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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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CONTENT

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CHALLENGES IN ANALGOSEDATION MANAGEMENT IN THE INTENSIVE CARE UNIT

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The primary goal of Intensive Care Unit (ICU) patients' pain and agitation management is to minimize patients' physical and psychological discomfort. As such, it is considered a vital ICU nursing challenge. Nonetheless, 79% of ICU patients report having experienced moderate to severe pain (1), and 71% have an agitation state at least once during hospitalization (2, 3).

Sedation practices in the critical care unit have been trending toward lighter sedation since the start of the new millennium, but patients continue to experience inadequate pain management and excessive sedation. While the analgosedation literature is relatively sparse, it offers a promising, patient-centered method for managing the triad of pain, agitation, and delirium, while reducing common complications associated with long-term ventilation (3).

Sedative and muscle-relaxant medications have been considered the best practice to promote ICU patients' comfort and tolerance to mechanical ventilation. However, the literature shows that this practice has increased adverse outcomes for ICU patients regarding health status, hospital stay length, infection development and mortality (4).

Pain is one of the most common symptoms among ICU patients. Undertreatment of pain at rest and during nursing and medical procedures causes increased patient's suffering; it induces pathophysiological and psychological adverse clinical responses (3, 5, 6). Notably, pain promotes catabolic hypermetabolism. The latter negatively affects wound healing, increases infection risk, alters hemodynamic function, and prolongs the need for mechanical ventilation (7). Patients also may experience pain either because of previously performed surgical interventions or painful diagnostic and therapeutic procedures. Furthermore, psychological reactions to pain undertreatment lead to psychomotor agitation and delirium (1, 8). The latter conditions often impose treatment with sedative drugs. Sedation objectives in the ICU are to reduce agitation and ensure patient's safety, to minimize the risk of voluntary or involuntary patient self-removal of invasive devices (such as an endotracheal tube, drainages and catheters), to optimize mechanical ventilation compliance to reduce respiratory work and oxygen consumption, improving patient's comfort, and providing amnesia and ease to promote adherence to stressful diagnostic and therapeutic procedures (8).

Sedation in the ICU involves the targeted reduction of the patient's level of consciousness through intermittent or continuous administration of medication. There is no universal recipe for sedation that is suitable for all patients. It is important to consider the significant variability among patients, taking into account their age and disturbances in the function of organ systems.

The condition of patients often changes during intensive treatment, and as the course of the illness evolves, so do the individual requirements for sedation. Because of this, an individualized

approach to sedation is important, which involves regular re-evaluation and constant reassessment and adjustment of the choice of sedatives.

The type and dosage of drugs administered to critically ill patients should be adjusted to achieve optimal treatment outcomes. When considering sedation, it should always be combined with an analgesic strategy and recommended approaches in the ICU, such as the concept of "analgosedation" (analgesia-first sedation). This involves prioritizing pain control in critically ill patients to prevent discomfort and improve their overall treatment tolerance. By managing pain effectively, unnecessary risks from oversedation can be reduced.

The primary goal of analgesia and sedation in ICU care is to provide sufficient comfort and ensure pain-free treatment while minimizing patient's anxiety, agitation and other complications. Optimal sedation facilitates patient cooperation with medical procedures and reduces the likelihood of complications such as hemodynamic instability and pulmonary risks. Prolonged and excessive sedation can lead to long-term cognitive impairments and extended recovery periods.

The consequences of inadequate sedation are not negligible, regardless of whether it is undersedation or oversedation.

The consequences of undersedation include the following: anxiety and restlessness, inadequate mechanical ventilation due to poor synchrony with the ventilator, hypertension and tachycardia, hypermetabolism and increased oxygen demand, myocardial ischemia, accidental extubating and other adverse events, including the removal of catheters or drains and long-term consequences, such as post-traumatic stress disorder and chronic cognitive impairments.

The consequences of oversedation include hypotension, bradycardia and reduced perfusion, increased dependency on vasopressor drugs, prolonged delirium and recovery of cognitive function, prolonged mechanical ventilation and associated complications like ventilator-associated pneumonia (VAP), thromboembolic complications, gastrointestinal paralysis, muscular atrophy and weakness, extended ICU stays and hospitalizations and immunosuppression.

The implementation of standardized sedation protocols in ICUs ensures consistent and effective management. These protocols guide clinicians in selecting appropriate sedation levels, regularly evaluating patient's conditions, and adjusting interventions accordingly. Sedation levels should be assessed at defined intervals, typically every 1–2 hours, or more frequently as the patient's needs change.

Absolute contraindications to light sedation are the following: respiratory instability requiring high ventilatory support, severe hypoxemia requiring high fractions of inspired oxygen (FiO2), severe hemodynamic instability and immediately post-cardiac surgery or similar critical procedures.

Relative contraindications to light sedation are high ventilatory demand and requirement for very high positive end-expiratory pressure (PEEP).

Deep sedation significantly increases the risk of delayed weaning from mechanical ventilation and the need for prolonged ICU care. Patients in deep sedation may not respond to physical stimuli or commands, leading to complications such as muscle atrophy, prolonged immobilization and increased mortality. Hence, it is emphasized that deep sedation should only be used in critically ill patients where absolutely necessary.

Sedative Drugs

Propofol is a potent sedative and hypnotic agent with bronchodilator and anticonvulsant properties. It acts on GABA-A receptors, producing rapid effects within 1 to 2 minutes of administration. However, the drug must be administered cautiously, considering its potential for side effects, such as respiratory depression, hypotension, and, in rare cases, propofol infusion syndrome. Continuous sedation with propofol is typically used for durations of 24–48 hours at a dose of 4–6mg/kg/h. The side effects include hypertriglyceridemia, lactic acidosis, and bradycardia, which necessitate careful monitoring and dose adjustments to avoid complications (15).

Propofol is metabolized in the liver and excreted via the kidneys, with minimal accumulation even after prolonged use. It provides smooth, predictable sedation with a favorable recovery profile, which allows for rapid awakening once the infusion is stopped. However, in cases of prolonged use, care must be taken to monitor for potential drug accumulation, particularly in patients with impaired liver or kidney function.

