words: *anesthesiology, drugs, intensive care, interaction***.**

1. Introduction

The concept of drug combination has been known and used since ancient times to treat diseases and reduce suffering of people. In the process of anesthesia or treatment in intensive care units, doctors have to reach therapeutic decisions which routinely include administration of several drugs, and almost every day they face anesthetic-drug interactions or drug-drug interactions. Speaking with the language of statistics, between 46% and 90% of the patients in intensive care units are exposed to potential drug-drug interaction, and this percentage is twice higher compared to patients in other units (1).

Critically ill patients and anesthesiology patients differ from other hospital patients and outpatients for several reasons: very often these patients have a serious degree of injury or are in an advanced stage of a disease, in advanced age, with often present impeded or altered absorption, metabolism disorders, reduced kidney and liver function and polypharmacy, and hence these patients are more vulnerable to drug-drug interactions. On the other hand, since these patients are closely monitored, some adverse events from drug-drug interactions are more acceptable than in patients who are not subjected to intensive care or are in the operating theater because vigilant monitoring enables effective and timely risk management and safe treatment (2).

2. Definition and positive effects of drug interactions

A drug interaction occurs when one or more drugs influence on pharmacokinetics and/or pharmacodynamics of one or several other drugs.

In anesthesiology, a drug interaction is defined as an influence of one anesthetic over the behavior of another anesthetic.

Combination of drugs can contribute to enhancement, diminishing or onset of a new effect. New effects can be therapeutic, that is, the idea of combination – interaction of drugs is creation of positive effects by their mutual application, such as:

- Production of synergistic effect on the target,
- Diminishing the necessary drug dosage until it produces the same effect,
- Toxicity reduction,
- Decrease of incidence and number of side effects,
- Minimization or delay in development of resistance.

However, a drug interaction can also cause side effects. In intensive care patients, about 16% of all side effects are caused by drug-drug interactions and are associated with a longer hospital stay, higher morbidity and mortality and increased hospital costs (3).

3. Types of interactions

Examination and modeling of drug interactions is one of the priorities of modern pharmacology (4).

Due to concomitant administration, drug interactions can appear across different stages of drug action (4). Therefore, drugs can be subjected to physical and chemical interaction prior to administration and absorption or across the processes of different pharmacological phases: pharmacokinetics, with potential influence on absorption, distribution, metabolism and elimination, or pharmacodynamics, with alteration of pharmacological effects (4,5).

These different mechanisms of interactions can generate negative results, with increased toxicity or interference without the therapeutic effect, but also can be used as a strategy for useful interactions, with a potential to increase the pharmacological effect and reduce toxicity.

3.1.Pharmaceutical Interactions

Pharmaceutical interactions occur prior to drug administration, and they are changes in the physical-chemical structure of one drug affected bythe action of another drug when combined in the same solution whether in a bag, syringe, or an infusion system. This type of interaction provides information about drug stability and compatibility that is examined with chromatography (6).

Whenever two or more drugs are mixed for anesthesia or other treatment, or when those drugs share the same infusion line, the question about their compatibility must be raised.

The combination of remifentanil and propofol is very common in some medical institutions. Literature data report that stability of this mixture combining these two drugs depends on time, the proportion of remifentanil -propofol and the recipient. Thus, it can be concluded that remifentanil can be combined with propofol, but the above mentioned conditions have to be taken into consideration (7).

The mechanism responsible for pain at the site of propofol injection is mediated by the kallikrein-kinin pathway and bradykinin production, a process that can be inhibited by lidocaine. But is it possible to combine propofol and lidocaine in order to prevent such pain? Are these compounds compatible? Literature reports that adding lidocaine to propofol increases the diameter of the lipid molecules, which makes this mix physically and chemically unstable and poses a potential risk of pulmonary embolism.

Figure 1 illustrates the pharmaceutical interactions of the most commonly used drugs in anesthesia.

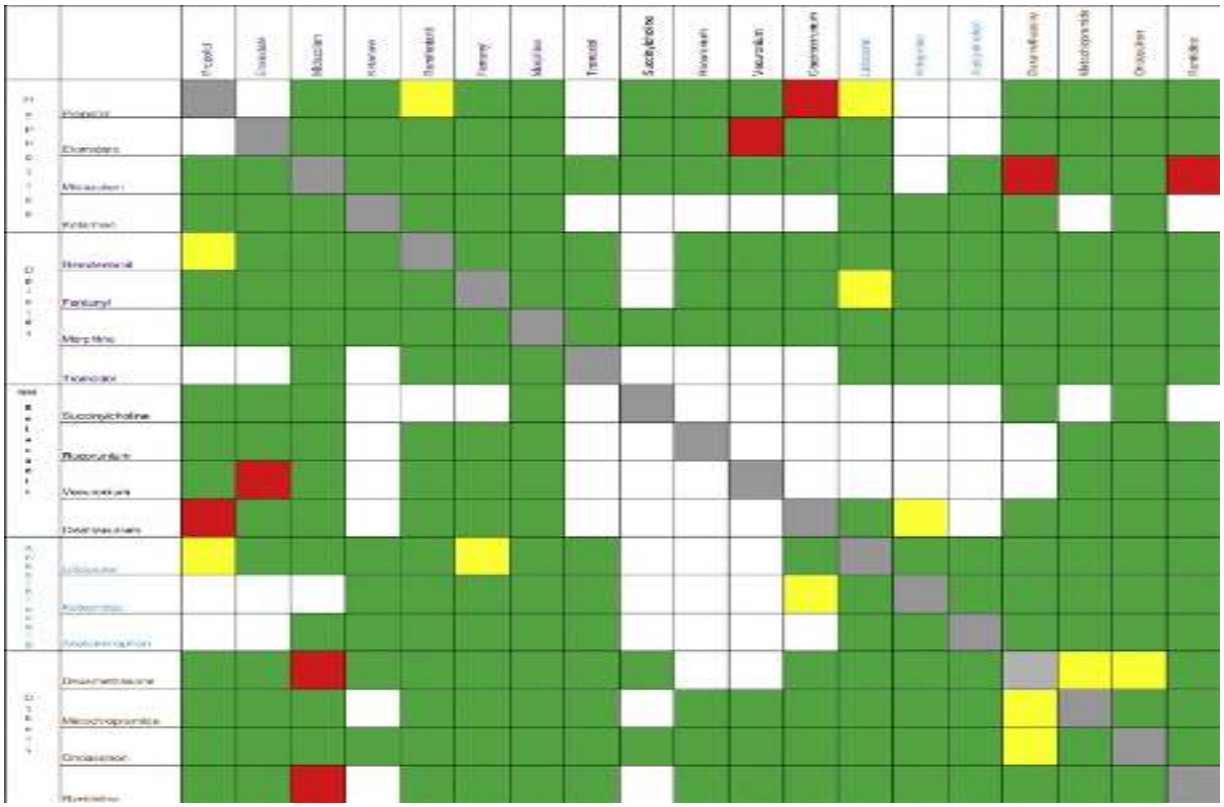

Figure 1. Pharmaceutical interactions of the most commonly used drugs in anesthesia.

Red box: incompatible; green box: compatible; yellow box: inconclusive [9].

3.2.Pharmacokinetic Interaction

Pharmacokinetics is officially defined as the measurement and interpretation of the changes in drug concentration in one or more parts in the organism in a unit of time, that is, it is mainly focused on drug plasma concentration.

Co-administration of drugs, herbal medicines and food can induce changes in the pharmacological bioavailability – drug concentration, described as pharmacokinetic interaction.

During pharmacokinetic interaction, the concomitant administration of one drug alters the absorption, distribution, metabolism and excretion of the other drug. Due to individual differences in these processes, pharmacokinetic interactions can be expected, but their intensity cannot be anticipated (10).

3.2.1Absorption

Absorption is defined as the passage of a drug from the site of administration into plasma.

The mainroutes of drug administration are as follows:

- oral,
- sublingual,
- rectal,
- application on other epithelial surfaces (e.g.,skin, cornea, vagina, and nasal mucosa),
- inhalation,
- injection.

Orally administered drugs are absorbed in the gastrointestinal tract at different sites with or without the help of different carriers, with passive or active transfer and at rate determined by the degree of ionization and liposolubility. The largest number of interactions at the level of absorption affects the absorption rate and, to a certain degree, the extent of absorption. Absorption rate is not important if the amount of the absorbed drug is not significantly changed. Delayed absorption can be clinically important in drugs with short life of half-elimination and when rapid maximum plasma concentration of the drugs is required. Very often, interaction at the level of absorption results in absorption decrease, not increase, and can be avoided if the application of two drugs is done in an interval of two to three hours.

The most significant mechanisms of a drug interaction at the level of absorption that would create conditions for changes in the absorption are: pH of the gastrointestinal tract, disorders in the intestinal microflora, motility and viscosity of the mucus, as well as pathological conditions of inflammatory, metabolic, neurological or autoimmune character.

Some drugs manifest instability in acidic media, such as penicillin G, erythromycin and digoxin, when variations in gastric pH influence the rate of drug degradation and bioavailability. In cases like this, pretreatment with omeprazole or an increase in pH will enhance the absorption (11).

Concurrent use of drugs and food containing bivalent metal ions can also change the pharmacological availability due to formation of insoluble, inactive complexes. The co-administration of norfloxacin with milk or yoghurt will reduce its bioavailability by 50%; this also refers to tetracyclines (11).

For example, sucralfate works by forming a barrier over the gastrointestinal mucosa, thus protecting it from ulcer development. It acts so as to reduce the bioavailability of fluoroquinolones by forming stable chelate complexes between aluminium in its molecule and fluoroquinolones and hence, absorption is reduced.

The rate of gastric emptying and intestinal motility define the rate and extent of the drug absorption (12).

Metoclopramide is a prokinetic that stimulates the serotonin 5-HT4 receptors, antagonizes the presynaptic inhibition of muscarinic receptors, and blocks the dopamine D2 receptors. Thus,

the release of acetylcholine leads to an increase in the intragastric pressure, which is responsible for acceleration of gastric emptying. When administered simultaneously with other drugs, metoclopramide tends to increase the absorption of other compounds because it exposes them more quickly to the intestinal absorption area (13).

On the other hand, opioids such as morphine, due to their action on opioid receptors in the myenteric plexus, and anticholinergic drugs such as atropine, by blocking the muscarinic receptors influence on reduction of motility and delayed gastric emptying. Both mechanisms tend to reduce the absorption of the concomitantly administered drugs (14).

Also, in conditions of hypovolemia or heart failure, transport through splanchnic circulation is reduced resulting in reduced drug resorption.

In case of intramuscular or subcutaneous administration, the absorption depends on the local blood flow, on drug ionization or lipid solubility to a great extent. For example, the administration of combined local anesthetic and vasoconstrictor will lead to reduced absorption of the local anesthetic and prolonged action. Transdermal route can be used for drugs that are highly soluble in lipids (e.g., fentanyl) where delayed absorption in the end creates permanent concentrations in the blood.

When anesthetic drugs are administered intravenously, problems with the absorption are avoided to a great extent. By using volatile anesthetics, the absorption can be under the influence of the gradient of the anesthetics' partial pressures in the alveoli and circulation, that is, ventilation-perfusion ratio or membrane pathology, but also of the ventilator parameters.

3.2.2 Interactions during Distribution

Distribution is the movement of a drug in the body. Once absorbed, the drug is distributed through systemic circulation to extra- or intracellular space until it reaches its target organ. If a drug from the beginning is in systemic circulation and then it is distributed to the other parts of the organism, then it is a one-compartment model. If a drug is first bound to a parenchymal organ and then is distributed to target sites, then it represents a two-compartment model, and achieving the full effect of the drug will be prolonged. With reference to volatile anesthetics and some intravenous drugs, one can talk of a three-compartment model, which is basically a depot of the drug in the organism (usually it is a fat tissue releasing a certain drug amount that goes to the effectors), and results in a prolonged recovery from the action of the anesthetic. Drug distribution is influenced by regional circulation, pH of the environment, drug chemical characteristics, drug lipid solubility, plasma protein binding and tissue binding. Regarding drug distribution, it is noteworthy that in this phase interaction can also happen, and one drug can change the distribution of another drug. The most common interaction in the phase of distribution is a result of the competitive relationship for the binding site of albumins or tissue proteins. The consequence is displacement of one drug and replacing it with another. Replacement of a drug at the binding site will quickly lead to an increase in concentration of the released drug, and this situation is followed by a compensatory increased metabolism and elimination of the free drug. This can result in a decrease of the total concentration of the displaced drug, but the free drug concentration remains similar to that before introduction of the other displacing drug. These interactions are usually clinically insignificant except in case of disordered metabolism or elimination, and clinical consequences include:

- toxicity due to transient increase in concentration of free drug before the steadystate is reached, or
- when the displacing drug additionally reduces the elimination of the first, then the free drug concentration is increased not only acutely but also chronically, which can lead to severe intoxication (15).

Secondly, drugs that diminish the heart minute volume can reduce perfusion of tissues included in redistribution of other drugs, thereby changing their extent of distribution. For example, reduced doses of propofol in presence of esmolol have been determined probably as a result of changes in the distribution.

3.2.3 Interaction at the Level of Metabolism

The most important clinical interaction includes the action of one drug on the metabolism of another drug. Metabolism is the process of biochemical drug modification for easier excretion from the organism. Liver plays the central role in drug metabolism, but this process can also be done by the kidneys, lungs, intestines, skin and placenta.

Drug metabolism is divided into two phases. Reactions of the first phase are oxidation, hydrolysis and reduction, whereas conjugation with glucuronic and sulphate acid are reactions of the second phase. Reactions of the first phase take place in the liver mediated by cytochrome P450 and CYP enzymes as the most important enzymes in drug metabolism. Drug interactions can happen due to induction or inhibition of cytochrome P450, which consequently affects changes in the metabolism of one drug. Therapeutic effects of enzyme induction or inhibition depend on pharmacological characteristics of a drug or its metabolites. If one drug is metabolized with cytochrome P450, and another drug inhibits or reduces enzyme activity, then plasma concentration of the first drug remains high for a longer period and their inactivation is delayed. The result of such interaction is prolonged therapeutic response that consequently increases the risk of toxicity. Inhibitory drugs have a competitive feature of binding to cytochrome P450 creating a stable complex that prevents binding of other drugs to cytochrome. Midazolam is a drug that is commonly used as a preoperative sedative, with variable behavior and influence on the metabolism of other drugs because of the inhibition of cytochrome P450 3A4. In comparison with fentanyl, midazolam reduces norfentanyl production by almost 95%. With reference to propofol, metabolism disorder has been reported and its increase in the blood concentration byaround 25%. Such changes in drug metabolism will probably cause events such as depression, hypotension and bradycardia. These events can likely be prevented if these interactions are taken into account. Other drugs that are frequently used and have influence on this enzyme as inhibitors are: dexamethasone, prednisolone, ketamine, antidepressants and alfentanil, amiodarone, alopurinol, ciprofloxacin, diltiazem, isoniazid, intraconazole, metronidazole, omeprazole, oral contraceptives, etc. Theinhibition of cytochrome P450 enzyme depends on the applied dose of the inhibitory drug, and the inhibition starts when minimally inhibitory drug concentrationin the liver is achieved.

If, on the other hand, drugs cause an increased enzyme activity, then concentration of the first drug rapidly reduces and fast inactivation happens. Drugs that are enzyme inducers are rifampicin, barbiturates, phenytoin and carbamazepine. Enzyme induction results ina reduced pharmacological effect of the drug except in cases when metabolites are pharmacologically active. The process of induction depends on the applied drug dose – inducer (16).

3.2.4 Interactions that Affect Excretion

Drugs can be eliminated from the body by excretion (for e.g., kidney excretion of sugammadex, and kidney and biliary excretion of rocuronium), biotransformation (for e.g., liver metabolism of propofol), or spontaneous degradation (for e.g., Hofmann degradation of cisatracurium).

The process of excretion consists of final elimination of compounds in unchanged form or biotransformed into highly polar metabolites. This process can occur via different routes such as sweat, tears, breast milk, bile, saliva, urine or in a gaseous form via the lungs.

Biliary elimination has to be emphasized since many hydrophilic drug conjugates are concentrated in the bile and are transported into the small intestine and are again regenerated into the active form of the drug that can be reabsorbed, hence, the cycle repeats (enterohepatic circulation). As a result of this process, a reservoir of the recirculating drug is created, which can prolong the action of the drug.

Kidney excretion is the principal way responsible for the elimination of majority of drugs and metabolites. However, any change in the drug binding to proteins and consequently change in its filtration, inhibition of the active tubular secretion, changes in the urine flow and changes in urine pH, are mechanisms by which one drug affects the rate of kidney excretion of another drug (15).

In this context, drug ionization can vary according to urine pH; acidic drugs display increased excretion in basic urine and basic drugs in acidic urine. This characteristic can be used as antidote strategy in cases of intoxication with phenobarbital, for e.g., when sodium bicarbonate is administered for urine alkalization and phenobarbital elimination (17).

3.3Pharmacodynamic Interactions

Drug pharmacodynamic interactions occur when the pharmacological effect of one drug has been altered by the effect of another drug in a combined regimen at the site of its action or by physiological mechanisms. There are three different types of interaction: additive, supra-additive (synergism) or infra-additive (antagonism).Additive interactions are present when two or several drugs with similar mechanisms of action are administered, and the effect of such combination is equal to the expected one by summing their effects. Additive behavior is typical for hypotonic agents and their concomitant use results in an increased number of adverse events because each individual action is not being enhanced, but, on contrary, it is replaced. This type of interaction can be seen when administering sevoflurane and propofol simultaneously.

Synergistic interactions appear when the combination of drugs results in a significantly higher effect in comparison to the expected one for the addition of the effects. This type of interaction is ideal for practicing anesthesia because the necessary dose of two drugs concomitantly administered is lower in comparison to individual separate drug doses. In other words, the effect of the drug is improved when both drugs are present.

The necessity of building synergistic models in anesthesiology imposes inclusion of drugs that act on different receptors and that such drugs would cover the complete hypnosis spectrum in case of hypnotic agents or complete analgesic spectrum in case of opioids. At this point, the risk of using drugs with poorly differentiated pharmacodynamic profiles to reach the expected goal has to be emphasized. For example, when speaking of dexmedetomidine, an α2 agonist receptor, as a drug with increased interest for application in anesthesiology and intensive care, it does not meet all characteristics of a hypnotic agent, nor those of an analgesic agent; it is unable to cover the complete spectrum of hypnosis of analgesia. What does that mean then? In case of requiring a deep hypnosis, its poor efficacy requires the addition of another hypnotic agent. The same principle is valid for analgesia.

Antagonistic or inhibitory interactions occur when the combination of drugs results in a lower effect than the excepted one by the summation of effects (18,19).

Types of pharmacodynamic interactions and examples are shown in Table 1.