Dexmedetomidine is a selective agonist of α2-adrenergic receptors with sedative, amnestic, sympatholytic, and mild analgesic properties. Its agonistic effect on α2 receptors reduces norepinephrine release in peripheral nerves and the brain (11). The sedative action of dexmedetomidine is mediated through inhibition of transmission in the **locus coeruleus**, a significant area in the brainstem responsible for maintaining and modulating wakefulness and attention. The analgesic effect of dexmedetomidine is not mediated through opioid pathways but rather through spinal α2 receptors.

Dexmedetomidine is administered as a continuous infusion, ensuring so-called cooperative sedation, characterized by the patient maintaining consciousness while achieving deep levels of sedation. Its onset of action is rapid, and sedation can be easily reversed by discontinuing the infusion. Patients can be awakened without agitation after stopping dexmedetomidine, remaining calm and communicative. When deeper sedation is unnecessary, they revert to a sleep-like state, with EEG patterns similar to natural non-REM sleep.

This drug has found a particular role during the weaning period of mechanically ventilated patients transitioning to spontaneous breathing. It is especially useful and recommended for sedating patients with delirium. The prevalence of delirium is lower in patients treated with dexmedetomidine compared to those receiving benzodiazepines. Clinical studies suggest that dexmedetomidine does not cause clinically significant depressive effects and does not result in respiratory depression. Measured respiratory rates and oxygen saturation levels remain stable during its use.

Benzodiazepines for many years, benzodiazepines were the most commonly used drugs for sedation in intensive care units (ICUs). Current recommendations for sedation in mechanically ventilated patients prioritize the use of propofol and dexmedetomidine due to the adverse effects associated with prolonged benzodiazepine use. Prolonged administration of benzodiazepines leads to deep sedation and serious complications, primarily due to drug accumulation in critically ill patients, especially those with hepatic or renal insufficiency, as well as elderly patients (12). The use of benzodiazepines is associated with an increased prevalence of delirium among ICU patients.

Benzodiazepines have sedative, anxiolytic, hypnotic and anticonvulsant properties. However, they lack analgesic effects. When administered in higher doses, especially in combination with opioids, they may induce profound sedation, muscle relaxation, respiratory depression, and cardiovascular instability. These effects are more pronounced in critically ill patients with respiratory insufficiency and organ dysfunction.

Midazolam is a short-acting, water-soluble drug from the benzodiazepine group. It is 2–3 times stronger than diazepam. It binds to specific receptor sites on the GABA-A receptor complex in the CNS, acting as a regulator of GABA-ergic agonist effects and resulting in sedative, anxiolytic, amnestic and muscle-relaxant effects. Due to its high lipid solubility and large volume of distribution, its effect starts quickly after administration. It causes minimal cardiovascular and respiratory depression (14).

The sedative effect appears within 1 to 2 minutes, making it particularly suitable for procedures requiring rapid sedation and short duration. It is metabolized in the liver via the cytochrome P450 system, producing an active metabolite (α-hydroxymidazolam), which is further metabolized in the kidneys. In cases of renal impairment, the active metabolite may accumulate, prolonging sedation and increasing the risk of respiratory depression. In clinical practice, the maximum dose of midazolam infusion is usually limited to 4.8mg/kg/day to prevent the development of tolerance or adverse effects. Prolonged use may result in withdrawal symptoms, which need to be managed carefully.

Lorazepam has a slower onset of action than midazolam but lasts longer and is 5–10 times more potent than diazepam. It can be used in bolus doses or continuous infusion. It is less lipid-soluble than midazolam and has no active metabolites, making it suitable for use in critically ill patients, including those with renal or hepatic impairment.

The sedative effect of lorazepam develops within 5–20 minutes and lasts for several hours. The drug is metabolized in the liver through glucuronidation and is excreted primarily by the kidneys. In patients with renal or hepatic dysfunction, the drug may accumulate, leading to prolonged sedation (15).

Adverse effects: Prolonged administration or high doses of lorazepam may cause lactic acidosis, hyperosmolarity and toxicity, due to the accumulation of propylene glycol (used as a solvent). In cases of suspected toxicity, the drug should be discontinued, and supportive care should be initiated.

Excessive sedation caused by benzodiazepines can be quickly resolved with the administration of flumazenil. Flumazenil is administered via intravenous injection in an initial dose of 0.2mg, which can be repeated at intervals of 1 minute, up to a total dose of 1mg. The onset of action occurs within 60 seconds, and the maximum effect of flumazenil lasts about 6–10 minutes, depending on the administered dose.

Inhalational anesthetics are used in the ICU primarily for continuous sedation during procedural sedation. For prolonged sedation of critically ill patients in the ICU, their use is limited due to the lack of devices that allow safe dosing and elimination of active compounds, as well as the sedative effects persisting without metabolite formation. Modern devices, such as the Anesthetic Conserving Device (AnaConDa™) or MIRUS™, are compatible with modern ventilators, facilitating inhalation sedation delivery. These devices minimize environmental exposure by efficiently capturing expired vapors.

Studies suggest the effectiveness of inhalational anesthetics for both short-term and long-term sedation, with faster recovery times compared to intravenous agents. The dosage of inhalational anesthetics in ICU sedation is typically low (0.2–0.3 MAC, which corresponds to sub-anesthetic concentrations), ensuring a balance between sedation and physiological stability. Their use is associated with reduced intracranial pressure, making them suitable for neurocritical patients, especially those with traumatic brain injuries or elevated intracranial pressure.

Haloperidol belongs to the first generation of antipsychotics. Its sedative and antipsychotic effects are due to its antagonism of dopamine receptors, particularly at the level of the central nervous system. This makes haloperidol effective in the treatment of critically ill patients in the ICU. It is used to manage acute agitation, with doses ranging from 0.2 to 5mg. Sedation typically occurs after intravenous administration in critically ill patients within 10–20 minutes.

Side effects of haloperidol include rigidity, spasms, extrapyramidal reactions (rigidity, tremors, spasms) and prolonged QT interval, which can rarely lead to ventricular arrhythmias. Intravenous administration is rarely associated with neuroleptic malignant syndrome (hyperreflexia, muscle stiffness and rhabdomyolysis).

Assessment of Analgesia Effectiveness Considering that the condition of critically ill patients changes during intensive care, the need for and intensity of analgesia also changes. Continuous assessment of pain levels is crucial. Monitoring the effectiveness of analgesia involves repeated measurements at specific intervals as well as the systematic tracking of its efficacy.

To assess pain intensity, various strategies and scales can be used. While changes in vital parameters (heart rate, respiratory frequency, blood pressure, oxygen saturation) can be indicative of pain, they should only be supplementary to clinical observation and not considered as valid primary indicators of pain for critically ill patients. Instead, direct communication with patients who can self-report their pain is preferred.

Medications for Analgesia the choice and combination of analgesics, as well as the careful titration of doses, significantly impact the treatment and outcomes of critically ill patients in intensive care units (ICU). The ideal analgesic should be one that acts quickly, has a short duration of action, does not produce active metabolites, and has a low risk of accumulation in the body. Significant progress in achieving optimal analgesia has been made using existing analgesics and the introduction of new drugs into clinical practice.

Opioid Analgesics are the most commonly used analgesics in the ICU. They are administered intravenously, either as bolus doses or via continuous infusion. Their pharmacological effects are achieved by stimulating μ, δ, and κ opioid receptors. Among these, the μ-opioid receptors are the most important for analgesic effects. Some opioids, in addition to stimulating opioid receptors, also act on non-opioid receptors (e.g., tramadol) or other mechanisms (e.g., tapentadol). Depending on the dosage used, their effects vary. The most commonly used opioids in ICUs are morphine, hydromorphone, fentanyl, sufentanil and remifentanil (13).

Selection and Method of Analgesic Administration in the ICU the central role in modern analgesia concepts in the ICU is played by opioids with a rapid onset of action and dose-dependent effects. Remifentanil is an excellent choice for analgesia in the ICU. It has a quick onset of action and is broken down by non-specific esterases in plasma, making its effects independent of infusion duration and organ function. This ensures a fast and predictable effect termination.

The use of shorter-acting opioids reduces mechanical ventilation periods (MVP), improves differentiation of sedation levels, and reduces brain dysfunction, while minimizing side effects and their impact on mortality. Opioids can be administered continuously or intermittently via intravenous boluses at defined time intervals. The latter method has advantages but requires individual dose adjustments for each patient to achieve adequate speed and intensity of analgesia. Continuous opioid infusion is the most commonly initiated with a loading dose or by increasing the infusion rate until a therapeutic concentration is reached, followed by maintenance infusion. This approach avoids excessive drug concentration in tissues, which can prolong drug effects. Intermittent administration, while technically feasible, is not commonly used due to its short-lasting effect, which lacks sustained analgesia. Special caution is needed for patients with liver or kidney failure, as drug accumulation in tissues can lead to unwanted effects. Intermittent administration can also ensure effective analgesia, avoiding drug accumulation in the body while maintaining a stable therapeutic effect. However, immediately after drug administration, concentrations may be too high, leading to side effects, and later drop below the required therapeutic level, making analgesia inadequate. The use of opioids as the sole analgesic in the ICU is not recommended. For critically ill patients, prolonged and excessive opioid use can lead to drug accumulation and numerous side effects, including prolonged sedation, respiratory depression, ileus and potentially increased intracranial pressure, and worsening thoracic mechanics. Other complications include hallucinations, delirium, hyperalgesia and others. Careful titration of opioids along with the concurrent use of non-opioid analgesics (paracetamol, nefopam, lidocaine, carbamazepine, clonidine, gabapentin, dexmedetomidine, ketamine) can reduce opioid consumption, the incidence of delirium and can improve analgesia (13). When using non-opioid analgesics within the multimodal analgesia concept in the ICU, their opioid-sparing effects must be carefully assessed to avoid excessive opioid use and minimize adverse effects.

Choosing Medications for Analgosedation the choice and balance between sedation and analgesia depends on individual needs, chronic illnesses, indications for sedation, clinical conditions, existing organ dysfunctions, comorbidities, concurrent therapies and allergies. The pharmacokinetics and pharmacodynamics of medications in critically ill patients are often unpredictable due to complex drug interactions, increased drug sensitivity, organ dysfunctions, protein-binding changes, hemodynamic instability and drug accumulation. Incorrect medication selection and dosing can lead to adverse outcomes.

It is critical for physicians administering sedation in the ICU to be fully informed about the benefits, risks and potential side effects of each drug.

Research findings indicate that the choice of sedative and its administration can significantly impact short- and long-term treatment outcomes. Important parameters for selecting sedatives include the specific indication, the pharmacokinetics and pharmacodynamics of the drug, individual patient's characteristics, cost-effectiveness, metabolism and the absence of active metabolites or adverse effects.

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THE BENEFITS OF ULTRASOUND GUIDED PERIPHERAL NERVE BLOCKS IN ORTHOPEDIC SURGERY

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Abstract

Introduction: Peripheral nerve blocks have an increasingly important role as an anesthetic technique for surgical anesthesia, postoperative analgesia, and fast discharge of patients after surgery involving the upper or lower extremities, alone or in combination with spinal or general anesthesia. Ultrasound guidance has become the most popular for performance of peripheral nerve blocks.

Methods: In our retrospective study, we included all patients that were admitted in our hospital for orthopedic procedures on lower and upper extremities who received peripheral nerve block, alone or in combination with spinal or general anesthesia in the last 5 years. Ultrasound guidance was used and local anesthetic Bupivacaine 0.5%. Dexamethasone 4 mg was given intravenously as an adjuvant to peripheral nerve blocks.

Results: The total number of patients included in our study was 300, the total number of performed peripheral nerve blocks was 302. 144 (48%) patients were male and 156 (52%) - female. The type of performed blocks was: 164 (54%) femoral, adductor canal blocks 22 (7.28%), 26 supraclavicular (8.60%), 77 interscalene (25.49%), 9 axillar (2.98%), 2 popliteal (0.66%), 1 iPACK and 1 TAP block (0.33%). Peripheral nerve blocks were combined with general or spinal anesthesia or performed as a sole technique for intraoperative analgesia in 17 patients (5.67%).

Discussion: In our hospital we performed ultrasound guided peripheral nerve blocks last years in combination with a general, spinal anesthesia or as a sole technic for intraoperative and postoperative analgesia. Our patients were very satisfied with good postoperative pain control, and no serious complications were observed.

Conclusion: Ultrasound guided peripheral nerve blocks are good choice for intraoperative anesthesia and postoperative analgesia, especially in older patients and patients with a lot of comorbidities.