Table 1. Types of pharmacodynamic drug interactions.

Interaction	Combined effect (C) compared to summing individual drug effect	Examples of favorable outcome	Examples of unfavorable outcome
SYNERGISM	C>A+B	**Aminoglycosides + Penicillin** Penicillin is a bactericidal antibiotic that kills bacterial cell wall that also enhances aminoglycoside transport into the cell and its bactericidal effect.	**Barbiturate + opioid agents** Both groups cause depression of the CNS acting on different target (tissues), but cause similar effects that are thus enhanced: sedation and respiratory depression.
ADDITIVE	C=A+B	**Aspirin + Acetaminophen** Acetaminophen has no anti-inflammatory effect but enhances the antipyretic and analgesic effect of Aspirin.	**Macrolides + Quinolones** Both antibiotic groups might cause heart arrhythmia.
ANTAGONISM	C<A+B	**Opioids + Naloxone** Naloxone as an opioid receptor agent blocks the effects of opioids in case of acute poisoning, i.e., respiratory depression.	**Warfarin + VitaminK** Added vitamin K impairs anticoagulation that is being maintained by Warfarin. This can lead to insufficient or unsuccessful anticoagulant therapy which shortens INR.

3.4. Thermodynamic Interaction

Thermodynamic interaction is an indicator of a drug-receptor interaction at a molecular level and shows the processes of affinity and intrinsic activity. Affinity and intrinsic activity are two separate steps in creating receptors' pharmacological response under the influence of drugs. Affinity is the strength of a drug to bind to its receptor. Intrinsic activity is the ability of a drug to activate the receptor to which it is bound, but some drugs differ in their potentials for activation depending on the tissue they are located although the receptors are same. When two drugs act on the same receptor and are simultaneously administered, the affinity coefficient (Ki) shall be considered in order to establish which of the two drugs will preferably bind to the receptor regardless of the internal activity. The concept of affinity is based on the concept of power, when the concentrations of both drugs are high, the saturation of the receptors by the higher affinity drug will prevail. A more potent drug usually has high affinity for the receptors, and so it binds

to a significant number of receptors even if administered in a lower concentration. Using several drugs that act on the same receptor is not advised and is outdated; it would be like using both captopril and enalapril for blocking angiotensin. These recommendations cannot be overlooked even in the case of opioids administered simultaneously when their mechanism of analgesia prevails over the same receptor. Therefore, the concept of affinity is probably the most important concept when multimodal anesthesia is applied. Based on the concept of multimodal anesthesia, it would be ideal to block our target from different points or regimes. Figure 2 illustrates the concept of multimodal anesthesia.

Figure 2. Multimodal anesthesia concept. Left: multimodal anesthesia, different drugs requiring different receptors (remifentanil R, propofol P and lidocaine L). Right: unimodal anesthesia, several drugs requiring one single receptor (remifentanil, fentanyl and methadone), the drug binding to the receptor would be that with the highest affinity [9].

Based on severity, drug interactions can be classified as:

- Major – the interaction may be life-threatening or can cause permanent impairment;
- Moderate –deterioration of a patient's clinical condition can be developed, or a patient's prolonged hospital stay that may require additional care;
- Minor – the interaction can be unpleasant, but not medically harmful.

Table 2 presents the pair of drugs, degree of severity as a consequence of their interaction.

Table 2. The most common prescribed pair of drugs with drug-drug interactions, severity and mechanism of interaction (20).

Drugs	**Severity**	**Mechanism of interaction**
Fentanyl - Midazolam	Major	Increases depression of CNS.
Dopamine -Noradrenaline	Moderate	Increases blood pressure and heart rate.
Adrenaline -Noradrenaline	Moderate	Increases blood pressure and heart rate.
Fentanyl - Fluconazole	Moderate	Increases the serum concentration of Fentanyl.
Acetylsalicylic acid -Enoxaparin	Moderate	Moderately increases the anticoagulant effect.
Midazolam Morphine	Moderate	Increases depression of CNS.
Adrenaline - Dopamine 1	Moderate	Increases depression of CNS depression.

Fluconazole - Midazolam	Moderate	(May) Moderately increase(s) the serum concentration of Midazolam.
N-acetyl cysteine NTG	Minor	Increases vasodilation effect of NTG.
Clarithromycin - Midazolam	Major	Increases the serum concentration of Midazolam.
Furosemide - Morphine	Moderate	Reduces the therapeutic effect of Furosemide.

4. Software programs for drug interactions

Drug-drug interactions are a significant problem. It is difficult to remember all drugs and their possible clinically important interactions. Software programs can help in avoiding or reducing the harmful effects of drug interactions. There are many programs, but the most significant are: ePocrates Rx, Tarascon, Pharmacopoeia Deluxe, the mobile PDR, Mobile Micromedex, Lexi-Interact, iFacts, the Medical Letter's Handbook of Adverse Drug Interactions, Mosby's Drug Consult Software and Clinical Pharmacology on Hand.

These programs have to meet the following basic characteristics: sensitivity, specificity, positive predictive value and negative predictive value.

Sensitivity is defined as the ability of the software program to recognize interaction drug pairs that are clinically important.

Specificity is defined as the ability of the software program to ignore interaction drug pairs that are not clinically important.

Positive predictive value is the probability that interaction recognized by the software program is defined as a drug interaction clinically important.

Negative predictive value is the probability when the software program ignores a drug interaction; it is defined as not clinically important.

Studies have assessed iFacts and Lexi-Interact software programs to be the most competent and comprehensive. Software programs can be of great help to health professionals, but they cannot be the unique or single information about drug interactions. Drug software programs have many limitations, and the main drawback is the inability for individualization because an interaction between two drugs does not depend solely on those two drugs, but also on a patient's condition and surrounding factors. It is necessary to develop new programs.

Lexi-Interact is a complete program for retrieval and analysis of interactions between drugs, food and alcohol. When entering the drug data (keywords), interactions can be anticipated, and each possible interaction is defined with a level of clinical importance. Levels of clinical importance are assigned large letters from the alphabet - A, B, C, D and X (Table 3) [21,22].

Table 3. Categorization of drug interactions in Lexi-Comp®Online program.

Grade/level of clinical significance	**Procedures**	**Description**
A	No known interactions.	Data show neither pharmacodynamic nor pharmacokinetic interactions between the chosen drugs.
B	No intervention is necessary during treatment.	Data show potential interaction between the chosen drugs. There is little or no evidence of the existence of a clinically significant interaction as a result of concurrent use of drugs.
C	Necessary follow-up of a patient throughout the treatment period.	Data show that the chosen drugs can have clinically significant interaction; the benefits of simultaneous use of these drugs overweigh the risk. Monitoring patients is indispensable in order to recognize on time the possible negative events. A small number of patients may require dosage adjustment.
D	Eventualrequirement for therapy adjustment.	Data show that both drugs can have a clinically significant interaction. Each patient has to be assessed whether the concomitant use of the drugs overweigh the risk. Procedures are to be undertaken in order to estimate the use and minimize toxicity resulting from simultaneous application of those drugs. Procedures include patient's monitoring, dosage adjustment, selection of alternative drugs.
X	Avoiding the combination.	Data show that both drugs can have a clinically significant interaction. The risk associated with concomitant use of these drugs is higher than beneficial effect in majority of cases. The combination of these drugs is mainly contraindicated.

5. Conclusion

The critically ill population and anesthesiology patients are a particularly vulnerable category of patients. A combination of drugs is necessary for their successful treatment. A good knowledge of the administered drugs and their interactions, as well as continuous monitoring of patients will result in successful treatment.

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REVIEW ARTICLE *UDK: 618.3-085.2.03 618.63-085.2.03*

DRUG CHOICES IN PREGNACY AND BREASTFEEDING

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Abstract

More than 50% of pregnant women use medications during their pregnancy. On the other hand, women who are breastfeeding even when they are sick, ask doctors weather it is safe to take medication during breastfeeding. In both cases using medications is possible if it is necessary and approved by doctors. If a woman is planning her pregnancy, and she uses medications, she must consult her doctors weather it is safe to take her therapy. If the drugs that they are using are harmful for fetus or babies, women should take contraception until therapy is substitute with safe medications. Smoking and drinking must be stopped during pregnancy and breastfeeding. Nevertheless, there are more and more women who are using medications during pregnancy.

Key Words: *breastfeeding, medications, pregnancy, toxicity.*

The incidence of congenital malformation that are connected to taking medication during pregnancy is 2-3%. Medications are reaching fetus through placenta.

Drags are affecting fetus by several mechanisms:

1. They can directly damage fetus or cause abnormal development of some organs, and that can lead to congenital malformations;

2. They can change placental functioning by narrowing of some blood vessels, and that can lead to decreased blood flow in placenta. Decreased blood flow leads to impairment in fetal growth and development, and very often these babies are with smaller weight;

3.Some drugs can cause contraction of uterus and this condition leads to decreased nutrition of the fetus. Contraction of some parts of the uterus can lead to generalized contractions and prethermal delivery.

Table 1. Influence of medications on fetal development in different phases.

Time frame	**Possible effect of the medication**	**Fetal condition**
20 days after fertilization	Death or no effect	Fetus resistant on congenital malformations

3-8 weeks after fertilization	No effect, Spontaneous miscarriage, Congenital malformations, Permanent damage that is not very significant, but in time it becomes more visible.	Organ development, Congenital malformations.
Second and third trimester	Changes in development and function of organs and tissues that are already developed.	Finished organ development.

Table 2. FDA Pregnancy Categories.

Pregnancy category	**Category descriptions**
A	Adequate,well-controlled studies in pregnant women hadnot shown an increased risk of fetal abnormalities in any trimester of the pregnancy, Animal NA.
B	Human No adequate,well-controlled studies in pregnant women AND Animal No evidence of harm to the fetus OR Human Adequate,well-controlled studies in pregnant women had not shown an increased risk of fetal abnormalities in any trimester of pregnancy, Animal Studies have shown adverse effects.
C	Human No adequate,well-controlled studies in pregnant women AND Animal studies have shown no adverse effects, Humans No adequate well-controled studies in pregnant women, Animals no study have been conducted.
D	Adequate well-controlled or observationalstudies have demonstrated a risk for fetus.However, the benefits of therapy may outweight a potential risk .For example, a drug may be acceptable in life-threatening situation or serious diseases for which safer drugs cannot be usedor are ineffective.
X	Adequate well-controlled or observational studies in pregnant women has demonstrated positive evidence of fetal abnormalities or risk.The use of the product is contraindicated in women who are or may become pregnant.

There are drugs that are extremely toxic for the fetus and they should never be given to a pregnant woman, and they can cause terrible malformations. Such is a case with Thalidomide.On the other hand, there are medications that cause malformation in animals but have no effects on humans.

Meclizine - a drug used as antiemetic is such a drug. Also, there are medicaments that can be replaced with more secure ones, such is a case with Heparin which is more secure drug thanWarfarin.There are drugs who have teratogenic effect of the fetus even after stoppingof their consumption.Isotretinoin is a retinol derivate drug, that is used for acne problems, and can be stored in the fat tissue and it takes 2 weeks to be completely excreted from body.Women that use this drug are supposed to take contraception for 4 weeks after the last consummation of this drug.After these 4 weeks, they can start planningtheirpregnancy.

Anxiolytics -Diazepam if taken in late pregnancy, can cause irritability and increased reflexes in newborns.

Antibiotics –Fluoroquinolones can cause abnormalities of bones and junctions of the fetus. Nitrofurantoin- in women with G6PD can cause rupture of the erythrocytes. Streptomycin can cause damage of baby's ear and hearing. Sulfonamides –when given in late pregnancy, can cause jaundice and fetal malformations. Tetracyclines– can lead to slower development of the bones and can cause brain,medulla spinalis damage and can lead to development of spina bifida.

Antihypertensive drugs (angiotensin -converting -enzyme) when taken in late pregnancy, can lead to kidney malformations, can cause decrease in amniotic fluid, and can give malformation of the face,legs, arms and lungs of the fetus. Beta blockers decrease heart rate of the fetus, can cause hypoglycemia and decreased development of the fetus. They cause hypotension in pregnant women. Calcium channels blockers can cause decelerated growth of the fetus. Thiazides are diuretics and they lead to decreased level of – Na, K,O2 in the cells and tissues of the fetus, and can cause decreased plates cells and can cause fetal decelerated growth.

Analgesics NASID - Naproxen, Ibuprofen, Aspirin, taken in large doses in the first trimester can lead to spontaneous miscarriage and later on they can cause early closure of ductus arteriosus, can cause jaundice and necrotizing enterocolitis and brain damage.In pregnant women they can cause bleeding during labor.

Vaccines -of live virus (rubeola and varicella) should be avoided in pregnant women. Other vaccines, such as against cholera, hepatitis, diphtheria, rabies, mumps, are given in pregnant women only if there is real danger of infection. Pregnant women should be protected and vaccinated against flu.

Psychoactive substances: Antidepressive dugs serotonin reap take inhibitors -(SSRI s) -paroxetine are often given during pregnancy because there is incidence of 7% to23 % of development of depression.The benefit is overcoming the damage of the drug. If pregnant women use Paroxetine, evaluating echotomography of the heart of the baby should be done regularly. Antidepressants can cause addiction in newborns. To prevent that, doses of these drugs should be decreasedin the last trimester. If the symptoms of depression are significantly worsened, antidepressants should be taken in normal doses. Not treated depression can lead to postpartum severe depression.

Cigarettes - 20% of pregnant women smoke during pregnancy although they know that nicotine is bad for babies and can cause decrease in weight. Congenital malformations of the heart, brain and face are more frequent in pregnant women who smoke. SIDS (sudden infant death syndrome) is syndrome that is more frequent in babies whose mothers are smokers. Placenta previa, abruptio placentae, early delivery infection of uterus, spontaneous miscarriages and premature born babies are more common in babies of mothers who smoke. Usually, these babies have weaker physical and psychological development and have episodes of strange behavior. These changes result of increased Carbon monoxide and nicotine levels. Carbon monoxides decrease oxygen delivery to organs and tissues. Nicotine on the other hand can cause spasms of blood vessels, and that can lead to decreased blood delivery of oxygen.

Alcohol -Women who regularly drink have twice more incidence for abortion and, they have babies with decreased weight. Fetal-alcohol syndrome is the most severe complication, and it occurs even in women who drink couple of glass of alcohol every day. This syndrome is manifested in congenital malformations of the face, impairment of brain development, behavioral and intellectual disorders of the child.

Caffeine- Consuming one cup of coffee daily does not interfere with the development of the baby. Caffeine is present not only in coffee but also in soda drinks, chocolate even in some dugs. The caffeine transfers the placenta easily, stimulates the heart in fetus and decreases iron absorption. Drinking 7 cups of coffee daily can decrease birth weight, can cause spontaneous miscarriages, and increases the percentages of stillborn babies.

Consuming the forbidden –illegal substances opioids, marihuana, cocaine, amphetamine, leads to higher incidence of infectious diseases including HIV, behavioral disturbances, the baby's addiction of opioids in newborn babies. These women have higher incidence of stillborn and spontaneous miscarriages.

Drugs during breastfeeding -Mothers who must take some medication during lactation period usually ask weather that drug is safe for her child and weather they can continue to breastfeed their babies. The answer depends on whether the drug enters the milk, whether is absorbed by the baby, how that drug has influence on that baby, how much of the milk baby is consuming, how that drug influences the baby. How much milk the baby is consuming,depends on how old is the baby and weather the baby has additional food intake.

Some medications like epinephrine, heparin, insulin, do not pass blood/milk barrierand it is suggested that these drugs are safe to be consumed by the mother. Some drugs enter the milk, but in very small quantities and so they can not cause damages in babies. But some medications like gentamicin, kanamycin, streptomycin, tetracycline, enter the mother milk, but the baby is absorbing them very little.

Mostly, the drugs that does not need prescriptions are considered to be safe to be taken during breastfeeding. Exceptions are antihistaminic. Aspirin and salicylates, if they are taken for long period of time, are considered as not safe to be taken by women who are breastfeeding. Acetaminophen and ibuprofen, are considered safe if they are taken in regular doses.

Antihypertensive drugs are considered safe to be taken during breastfeeding. Beta blockers can be taken during breastfeeding, but the baby needs to have regular and frequent controls so that we can have a prompt reaction if bradycardia and hypotension occur.

Warfarin can be taken by women who are breastfeeding. Exception is if the baby is bornas premature. Caffein and tefillin can be consumed by mothers who are breastfeeding, but checkups should be done regularly if irritation or tachypnea occurs. Anxiolytics, antidepressants, which are given as regular therapy, demand that the baby should be under control. These drugs remain in body for a long period of time, so babies in the first months of their lives could be affected, especially their nervous system. Benzodiazepines can lead to lethargy, somnolence and weight loss. Babies eliminate phenobarbital very slowly so this drug can cause somnolence. Therefore, dose should be diminished. Drugs that should not be used in breastfeeding period are amphetamines, chemotherapy drugs, chloramphenicol ergotamine lithium, radioactivesubstances, and some illegal ones.

Anesthesia for non-obstetric procedures in pregnant women.

In 1-2% of the pregnant women sometimes operation must be performed. The most frequent causes for the operations are appendicitis,torsion of the ovaries and trauma. Regional anesthesia is the first choice when that is possible. Gynecologists and neonate-pediatrists should be consulted. NSAID should be avoided because of the risk of premature closure of ductus arteriosus. It is recommended the low doses of aspirin to be given. From 15thto 56th day of development of human embryo, is the most sensitive of teratogenic substances. Although studies are incomplete, sedatives, hypnotics and opoids don't have damaging effects on embryo as it was considered before. Benzodiazepines are not teratogenic if they are used once during pregnancy, but there is higher incidence palatoschisis after more frequent use of these drugs. Midazolam, opioids and propofol are drugs of choice for small gynecological interventions.

Breastfeeding and Anesthesia

Solubility of the drugs in lipids of the milk,and quantity of the milk that baby is consuming during one breastfeeding,aredefining the complete dose of the drug that is in the milk. The most of anesthetics are liposoluble. In the blood lipids are in 0,37%, in the milk 4.75and in the brain 10-12%. That means that the most quantities of the anesthetics are found in the brain of the mother. Lip solubilityindexis lower in the milk compared to those of the brain. That is why concentrations of the drugs is smaller in the milk then in the brain. Howie 2006, and Lang 2003, said that women who are breastfeeding, who after the operation are awake, are capable of breastfeeding their babies without any doubts. Women who are breastfeeding their babies after the operations usually are prescribed to take antibiotics analgetic.The quantity of the drug in the milk depends onthe milk/plasma index. If that index is smaller, it means that drug I is shorter period of time in the milk and is excreting faster.

Table 3. Milk/plasma.