***Key Words**: ultrasound guidance; orthopedic surgery; peripheral nerve blocks.*

Introduction

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

Peripheral nerve blocks have been part of anesthetic techniques used for upper extremity surgery for decades. The interscalene block was described a century ago, in the early 1900s. These blocks at the beginning were done by identifying anatomical landmarks and eliciting paresthesia. The introduction of the nerve stimulator technique in the late 1980s made a change in practice, but introduction of the ultrasound technique during the last decade has further enhanced the performance. A Cochrane review suggests that the ultrasound-guided block technique further improves the success and ease of performance, and it is now commonly used by younger colleagues (2).It offers a lot of practical advantages for nerve blocks, good visualization of the anatomy, more informed guidance for the needle pathway to the nerve while avoiding structures that might be damaged by the needle (3). Ultrasound guidance reduces the block performance time, the number of needle passes and shortens the block onset time using lower LA doses (4). Significant impact is reduction in block-related complications, nerve injury, intraneural injection of anesthetic, reduced incidence of systemic local anesthetic toxicity, intravascular injection, direct visualization of non-neural structures, e.g., pleura and kidney.

Peripheral nerve blocks provide surgical anesthesia and minimize the need for general anesthesia, opioid requirements are reduced, as are opioid-related side effects. Peripheral nerve blocks with long-acting local anesthetic can provide prolonged analgesia (5).

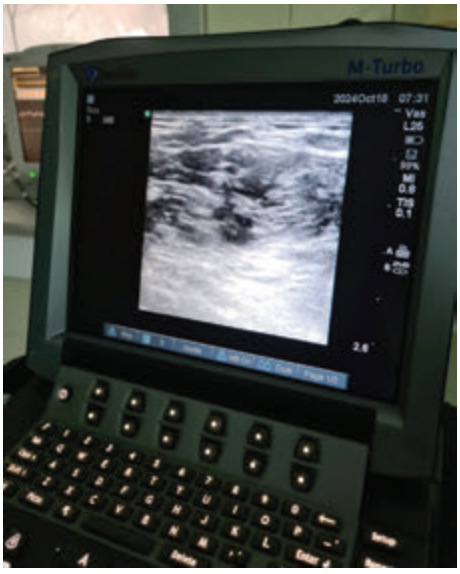
Regional anesthesia and peripheral nerve blocks improve the cardiovascular, pulmonary, gastrointestinal, coagulative, immunological and cognitive functions, especially for elderly and high-risk patient populations undergoing surgery (6).

Peripheral nerve blocks can be used alone or in combination with general anesthesia for intraoperative analgesia. It depends on the site of surgery, refusal or acceptance of the patient. The depth of GA is reduced and the use of intraoperative opioids minimized, so we have early return of cognitive function (7). Especially, upper extremity nerve blocks of plexus brachialis have an obvious place as a sole anesthetic technique or as a powerful complement to general anesthesia.[2] A failed peripheral nerve block is associated with patient's discomfort and unnecessary conversion to general anesthesia. The reported success rate of ultrasound-guided blocks ranges from 55% to 100% (8).

Some additives to local anesthetics can hasten the onset of nerve block, prolong block duration or reduce toxicity. Recent studies suggest that giving additives intravenously or intramuscularly can provide the same benefits of perineural administration while reducing the potential for neurotoxicity. Dexamethasone is the most popular additive, and it can be used perineural or intravenously with the same prolongation of the blocks. Dexamethasone reduces postoperative opioid consumption, has an important effect in reducing postoperative nausea and vomiting (9).

Methods

In our study, we included all patients, ASA 1-3, that were admitted to our hospital for orthopedic procedures on lower and upper extremities who received peripheral nerve block, alone or in combination with spinal or general anesthesia in the last 5 years. Peripheral nerve blocks were performed following protocols for patients' safety. The nerve blocks were performed usually 15 to 30 minutes before the surgery. Ultrasound guidance with a 6–13MHz linear ultrasound probe (M-Turbo, SonoSite ultrasound) (Picture 1) and Stimuplex needle by B/Braun were used.



Picture 1. SonoSite Ultrasound.

The procedure was explained to all patients. They were monitored with standard monitoring (EKG, sPO_2, BP) and i.v. canula was inserted with an infusion of 0.9% Saline. Bupivacaine 0.5% was used in dose depending on the type of peripheral nerve block and the patient. We did not use perineural dexamethasone or any adjuvant to local anesthetic, we used dexamethasone 4mg intravenously.

In the operation room, our patients received general or spinal anesthesia, or in some cases peripheral nerve block was a sole technique for intraoperative anesthesia. All patients during surgery received famotidine 20mg, metoclopramide 10mg, paracetamol 1gr and ketoprofen 160mg. Spinal anesthesia was performed after putting the patient in a sitting position, using Bupivacaine 0.5% in a dose depending on the type of surgery and the patient, in combination with fentanyl 0.2ml. Introduction in general anesthesia was with midazolam, fentanyl, propofol and rocuronium. After intubation, general anesthesia was maintained with sevoflurane. The dose of fentanyl used intraoperatively was reduced, because general anesthesia was combined with nerve blocks of plexus brachialis.

During surgery for upper extremities, especially for shoulder procedures in the sitting position we used NIRS monitor, cerebral oximetry on both cerebral hemispheres (Picture 2).

Picture 2. Sitting position and NIRS monitor.

Results

The total number of patients that were included in our study was 300. They were admitted to our hospital for elective orthopedic surgery, or with fractures for emergency surgery. The total number of performed peripheral nerve blocks was 302.

Table 1. Gender of population.

Gender		Total
Male	Number	144
	%	48%
Female	Number	156
	%	52%
Total	Number	300
	%	100%

Table 1 shows gender of included patients: 144 (48%) patients were male and 156 (52%) - female.

Table 2. Type of performed blocks.

Type of peripheral nerve block	Number	%
Femoral	164	54.3%
Adductor canal block	22	7.28%
Supraclavicular	26	8.61%
Interscalene	77	25.5%
Axillar	9	2.98%
Popliteal	2	0.66%
iPACK	1	0.33%
TAP	1	0.33%
Total	302	100%

Table 2 shows the type of performed blocks: 164 (54%) femoral blocks, 22 adductor canal blocks (7.28%), 26 supraclavicular blocks (8.60%), 77 interscalene blocks (25.49%), 9 axillar blocks (2.98%), 2 popliteal blocks (0.66%), 1 iPACK and 1 TAP block (0.33%). One patient received both interscalene and axillary block, and one patient received femoral plus iPACK block. Peripheral nerve blocks performed for surgery on lower extremities were combined with general or spinal anesthesia, but blocks for upper extremities were combined with general anesthesia or performed as a sole technique for intraoperative analgesia in 17 patients (5.67%). The youngest patient who was operated only with peripheral nerve block was 17 years old, and the oldest was 78 years old.

The average duration of analgesia after peripheral nerve blocks in our patients was 20.5 hours.

Discussion

Ultrasound-guided regional anesthesia has become very popular in recent years. The use of ultrasound optimizes the technique of peripheral nerve blocks and reduces the dose of local anesthetic used (10). A Cochrane review suggests that the ultrasound-guided block technique improves the success and ease of performance (11). This re-review supports the efficacy of the ultrasound-guided block technique but also addresses the importance of experience and the training curve of ultrasound vs. other techniques. Neal et al.concluded that there is high-level evidence supporting ultrasound guidance, contributing to superior characteristics with selected blocks (12).

In our hospital, we performed ultrasound guided peripheral nerve blocks last years in combination with general anesthesia, spinal anesthesia or as a sole technique for intraoperative and postoperative analgesia. In cases for lower extremity surgery peripheral nerve blocks were combined with spinal or general anesthesia, but for upper extremity surgery peripheral nerve blocks were used alone or in combination with general anesthesia.

After surgery in spinal anesthesia, all patients spent 5-10 minutes in the recovery room, and were sent to the surgical ward in a stable condition. Patients operated under general anesthesia in combination with nerve block were awakened and extubated in the operation room, and after 15 minutes spent in the recovery room, they were sent to the surgical ward in a stable condition. Consumption of opioids during the general anesthesia was minimized, as we expected, with an early recovery of the cognitive function. The postoperative pain in both groups (GA or SA) was reduced in the first hours postoperatively.

On the occasion of lower extremity surgery, femoral nerve block was performed in most of the cases, 164 (54%), admitted for knee and hip surgery. No complications or adverse events were detected. Postoperative pain and the need for additional analgesics were reduced in the first 24 hours postoperatively. A recent systematic review limited to English language publications up to 2009 concluded that single-shot or continuous femoral nerve block was superior to PCA or opioid alone for acute pain control in the first 72 hours after knee replacement. Also, they found that single-shot FNB leads to lower pain scores during movement at 24 hours and at 48 hours; lowers opioid requirement at 24 hours and at 48 hours and lowers risk of nausea and vomiting (13). In our cases, no rebound pain was observed, and all patients were verticalized next day.

Adductor canal block was performed in 22 cases (7.28%), in patients admitted for knee arthroplasty or ligamentoplasty. No complications or adverse events were detected.

Popliteal nerve block was performed only in 2 patients, admitted for surgery of Hallux valgus, combined with spinal anesthesia. The next day both were discharged home with no complaint of pain and very satisfied.

The upper extremity blocks we used in our practice were interscalene, supraclavicular and axillar nerve block. The total number of patients who received these blocks was 112 (37.07%). Most of the patients were admitted for elective surgery, but some of them were admitted with fractures of upper extremity.

Upper extremity plexus blocks have an obvious place as a sole anesthetic technique or as a powerful complement to general anesthesia, reducing the need for analgesics and hypnotics intraoperatively, and provide effective postoperative pain relief (2). 17 (5.66%) patients for upper limb surgery were operated only with nerve block of plexus brachialis. In other cases, the plexus brachialis nerve blocks were combined with general anesthesia. During general anesthesia, only 2ml of fentanyl was given in the beginning for induction. Intraoperatively we did not use more opioids because analgesia with the peripheral nerve block was enough. Because of a small dose of opioids, our patients were awakened from general anesthesia very quickly and with no complaint of pain. Postoperative analgesia with nerve blocks was excellent and the need for additional analgesics was reduced in the first 24 hours.

The upper extremity blocks with their motor and sensor components, especially interscalene blocks have the same meaning as a spinal anesthesia for lower extremity surgery. Ultrasound guidance was used, single shot performed with a long-lasting local anesthetic bupivacaine 0.5%. The blocks were successful at the first attempt. No serious complications, regarding to intravenous application, nerve damage, local anesthetic toxicity, pneumothorax or Horner's syndrome were observed. In two young male patients, transient difficulty with breathing (mild shortness of breath) was observed after interscalene block, but after 30-40 minutes it disappeared. Some studies reported a high incidence of Horner's syndrome. Tran et al.compared ultrasound-guided supraclavicular, infraclavicular and axillary brachial plexus blocks for upper extremity surgery of the elbow, forearm, wrist and hand (14). They found all three blocks to be effective; however, the axillary block required longer time to perform, and the supraclavicular block was associated with a higher incidence of Horner's syndrome. Gamo K et al.examined the outcomes and levels of patients' satisfaction in 202 consecutive cases of ultrasound-guided supraclavicular brachial plexus block (SBPB) in upper limb surgery and found that a total of 20 patients (10%) developed a transient Horner's syndrome (15). No nerve injury, pneumothorax, arterial puncture or systemic anesthetic toxicity were recorded. Vaghadia H et al.compared ropivacaine 0.75% versus bupivacaine 0.5% for supraclavicular brachial plexus anesthesia (16). After informed consent, 104 ASA I–III adults participated in a randomized, double-blind, multi-center trial to receive 30ml of either ropivacaine 0.75% or bupivacaine 0.5% for subclavian perivascular brachial plexus block prior to upper limb surgery. Onset and duration of sensory and motor block in the distribution of the axillary, median, musculocutaneous, radial and ulnar nerves were assessed. Onset times and duration of sensory and motor block were similar between groups. The mean duration of analgesia for the five nerves was between 11.3 and 14.3 hours with ropivacaine, and between 10.3 and 17.1 hours with bupivacaine. The quality of muscle relaxation judged as excellent by the investigators was not significantly different. The median time to the first request for analgesia was comparable between the two groups (11–12 hours). In our cases muscle relaxation was excellent, the shortest duration of analgesia was 13 hours, and longest duration was 30 hours in a male patient. In our practice we did not use dexamethasone or epinephrine in combination

with local anesthetics. We used dexamethasone 4mg given intravenously at the beginning of the surgery. In one study dexamethasone was observed to increase median block duration by 37% (95% confidence interval: 31-43%). Dexamethasone was also observed to reduce pain scores on the day of surgery (P=0.001) and postoperative day 1 (P<0.001). There was no significant difference in duration of nerve blocks when epinephrine (1:400,000) was added to ropivacaine with or without dexamethasone (17).