Drug	**Milk/plasma index**	**References**
Lidocaine	0.17-0.35	Giuliani 2001
Aspirin	0.033-0.05	Findlay 1981
Paracetamol	1.0	Notarianni 1987
Naproxen	0.01	Spigset 2000
Ibuprofen	0.008-0.06	Spigset 2000
Indomethacin	0.01-1.48	Spigset 2000
Codeine	2.16-2.46	Spigset 2000
Morphine	2.45	Spigset 2000
Pethidine	0.68-1.59	Spigset 2000
Fentanyl	2.10	Spigset 2000
Halothane	1.0	Cote 1976
Thiopentone	1.0	Anderson1987

Propofol	1.0	Schimitt 1987
Midazolam	0.15	Matheson 1990
Nitrazepam	0.27	Matheson 1990

Conclusion

With good communication between the doctor and mother, the security of the pregnant woman and mother of a newborn child is increased. Teamwork of the gynecologist, neonatologist and anesthesiologist, as well as good education are imperative for treating these patients.

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ALLERGIC REACTIONS IN INTENSIVE CARE UNIT

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Abstract

Allergic reactions are adverse effects as a result of the action of a certain antigen that causes an immune reaction. An antigen can be a drug, biological agent, toxin, chemical substrate or other substance to which a patient is exposed,and that exhibits a local or systemic reaction. The most severe reaction of hypersensitivity is anaphylaxis. In the process of causing anaphylaxis, a reaction is life-threatening and patients usually have skin, respiratory and gastrointestinal symptoms.

In certain number, allergic reactions also appear in patients in an intensive care unit. Recognizing and establishing a diagnosis in critically ill patients is quite serious challenge for two reasons: these patients have similar symptoms from another medical cause, and because they are usually sedated and on mechanical ventilation, which can mask the clinical picture. Treatment begins with quick recognition, diagnosis.and removal of the causative agent. The first step is to secure theairway. The second one is fluid resuscitation and blood pressure maintenance with or without vasopressors. The third part is pharmacological action on the resulting immune reaction.

Key Words:*allergic reactions, anaphylaxis,drugs, hypersensitivity.*

Introduction

Allergic reactions are side effects caused by a certain antigen that causes an immune reaction. An antigen can be a drug, biological agent, toxin, chemical substrate or other substance to which a patient is exposed, and that exhibits a local or systemic immune-predicted reaction.

The most severe reaction of hypersensitivity is anaphylaxis. In the process of causing an anaphylactic reaction which is life-threatening, it is usually manifests itself with skin, respiratory and gastrointestinal symptoms.

Milder forms of hypersensitivity reactions are more common with lower involvement of organ systems.

In the general population, the incidence of anaphylactic reactions ranges from 10 to 20 per 100,000 patients per year (1,2).

Side effects of the drug occur in 25% of hospitalized patients, but immunological allergic reactions are less than 15%.

In the intensive care unit, allergic reactions are difficult to diagnose because patients are sedated and on mechanical ventilation. In a critically ill patient who is intubated and sedated,

alrergic reactions are difficult to be distinguished from signs of septic shock if the main clinical manifestation is hypotension. Even when the diagnosis of anaphylactic shock is established, identifying the causative agent is a problem.

Pathophysiology of Allergic Reactions

Hypersensitivity reactions can involve all important components of the immune system, namely: cellular elements, immunoglobulins, complement and cytokines. The antigen reacts with cellular elements or immunoglobulins, causing the release of chemical mediators, which on the other hand include vasoactive amines (histamines, proteases), inflammatory leukotrienes, prostaglandins, platelet activating factor and the complement system. These mediators then interact with organ systems and cause clinical symptoms of allergic reaction and anaphylaxis (3).

Mediators of Allergic Reactions

Histamine is a low molecular weight amine stored in the granules of mast cells and basophils. It is released as a result of the action of a specific antigen.

When released, histamine increases capillary permeability, causes bronchospasm and vasospasm, and causes hypersecretion of mucous glands.

When released systemically, histamine acts within 1-2 minutes and is rapidly metabolized within 15 minutes.

Leukotrienes are metabolites of arachidonic acid, and also cause bronchospasm and vasospasm. Leukotrienes C4, D4 and E4 are produced by mast cells and basophils. These leukotrienes are more potent than histamine and have a longer-lasting effect on smooth muscles. Prostaglandins and thromboxane, also metabolites of arachidonic acid, are produced by fat cells. Prostaglandin D2 is the primary prostaglandin produced by mast cells and is a potential bronchoconstrictor and causes platelet aggregation and lysis (3).

Immunological Potential

The immunological potential of the antigen depends on the size. Low molecular weight antigens require binding to a specific carrier protein to be recognized by the immune system. In the case of penicillin G (356mol weight), it binds to circulating serum proteins in the form of a hapten which in turn has a strong immunological potential.

In the case of a biological agent, the immunological potential depends on the quality and type of the material.

Classification of Allergic Reactions

Type I- Allergic reactions mediated by IgE,

Type II- Cytotoxic hypersensitivity,

Type III- Allergic reaction with deposition of an immune complex,

Type IV- T-cell mediated allergic reaction.

Clinical Manifestations of Allergic Reactions in an Intensive Care Unit

Anaphylactic Reaction

An anaphylactic reaction is defined as a serious allergic reaction mediated by IgE. Anaphylaxis occurs suddenly, involves several organ systems, and can cause death (1,2). Clinical manifestations of anaphylaxis include urticaria, bronchospasm, hypotension, angioedema, laryngospasm, nausea, vomiting and others. In patients who have hypotension caused by anaphylaxis, they have a clinical picture of distributive shock, and we usually define it as anaphylactic shock.

Inflammatory mediators, including histamine, cause vasodilation and increased vascular permeability. The anaphylactic reaction occurs about 30 minutes after exposure to the allergen. The risk of death is greatest in the first few hours, especially if it is not promptly recognized and treated. If death occurs, it is usually the result of asphyxia from airway obstruction and collapse.

In the intensive care unit, it is challenging to recognize a patient with anaphylactic shock.

The diagnosis of anaphylactic reactions in critically ill patients in the intensive care unit is a real challenge. The first reason is that the symptoms that are a sign of an allergic reaction are present in critically ill patients as a result of other causes of the primary disease. The second reason is that the patients who are sedated on mechanical ventilation do not manifest the overall clinical specific picture of an allergic reaction. The occurrence of anaphylaxis in a sedated patient is mostly with altered symptomatology. If there is no dermatological reaction, it is very difficult to recognize it. The most common causes of anaphylaxis in intensive care units are drugs, biological material, vaccines, food, anesthetics, latex and less often some other environmental factors. In hospitalized patients, drug-induced anaphylaxis accounts for about 6% of all drug-induced side effects.

Anaphylactic reactions differ among themselves by the mechanism of occurrence and the mediators that participate in the process. These reactions are mostly caused by the activation of IgE as mediators, while the reactions caused by non-IgE mediators are created as a result of the release of mediators from mast cells and basophils. However, the symptoms and treatment of both types of allergic/anaphylactic reactions are the same.

Dermatological Symptomatology

Skin reactions are the most common hypersensitivity reactions. The most often these phenomena are mild and resolve spontaneously. Less commonly, some skin manifestations may progress and develop into potentially life-threatening reactions, such as toxic epidermal necrosis or Steven-Johnson syndrome. The pathogenesis of these phenomena is unclear, but it is assumed that they occur with the mediation of T-cells. The symptoms of these life-threatening dermatological

reactions are delayed and are usually several days or weeks after exposure to the antigen. They are characterized by an acute macular rash and ultimately necrosis of the skin and mucous membranes.

Many of the patients have eye complications and half of those who survive have permanent complications (3).

Respiratory Symptomatology

Respiratory symptoms that are caused by an immune mechanism are usually part of complex phenomena, such as anaphylaxis, but they can also be an independent phenomenon. Acute asthmatic reaction and rhinitis occur as reaction to hypersensitivity to drugs (aspirin, non-steroidal anti-inflammatory drugs), food additives or other allergens from the environment.

Allergic Vasculitis

Allergic vasculitis occurs as a result of deposition of immune complexes in small blood vessels. Clinical findings include skin lesions, purpura, joint pain, fever, urticaria, lymphadenopathy, etc. These phenomena are followed by elevated sedimentation. The systemic reaction is usually prolonged (1-2 weeks).

Vasculitis can involve multiple visceral organs, such as kidneys, lungs, liver, joints and central nervous system.

Very rarely the clinical picture can be severe, as glomerulonephritis, intestinal nephritis and various degrees of hepatocellular injury can occur as complications.

The most common cause is drugs: allopurinol, beta lactam antibiotics, sulfonamide, thiazide diuretics and phenytoin.

Angioedema

Angioedema is defined as a condition of swelling of the mucosa or submucosa, involving the larynx or pharynx. The swelling can spread to the mucous tissue of the face, gastrointestinal tract, lower limbs and genitals.

Angioedema can be the result of an allergic or non-allergic reaction. The life-threatening form of angioedema can be of genetic origin (C1 esterase inhibitor deficiency) or caused by the action of an antigen. The most common reasons that cause the release of bradykinin, which is the main mediator in the occurrence of angioedema, are ACE inhibitors. This type of drug-induced angioedema is mediated IgE type I hypersensitivity reaction that begins rapidly after drug administration. The incidence of angioedema caused by ACE inhibitors in the general population is about 0.1 to 0.7%. Differentiating between allergic and non-allergic angioedema in clinical practice is not always necessary since the therapy is the same.