Srikumaran U et al. concluded that peripheral nerve blocks for upper-extremity procedures improve postoperative pain control and patients' satisfaction, can be administered safely, and have a low complication rate. They are also associated with enhanced participation in postoperative rehabilitation, decreased hospital stays and decreased costs. For our patients who received peripheral nerve block for intraoperative anesthesia and postoperative analgesia, we concluded the same (18). Our patients were very satisfied with good postoperative pain control, and no serious complications were observed. The most of them were discharged home the next day after surgery in a good condition and very satisfied. No rebound pain and readmissions were detected.

Conclusion

Ultrasound guided peripheral nerve blocks are a good choice for intraoperative anesthesia and postoperative analgesia, especially in older patients and patients with a lot of comorbidities. Peripheral nerve blocks give us better intraoperative stability of patients, fast awakening from general anesthesia and very satisfied patients with no pain after surgery.

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MAPPING THE CURRENT AND FUTURE CLIMATE EXTREMES AND HEALTH THREATS TO VULNERABLE POPULATIONS IN KOSOVO

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Abstract

Introduction: Climate change affects human lives and health in different ways. High temperatures and heat waves are associated with excessive morbidity and mortality, especially among vulnerable categories of the population. In addition to deaths, high temperatures can increase pressure on the healthcare system by increasing emergency room visits, hospitalizations, premature births, causing mental health problems and other negative health outcomes. Infectious diseases that are transmitted through food and water have a high incidence rate and can be exacerbated by climate extremes such as heat waves, floods and droughts. As the climate continues to change, the risks to health systems and facilities including hospitals, clinics and community care centers are increasing, among others reducing the ability of health workers to protect people from a range of climate hazards.

Objective: The main objective of the study is to investigate and create an initial database of data and indicators for assessing the risk of climate change on the health of the population and the health system in Kosovo, as a tool to adapt to climate changes and reduce the risks for the population health and healthcare systems and facilities – including hospitals, clinics and community-based care centers.

Materials and methods: For conducting the assessment, data, information and publications in the hydrometeorological, health and other relevant sectors, as well as relevant international publications were used. A vulnerability assessment is translated through the definition and analysis of the climate, public health and environmental health profile of Kosovo and the expected climate extremes in future scenarios, the organization and preparedness of the health sector, as well as the research of the current health profile of the population in Kosovo.

Results and discussion: the current and future climate profile of Kosovo is analyzed with a focus on the most important climate extremes such as heat waves and floods. Testing the RCP 4.5 and 8.5 future climate scenarios showed an increase in the average annual temperature and number of tropical days on almost the whole territory of the country with a maximum of 4^0C and a decrease of the precipitation especially in the summer period for more than 30% (in the period 2071-2100) compared to the baseline scenarios.

We analyzed the demographic structure and some determinants of health of the population of Kosovo, vulnerable groups such as the elderly, the chronically ill, especially those with cardiorespiratory diseases, people with low incomes and low education, outdoor workers and the homeless, as well as the risk regions in the countries where the highest average temperatures or the highest atmospheric precipitation are registered. There is a particular risk in the northern part of the country, where the older population with low incomes and education is large. Fewer economic opportunities, higher poverty rates, greater distances to health centers and fewer services are available there. These structural factors thus further compromise the existing poor situation in which the aging population, including their long-term care, remains subject to lower quality care in rural and more northern areas. The highest mortality rate is expected to be registered among the most vulnerable population over 65 years of age.

Finally, a mapping of the risks of climatic extremes in Kosovo was prepared with indicators for further monitoring and assessment of vulnerability. In **conclusion**, high temperatures, rainfall and floods are presented as the biggest current and even more future climate and health risks in the area of Kosovo, which will also be a serious threat and burden for the health system.

Key Words: *Climate profile; climate extremes; Kosovo; public health; risk map; vulnerable population groups.*

Introduction

Climate change is affecting human lives and health in a variety of ways. It is also threatening the basic ingredients of good health – clean air, safe drinking water, a nutritious food supply and safe shelter – and has the potential to undermine decades of progress in global health.

Between 2030 and 2050, climate change is expected to cause estimated 250,000 additional deaths per year from malnutrition, malaria, diarrhea and heat stress alone. The cost of direct health damage is estimated to be between US$ 2-4 billion per year by 2030. Areas with weak health infrastructure – mainly in developing countries – will be the least able to cope without adequate preparedness and response assistance (1). High temperatures and heat waves are associated with excessed morbidity and mortality, particularly among vulnerable populations. In addition to deaths, high temperatures can increase the strain on the healthcare system by increasing emergency room visits, hospitalizations, preterm births, mental health problems and other negative health outcomes. According to one of the latest reports of the European Environment Agency (EEA), in the period 1980-2022, 5,582 deaths directly caused by floods and 702 lives lost from fires were registered in Europe. In addition, as many as 11% of hospitals in European countries were exposed to the devastating effects of floods. The lack of safe drinking water and the consequences of uncontrolled discharge of sanitary wastewater have been felt by approximately 30% of the affected population. To this the emergence of infectious diseases can be added due to the appearance of fecal bacteria in bathing water, non-communicable diseases such as asthma and allergies due to damage to fences or episodes of drought and of course the serious impact of these extremes on the mental health of children or farmers in the affected regions (2). Mapping flood deaths or other effects of a given event can be useful for identifying risks to current and future populations. Mapping can be done at a local level, by linking to census indicators for small areas, or on a larger scale to show which geographic areas of a country are the most at risk from flooding.

The World Health Organization (WHO) has issued several documents as guidance for assessing risks in the health sector. Namely, as the climate continues to change, the risks to health systems and facilities – including hospitals, clinics and community-based care centers – are increasing, reducing the ability of health workers to protect people from a range of climate hazards. Health facilities are the first and last line of defense against the impacts of climate change as they can be responsible for large greenhouse gas emissions while also providing essential services and care to people affected by extreme weather events and other long-term climate hazards.

Many actions will need to be taken by sectors and decision-makers outside the health facility, and therefore health sector workers will need to influence, inform and demand interventions from local and national governments and policymakers (such as issuing improved Wash Sanitation and Hygiene (WASH) standards for health facilities) (3,4,5).

Some new international databases of climate change health indicators have also recently been published that can be used to assess climate change vulnerability at the national level. Namely, the Lancet Climate Change Countdown Report 2021 presents some useful indicators and calculations such as: exposure of vulnerable populations to heat waves, heat-related mortality, health and weather extremes, climate-sensitive infectious diseases, food security and malnutrition (6).

The basic steps for assessing vulnerability and adaptation of the health sector to climate change are thoroughly described and include vulnerability assessment (climate-sensitive health risks and outcomes), capacity assessment, assessment of future health risks, assessment of adaptation and integration of health policy into the global policy process for climate change adaptation (7).

Assessing health vulnerability to climate change in Kosovo is of great importance for adaptation and coping with climate change. The main concerns are urban air pollution, water scarcity, uncontrolled waste and wastewater disposal in Prishtina and other large cities, which can play a role in serious health outcomes resulting from the emission of atmospheric pollutants. PM2.5 particles can peak above 130μg/m3 monthly average in urban monitoring. The health information system in the country is under review and is not able to provide the data needed to adequately compare the burden of disease with that of higher-income countries. Food and water-borne infectious diseases, which have a high incidence rate in Kosovo, can be exacerbated by climate extremes such as heat waves, floods and droughts. On the other hand, vector-borne infectious diseases are currently of less concern in Kosovo or there is insufficient published data on them (8).

The study's main objective is to investigate and establish a baseline database and indicators for assessing the current and future risk of climate change on the health of the population and the health system in Kosovo.

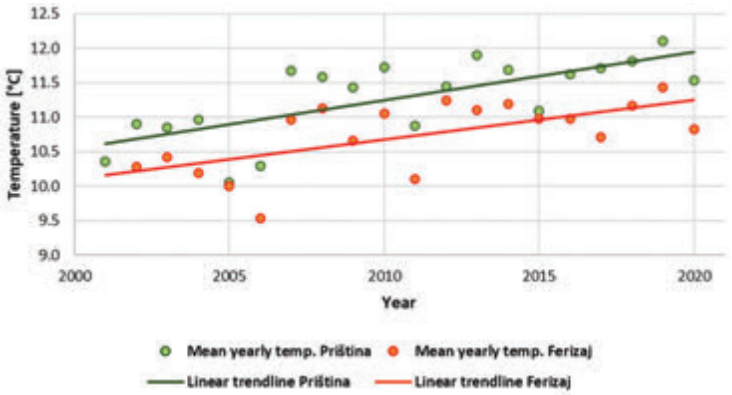
Materials and Methods

The main methodological approach for assessing the vulnerability of the health sector in Kosovo to climate change was conducted by reviewing the basic demographic, economic, climatological, ecological and health profile of the country relevant for the assessment. In addition to current policies and national studies on the subject, which are scarce in Kosovo, the review also focuses on relevant international documents and studies. A survey was conducted on the current burden of disease in the population of Kosovo (basic health-epidemiological profile), in particular

the conditions expected under available climate change scenarios for the region, as well as an overview and analysis of vulnerable population groups, and research into other risk factors/ health determinants of those diseases (besides climate change). One of the main products of the study was the mapping and prioritizing of current and future health risks from climate change in Kosovo. For our study, future climate scenarios Representative Concentration Pathways (RCP 4.5, 8.5) were analyzed in three time periods (2021-2030; 2036-2065; 2071-2100) for two climate extremes temperature and atmospheric precipitation. The basis for mapping the scenarios and assessing climate extremes for Kosovo was made based on mapping climate scenarios in the Western Balkans Climate Change Study (9).

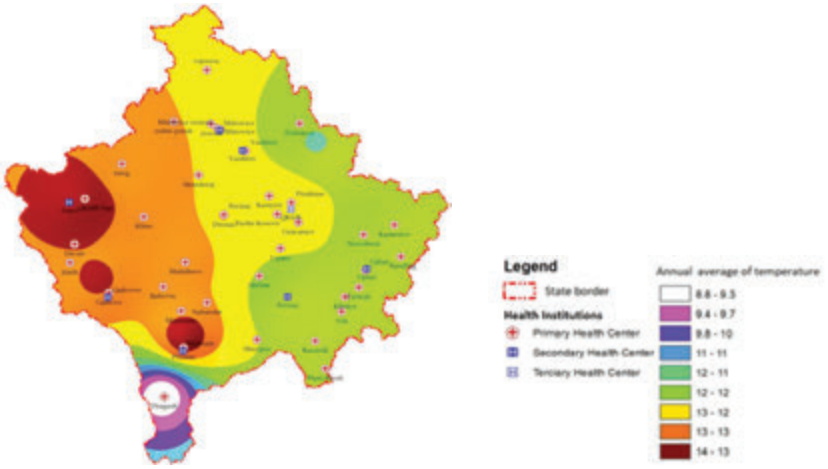
Results

Kosovo has a predominantly continental climate, with warm summers and cold winters. Average temperatures range from -27°C in winter to 39°C in summer. The Kosovo Hydrometeorological Service has recorded temperature increases observed at the Prishtina and Ferizaj stations in the range of 1.3 and 1.0°C between 2001 and 2020 (Graphic 1).



Graphic 1. Mean yearly air temperature in Prishtina and Ferizaj meteorological stations 2001 - 2020 with linear trendlines.

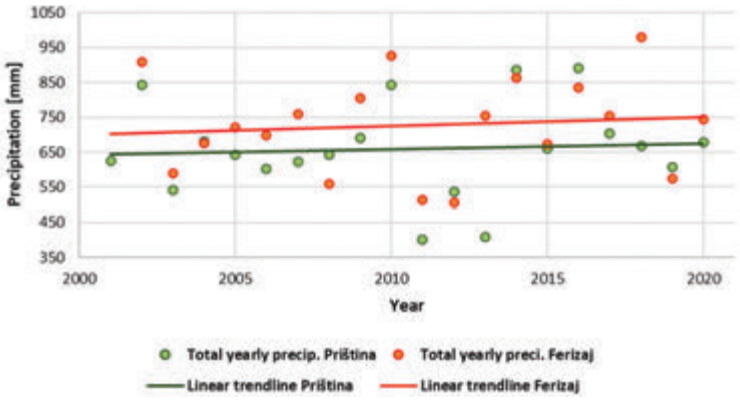
Source: Meteorological data, monthly average, 2001 – 2020; Hydrometeorological Institute of Kosovo 2020.