Providing an airway is the main goal in angioedema. If there is a life-threatening obstruction, immediate tracheotomy is recommended. Out of the drugs that can be given at first, the choice is epinephrine, intravenously or in the form of an aerosol. Corticosteroids or antihistamines can be given, but they are not fast acting. Removal of the antigen is of crucial importance.

Acute Interstitial Nephritis

The acute interstitial nephritis is a form of allergic reaction that attacks the kidneys. Some drugs are described in the literature as potential triggers, and some of them are used in the intensive

care unit. These include penicillin, proton pump inhibitors and nonsteroidal anti-inflammatory drugs.

It is assumed that the drug acts as an antigen/hapten mimicking a renal antigen that triggers the formation of an immune complex which, on the other hand, is deposited in the renal parenchyma. The traditional triad of symptoms, fever, rash and joint pain is described for the first time in methicillin-induced glomerulonephritis. Other non-specific symptoms are pain and hematuria (4). The only way to make a definitive diagnosis is a kidney biopsy, a procedure that has its own risks. A kidney biopsy is indicated only in very severe cases when discontinuation of the drug considered to be the antigen/causing agent does not lead to improvement and if all other causes of renal failure are excluded.

Acute glomerulonephritis as an allergic phenomenon usually occurs after the administration of penicillin antibiotics. Other preparations (piperacillin), cephalosporins (ceftriaxone, cefotetan) and vancomycin are also possible causes of this allergic reaction. The onset of clinical symptoms of acute glomerulonephritis caused by drug allergy can range from several days to several weeks (5). The most often, this form of allergic glomerulonephritis is reversible, and the symptoms subside slowly over several weeks and months.

Proton pump inhibitors are the second possible cause of allergic acute glomerulonephritis. In a review study, 60 cases were described, out of which 59 were proven by kidney biopsy (6).

Corticosteroids are recommended as therapy for allergic glomerulonephritis. A dose of 1mg/kg of prednisone per day for 1-2 months is prescribed as therapy. Because of the possible side effects, corticosteroid therapy is acceptable only in very severe forms that do not improve after exclusion of the causative drug.

Therapy for Allergic Reactions

In the therapeutic strategies for allergic reactions, the most important thing is the rapid recognition and removal of the possible antigen/causing agent and supportive therapy.

Treatment for Anaphylaxis

The most important part of treatment is quickly establishing a secure airway. After providing an airway, adequate rehydration with fluids and maintenance of blood pressure, if necessary, with vasopressors is recommended. The third part is the pharmacological effect on the immune process in the already occurring allergic reaction.

The drug of choice is epinephrine at a dose of 0.3-0.5mg intramuscularly for adults and 0.01mg/kg for children, and this dose can be repeated every 5 minutes if necessary (7).

Fluid resuscitation should be started quickly and aggressively. If it is not possible to maintain the blood pressure, the inclusion of a vasopressor is recommended, and the most appropriate choice is vasopressin in case of an epinephrine-resistant reaction. Vasopressin has been described in the literature as quite effective in the case reports of anaphylactic shock (8).

The second recommended line of medication is corticosteroids and antihistamines. Systemic administration of corticosteroids has not been shown to be useful in the acute phase because the action of these drugs is delayed, after 4-6 hours. Corticosteroids may be useful in patients with bronchospasm, a history of asthma and in patients with severe dermatologic reactions.

Corticosteroid therapy and antihistamines are not helpful and are not recommended in non-immune angioedema.

Conclusion

Allergic reactions to drugs are manifested by a different clinical picture. In certain number, they also appear in patients in an intensive care unit. Recognizing and establishing a diagnosis in critically ill patients is quite a serious challenge for two reasons: these patients have similar symptoms from another medical cause and because they are usually sedated and on mechanical ventilation, which can mask the clinical picture.

Treatment begins with quick recognition, diagnosis, and removal of the causative agent. The first step is to secure an airway. The second is fluid resuscitation and blood pressure maintenance with or without vasopressors. The third part is pharmacological action on the resulting immune reaction.

Quick recognition and appropriate therapy lead to success, saving the patient's life and withdrawal of symptoms.

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REVIEW ARTICLE *UDK: 616.1-005.1-008.811.4-085.451.1*

CONTEMPORARY APPROACH IN TREATMENT OF HYPOVOLEMIC SHOCK

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Abstract

Acute circulatory failure or shock, regardless the etiology, is a life-threatening condition that needs prompt and adequate treatment, as it may progress to organ failure and death. Aggressive treatment of shocked patients must be early and appropriate in order to prevent or limit vital organ injury. Fluid resuscitation with vasopressor coadministration is the first line strategy in the first few hours when treating patients with shock. In bleeding patients with hypovolemic shock, fluid resuscitation and volume restoration are the mainstay of therapy. Giving 1.5L balanced fluids in the first hour and an antifibrinolytic in the first 3 hours after the injury is crucial for preventing tissue damage because of hypovolemia. Crystalloids should be used judiciously until blood products are ready for use with a rate of 1:1:1. Because no human studies exist to support the routine use of vasopressors in the trauma setting, in order to avoid further tissue hypoperfusion and hypoxia due to vasoconstriction, adequate fluid resuscitation should be a priority. Significant benefits of permissive hypotension resuscitation in terms of reduction of mortality due to exsanguination after traumatic hemorrhage were reported. In non-bleeding patients with hypovolemic shock when fluid resuscitation is insufficient adding a vasopressor is recommended. According to the guidelines for treatment of shock, Norepinephrine is the first-choice vasopressor in patients with hypovolemic shock, but when the resuscitation with fluids and vasopressors as a first line strategy is failing, an inotrope should be added to support the failing circulatory system. Recent recommendations for management of shock are strongly against the routine use of inotropes as a first line therapy in patients with hypovolemic shock, but when it comes to usage of inotropes as a rescue therapy dobutamine is the drug of choice.

Key Words: Hypovolemic Shock; Hemorrhagic Shock; Shock.

When it comes to the term "Shock", the first written descriptions were focused on the hemorrhagic shock. No matter the cause and the mechanisms of shock development, often, the shock progression leads to multiorgan failure as a result of an imbalance between the tissue demand and supply of oxygen and nutrients.

Definition and Types of Hypovolemic Shock

Hypovolemic shock is defined as a condition of inadequate organ perfusion caused usually by an acute loss of intravascular volume which reduces the cardiac preload and impairs the systemic circulation and microcirculation. From the clinical point of view, the simplest way of hypovolemic shock differentiation which could have significant therapeutic implications is when we could make a clear distinction in between a hemorrhagic hypovolemic shock and non-hemorrhagic hypovolemic shock. According to Adams HA et al. hypovolemic shock could be divided into four subtypes: (1) Hemorrhagic shock resulting from acute hemorrhage without

major soft tissue injury, (2) Traumatic hemorrhagic shock resulting from acute hemorrhage with soft tissue injury with release of immune system activators, (3) Hypovolemic shock in the narrower sense resulting from a critical reduction in circulating plasma volume without acute hemorrhage, and (4) Traumatic hypovolemic shock resulting from a critical reduction in circulating plasma volume without acute hemorrhage, due to soft tissue injury and the release of immune system mediators (1). The mainstay of hemorrhagic hypovolemic shock is the bleeding while the difference between hemorrhagic shock and traumatic hemorrhagic shock is that in the second group because of the trauma, besides the blood loss, tissue damage and consecutive inflammation, activation of coagulation is present as well, having significant impacts in the shock pathophysiology. The simple hemorrhagic shock is a condition of an acute bleeding from an isolated injury to a large blood vessel, gastrointestinal bleeding, nontraumatic vascular rupture as an aortic aneurysm rupture, obstetric hemorrhage as in patients with uterine atony, and hemorrhage in the region of the ear, nose and throat (vascular erosion). In cases of traumatic hemorrhagic shock, blood loss is accompanied with soft tissue injury which implies systemic inflammation activation, as well as coagulation cascade activation both aggravating the condition. Polytrauma is the typical example of this type of shock, which is usually caused by a road traffic accident and falls from a height. In these patients the presence of diffuse bleeding, hypothermia and acidosis could lead to life-threatening coagulopathy (2). In polytraumatized patients even minutes after the damage, a strong immune response of an unspecific inflammation is met which leads to leucocyte activation, release of enzymes, interleukins, prostaglandins and other bioactive substances which will increase the vascular permeability and promote capillary leak leading to further intravascular fluid loss. Tissue damage causes capillary and microcirculatory disruption and destruction of endothelial membrane-bound proteoglycans and glycosaminoglycans by itself, but is even more worsened by the systemic inflammatory response promoting a capillary leak syndrome, which makes the volume loss even more complicated. It should not be forgotten that the systemic inflammatory response following the tissue damage would have a negative impact on the vascular tone leading to vasoplegia. External and internal fluid loss with or without inadequate fluid intake are the main causes of hypovolemic shock in the narrower sense. Hyperthermia could lead to significant fluid loss with intravascular volume depletion, as well as persistent vomiting and diarrhea where electrolyte imbalance is ensured as well. Conditions as diabetes insipidus, traumatic brain injuries with cerebral salt wasting syndrome, hyperosmolar diabetic coma or diabetic ketoacidosis could lead to an uncompensated renal loss of fluids leading to severe hypovolemia. The phenomenon of third space shift and accumulation of large quantities of fluids could be a cause for hypovolemic shock as well, and this pathophysiological mechanism is met in patients with abdominal compartment syndrome, in patients with ileus, as well as in patients with liver cirrhosis. Traumatic hypovolemic shock without hemorrhage is met in patients with severe burns, chemical burns, deep ulcerative and necrotizing skin lesions, as well as in soft tissue inflammation.

Systemic Responses and Clinical Manifestations of Volume Loss

In patients with hypovolemic shock because of the volume depletion, a strong activation of the sympathetic nervous system with release of significant amount of catecholamines, as well as antidiuretic hormone is ensured to happen as a physiological compensatory mechanism. This is supposed to increase the vascular tone, as well as heart rate in order to preserve or even increase the cardiac output in order to maintain homeostasis. The release of antidiuretic hormone leads to increased fluid tubular reabsorption in order intravascular volume to be preserved. The main goal of every single compensatory mechanism is to sustain a normal perfusion pressure. When the cause of the hypovolemic shock is not treated adequately, further worsening of the circulation is expected where hypotension and tachycardia are seen in shocked patients followed by lowered

cardiac output, as well as low perfusion pressure leading to tissue oxygen demand and supply mismatch. The loss of adequate tissue perfusion and oxygen supply is the essence of cellular metabolism transformation from aerobic to anaerobic which leads to accumulation of acidic metabolic byproducts. When the cellular energy is wasted and ATP is not available anymore in an adequate amount, cellular swelling occurs because of Na/K pump disfunction. Systemic acidosis leads to further vasodilation and lowering of the systemic blood pressure, but also impairs the cardiac contractility as it has a substantial cardio depressive effect. Acidosis by itself, as well as inadequate oxygen tissue supply are significant trigger factors for activating a compensatory mechanism of tachypnea by stimulating the central and peripheral chemoreceptors to increase the respiratory rate in order to provide better tissue oxygenation. As in every state of shock the intravascular blood volume is centralized to the heart while significant splanchnic and renal vasoconstriction occurs, which leads to tissue hypoxia and absent urine production in order to preserve as much volume as possible. Poorly perfused tissues will fail in doing their own function, so elevated transaminases, acute renal failure, anxiety, coma or even death could occur if adequate treatment is not established as soon as possible (3).

Diagnostic and Therapeutic Approach in Patients with Hypovolemic Shock

Rapid diagnosis of hypovolemic shock, as well as discovering the etiology of volume loss is more than essential for preventing compensated shock to convert in decompensated irreversible state where there is a point of no return. In polytraumatized patients with visible bleeding, the diagnosis of hemorrhagic shock is more than obvious, but beside clinical signs and symptoms following all trauma protocols, an initial CT scan is a gold standard diagnostic method to reveal injury related internal bleeding. The most significant clinical signs of hypovolemic and hemorrhagic shock that should not be missed are hypotension where SBP is lower than 90mmHg, tachycardia, tachypnea, anxiety, agitation, lethargy, as well as coma, anuria, paleness, cold and sticky skin and delayed capillary refill. Pulse palpation is essential because low filled and filiform pulse or even absent pulse on peripheral arteries can be seen in different stages of shock. When one is uncapable to palpate a pulse on a radial artery, it is expected that SBP is lower than 80mmHg, lower than 70mmHg for femoral artery and lower than 60mmHg for carotid artery respectively (3). Early recognizing of hypovolemia and detecting its cause in terms of an absent hemorrhage is crucial for good outcome, because even in younger patients compensatory mechanisms could be exhausted perceiving multi-organ failure and death. Metabolic distortions were previously discussed, so elevated serum levels of lactate are more than expected. The serum lactate level should be examined in all shocked patients, not only for diagnosis of circulatory insufficiency, but rather for following up the evolution of shock, as well as a marker for evaluation of the therapeutic approach effectiveness (4).

The main therapeutic endpoint in patients with hypovolemic shock should be restoration of hemodynamics and preserving tissue perfusion through managing the volume status of the patient. In order to restore the hemodynamics as soon as possible, aggressive fluid resuscitation in a narrow timeframe should be achieved. Aggressive fluid resuscitation demands at least two wide bored peripheral veins (16G) and a Central Venous catheter which should be placed immediately. The resuscitation fluids choice and the infusion rate of fluids in hypovolemic patients are the state-of-art activities in every intensivist's daily practice. It is well known that even in actively bleeding patients, giving of blood products prevents death, but one cannot be concentrated only on fluid resuscitation, and rather multidisciplinary approach with surgeons should be established for bleeding termination on time achievement. Nowadays the old techniques

of emergency surgeries for definitive treatment of deeply shocked traumatized patients are exchanged with so called Damage Control Surgery. This term was adopted by trauma surgeons to describe the use of abbreviated surgeries to rapidly temporize life threatening injuries with delay of definitive repair after adequate resuscitation (5). Damage control surgery should be done as soon as possible after patient's admission (6).

When it comes to fluids, a vigorous choice has to be made in every patient depending on what type of hypovolemic shock is present. The American College of Surgeons has recommended the use of crystalloids (Ringers lactate or normal saline) in terms of fluid resuscitation of hypovolemic shock (7), while according to Healey MA et al. Ringer lactate is preferred over normal saline in patients with massive hemorrhage (8). In the previously cited study, it has been proven that patients with massive hemorrhage resuscitated with normal saline have experienced more physiologic derangements, as well as hyperchloremic metabolic acidosis was more frequently seen, which was also stated by another study (9). The usage of balanced crystalloids in initial dose of 10-20ml/kg with possibility of repetition of the dose until achievement of hemodynamic stability has been recommended (Recommendation level B) (10). Besides crystalloids in terms of fluid resuscitation of hypovolemic patients, colloids are recommended to be used for rapid volume restoration as well (7). There are studies that have proven that usage of albumin solutions in the initial resuscitation stage is not more effective than using crystalloids (11,12). One meta-analysis of 1,622 patients included in 26 randomized controlled studies, has provided a conclusion that the usage of colloids in the resuscitation process corelated with increased absolute risk for death of 4% (13). Back in 1980, Shoemaker et al., found an association between increased cardiac output, oxygen delivery and survival in critically ill surgical patients that underwent aggressive fluid resuscitation named and popularized as "supra normal" resuscitation (14-16). The supra normal resuscitation implies giving a large volume of crystalloids to drive a supra normal levels of cardiac output in terms of circulation improvement. Balogh et al., in 2003 have also found a strong correlation between the supra normal model of resuscitation and the frequency of abdominal compartment syndrome, multiple organ system failure and mortality (17). Later, it was found that infusing large volume of fluids in aims of resuscitation interferes and impairs a lot of biochemical processes and basic cellular functions possibly aggravating the condition of already shocked organs. Another study showed conclusions against the supranormal model of resuscitation (18). According to the retrospective study of over 3,000 trauma patients done by Ley et al., infusion of ≥1.5 liters of crystalloid in the emergency department was independently associated with increased mortality (19), while in another study it was proven that giving even more than 500ml crystalloids in the prehospital period is associated with increased mortality (20). It was believed that usage of hypertonic saline in early resuscitation of hypovolemic patients has plenty positive effects including improving cardiac output, microcirculation anti inflammation and alleviating endothelial injury and swelling, but later few studies came with a conclusion that using hypertonic saline in early stages of resuscitation has no benefit over normal saline neither dextran's and promotes coagulopathy as well (21-23).

Permissive hypotension is another significant task that should be discussed in terms of resuscitation of hypovolemic patients. Actually, the findings of Cannon et al., that bleeding has been minimized when hypotension establishment came first, before accomplishment of surgical hemostasis, was the essence of implementing a restrictive resuscitation model when it comes to usage of fluids. The main goal of permissive hypotension is to maintain the minimal necessary blood pressure in order to preserve vital organs perfusion without causing any harm. A large animal meta-analysis study confirmed that conducting a hypotensive resuscitation has better survival outcome over the normotensive resuscitation (24). Some studies found that delayed resuscitation is better than early prehospital resuscitation (25). Another study has shown that using the hypotensive approach with target value of 70mmHg for SBP is better than using a target value of 100mmHg SBP in patients with blunt trauma (26). Hypovolemic patients with

traumatic brain injury should be discussed as a special category where permissive hypotension may not be proper manner of resuscitation because the underlying brain injury that aims well preserved perfusion, in order to preserve the brain cell function. In patients with TBI the systolic blood pressure during the resuscitation should not be lower than 90mmHg, and early vasoconstrictor installation is recommended in order to sustain adequate cerebral perfusion pressure (27). According to the study of J. Silva et al., hypotensive resuscitation and conservative approach, with balanced crystalloids and blood, is the most appropriate approach in management of hemorrhagic shock (28). Despite all studies that suggest restrictive and conservative approach in ongoing fluid resuscitation on a hypovolemic patient, there is no clear statement about what is the lowest target value of SBP that has not any harmful consequences, neither how long hypotensive resuscitation should be performed without leading to any adverse events in the already shocked ones. When it comes to fluid resuscitation in patients with hypovolemic shock, it is worth mentioning that liberal resuscitation approach with crystalloids and artificial colloids increases hydrostatic pressure without repairing the endothelial injury leading to edema and edema associated complications.

In severely injured trauma patients with hypovolemic shock, because of major bleeding, it should be given 1 to 2g tranexamic acid during the early stage of resuscitation inside the first 3 hours of the bleeding onset according to the CRUSH II study (recommendation grade: A) and according to the study an early administration of Tranexamic acid safely reduced the risk of death in bleeding trauma patients, but treatment beyond 3 hours of injury is unlikely to be effective (29,30).

As it was previously mentioned, hypovolemic patients should be resuscitated with combination of crystalloids and blood products, but the threshold when to give blood and blood products may not be as clear as it seems. Actually, giving blood to the bleeding patient is recommended when more than 30% of the circulating blood loss will occur, or when the patient is still hypotensive despite administration of 2 liters of fluids (31). Because, when to give and how much to give, is a state-of-art practice. The National Institutes of Health, the American College of Physicians, the American Society of Anesthesiology, and the Canadian Medical Association created guidelines that recommend giving blood at a hemoglobin level between 6 and 8g/dl as a threshold for transfusion in patients without known risk factors (32-35). They strongly recommend no prophylactic blood transfusion in patients with hemoglobin levels greater than 10g/dl who are not expected to benefit from blood transfusion. A higher hemoglobin level maintenance (>10g/dl) is a desirable goal in actively bleeding patients, in elderly patients as well as in individuals who are at risk for myocardial infarction.

Achieving early bleeding control and termination, are stated as possible when plasma is given in the very early hours after the injury. There are few studies that recommend giving fresh frozen plasma early during ongoing resuscitation (36-39). According to the PROMMT and PROPPR studies lowering the plasma to RBC ratio during resuscitation of a hemorrhagic shock in the first 24 hours, as well as establishing a 1:1:1 transfusion ratio, increases survival rate in the first 24 hours. Also, these studies recommend early plasma transfusion in hypovolemic bleeding patients (40,41). It is believed that giving plasma in the severely injured patients with shock, may lower the early death because of improving the coagulopathy, mitigating thrombocytopenia and loss of coagulating factors, repairing the endothelial injury and glycocalyx debridement, as well as minimizing vascular endothelial injury and fluid translocation into the interstitial space. According to the previously cited studies thrombocytes are recommended while managing hemorrhagic shock in the early resuscitation period in the ratio 1:1:1 (40,41).

When guiding damage control resuscitation of patients with hemorrhagic shock, the usage of TEG and ROTEM in therapy adjustment is strongly recommended (42). Measuring the levels of

fibrinogen in the early phase of bleeding is recommended as well. American College of Surgeons Committee on Trauma recommends transfusing cryoprecipitate to maintain fibrinogen levels ≥180mg/dL, while European guidelines describe a minimum cutoff fibrinogen value of 150–200mg/dL.

Hemodynamic instability is a mainstay of shock, especially in patients with massive bleeding. Besides fluid therapy and blood products transfusion as a resuscitation measure when no response is seen, the need for early circulatory pharmacological support is more than essential. Norepinephrine is the first-choice vasopressor in patients with hypovolemic shock, but when the resuscitation with fluids and vasopressors as a first line strategy is failing, an inotrope should be added to support the failing circulatory system. Recent recommendations for management of shock are strongly against the routine use of inotropes as a first line therapy in patients with hypovolemic shock, but when it comes to usage of inotropes as a rescue therapy, dobutamine is the drug of choice (43).

According to the ESICM Consensus, blood lactate levels should be measured frequently because the shock is a dynamic process, and lactates change over time due to therapy. Despite measurement of lactate, the process of monitoring should consist of early type of shock recognition using echocardiography, estimating cardiac function to detect and prevent cardiac suffering in essentially non-cardiogenic shock states. Routine measurement of cardiac output for patients with shock responding to the initial therapy is not recommended, (Recommendation Level 1; QoE low), but measurements of cardiac output and stroke volume to evaluate the response to fluids or inotropes in patients that are not responding to initial therapy is recommended (Recommendation Level 1; QoE low C). Sequential evaluation of hemodynamic status during shock is recommended as well (Recommendation Level 1; QoE low C). In aim of personalizing therapy, it is not recommended using of CVP neither ventricular filling pressures as a sole method for guiding fluid administration, but rather using more than one dynamic variables for predicting and monitoring fluid responsiveness are recommended. Measuring of pulmonary artery pressure, as well as any other invasive procedures are not routinely recommended except in patients with right ventricular failure, but rather echocardiography as a non-invasive method of monitoring is recommended to be used as a monitoring tool (43).

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The guidelines for authors adhere to the uniform Requirements for Manuscripts submitted to Biomedical Journals: www.nlm.nih.gov.

Language and style of the manuscripts should be clear, simple to according the language, anesthesiological and medical taxonomy.

The manuscript has to be written in **English Manuscripts** should be written in **Microsoft Word** (*.doc format) with **Times New Roman** font and **size 12**. Margins on left, up and bottom should be 3 cm and right margin should be 2,5 cm.

The inline space should be 2. Do not use Bold or Italic letters for the whole text (only for parts that have to be emphasized). Manuscript should not exceed 10 pages (without the references).

Abbreviations and correct medical terms should be used according to the International Committee of Editors of Medical Journals (http://www.icmje.org). Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

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Manuscript should be organized in:

- Title page
- Text organized in IMRaD
- Acknowledgments
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Review articles, case reports, therapeutic and technological innovation, discussions, critics, impressions from meetings, information for international conferences and reviews of new books or variate may be written in different sequences and manners.

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The title of the manuscript written in CAPITAL LETTERS.

Authors Surname and Name initial (Jovanov J, maximum 6 authors), without academic or other titles.

Name and address of the institution where the authors come from whit the subscribed digits

Abstract in English. Abstract should include up to 250 words and should contain goals of the paper, important elements from the methodology, concisely displayed results and conclusion. Each abstract at the end must have **Key words:** in alphabetical order.

TEXT

- Introduction
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- Results
- Discussion
- Conclusion

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Introduction section should include a literature overview in relevance to the elaborated problem. In this sections 3-5 key references are citied and this section should not be longer than 2 pages.

Material and method sections includes detailed description of the performances in the research as well as the statistical analyses used. This section should include: time during what the research was conducted, type of the study, place of where the research was undertaken, randomization or stratification used (clear description of the examined groups), exclusion and inclusion criteria, method, analysis types, apparatus and instruments used and referent values of the examined features (in SI-International System units).

Results are displayed in simple manner with text, images, tables and charts that are submitted in the text where author wants to stand, titled and numbered appropriately. Additionally, on separate document all carts images and tables are send together with the manuscript.

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Discussion section emphasize the key finding of the actual research and compares these result to other relevant literature data.

Conclusion section should not include more than 150 words and shoul be drown from the relevant elaborated results.

Acknowledgment and Author contributions sections are displayed after the conclusion and before the reference section.

REFFERENCES

This sections include only the citied references. **The references** are listed in order of appearance in the paper and the citation is standard numbers enclosed in small brackets in the same line with the text ( ).

For each reference if more than three authors appear provide the names of the first three authors and followed by **et al.**

1. Examples:

Journal references:

Nirmala BC, Kumari G. Foot drop after spinal anaesthesia: a rare complication. Indian J Anaesth. 2011; 55: 78 – 79.

Lynch EP, Lazor MA, Gellius JE, et al. The Impact of Posoperative Pain on the Development of Postoperative Delirium. Anesth Analg 1998; 86:781-785.

2. Journal supplements:

AzmanJ, Frkovic V, Bilic L, et al. Korelacija I regresija. Acta Med Croat 2006;60 (suppl I):81-89.| 70 |

3. Books

Brown, D.L. Spinal, epidural, and caudal anesthesia. In R.D. Miller Miller's Anesthesia, 6th edition. Philadelphia: Elsevier Churchill Livingstone; 2005.p 98-198

4. Doctoral or master thesis

Jelisavac Cosic S. Urokinazni I tkivni aktivator plazminogena i njihov inhibitor u raku dojke (Master thesis). Zagreb: Farmaceutsko-biohemijski fakultet 2004, p.50

5. Electronic reference

Dag Stat. Mackinnon A. Available from: http//www.mhri.cdu.au/biostats.Accessed May 5th 2006.

Webster NR. The anaesthetist as peri-operative physician. Anaesthesia. http://dx.doi.org/10.1046/j.1365-2044.2000.01722.x

References used from abstracts are marked as (abstr)., and from letters with (letter)

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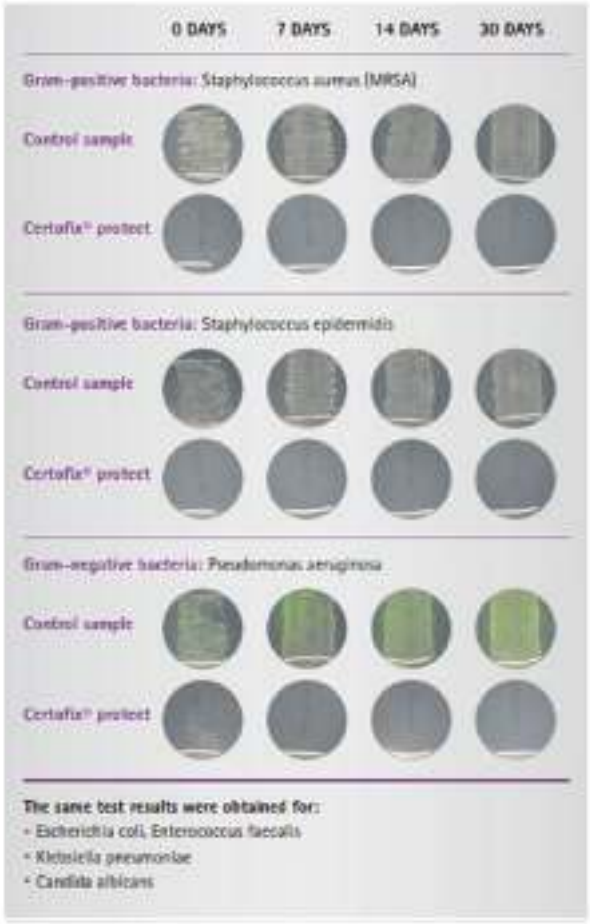

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