Map 1. Average annual temperature in Kosovo in 2022 in relation to the location of health facilities.

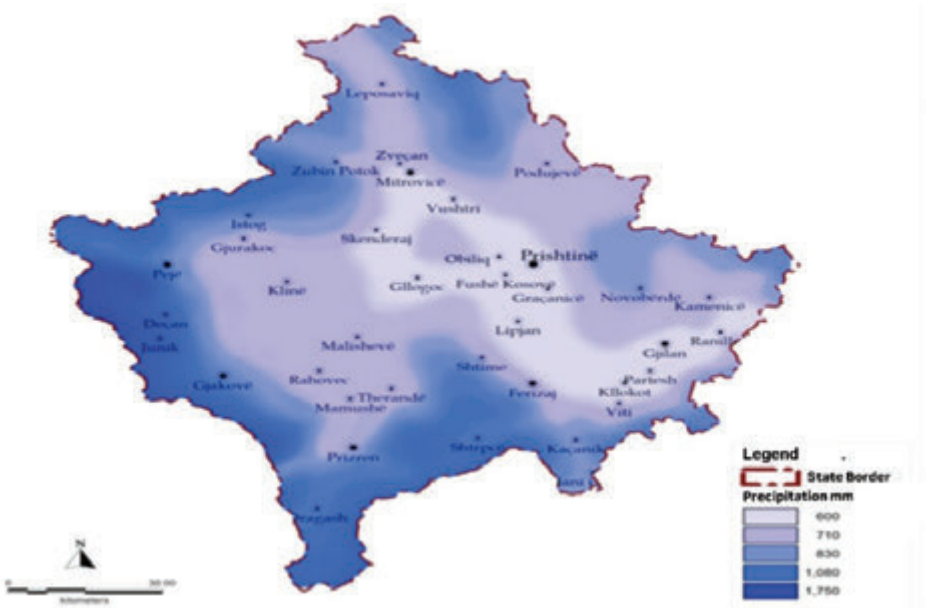
In terms of regional differences, data on average temperatures on the territory of Kosovo for 2022 show the highest temperatures in the southwestern part of the country (Peja, Gjakova, Prizren) (13-15 ^{0}C) (Map 1).

Annual precipitation in Kosovo ranges from 600mm in the eastern Kosovo plain to 1.300mm in the western mountains (Map 2). Precipitation variations depend on topography, altitude, longitude and proximity to large bodies of water. A slight increase in annual precipitation was observed in Prishtina (31.5mm) and Ferizaj (45.4mm) stations (Graphic 2).



Graphic 2. Annual precipitation amounts at the Prishtina and Ferizaj meteorological stations in the period 2001-2020.

Source: Meteorological data, monthly average, 2001 – 2020; Hydrometeorological Institute of Kosovo 2020.



Map 2. Atmospheric precipitation zones in Kosovo.

Compared to other climate extremes since the 1980s, the frequency of extreme precipitation events in the form of heavy rains and droughts has increased, including the droughts in Kosovo in 1993, 2000, 2007, 2008 and 2013 (Map 2).

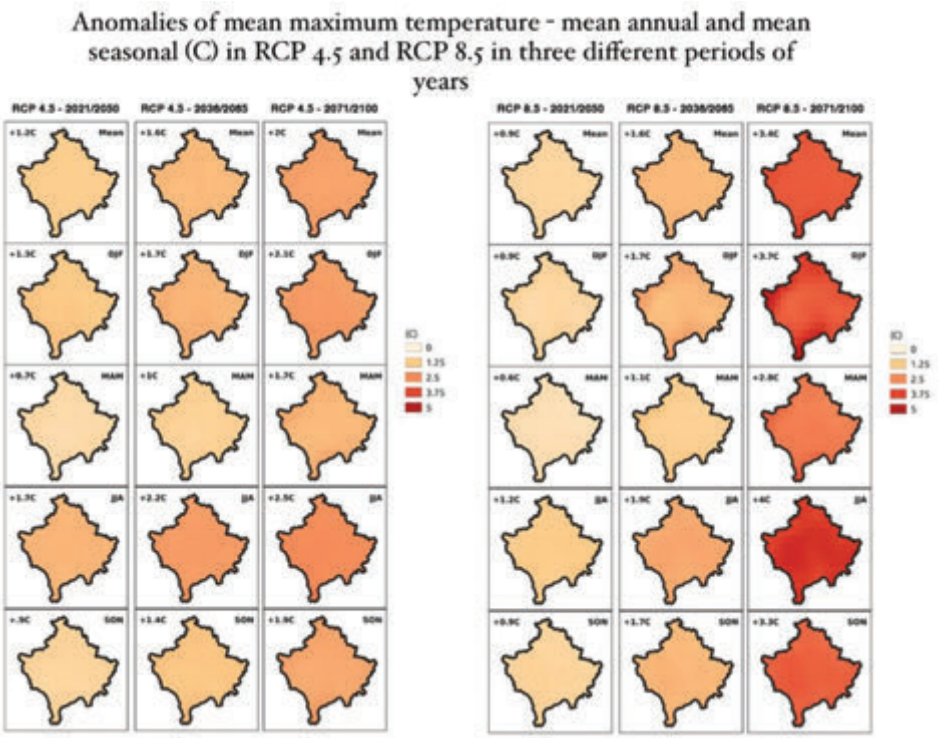
Kosovo is susceptible to floods and they occur frequently. Floods occur after storms in mountainous areas, continuous rains in lowland areas, and melting snow, accompanied or not by bad weather conditions. The main causes of floods in Kosovo are precipitation, uncontrolled construction in areas along rivers, dumping of solid waste in rivers, and failure to maintain riverbeds. The largest percentage of floods are in the river basins of the following rivers: Drim 50%, Iber 24%, Lepenec 20%, Morava 6%.

Periods of severe droughts have been recorded in Kosovo in 2008, 2014, 2018 and 2019. This has resulted in water shortages for crops and major concerns for farmers and the local economy. A prolonged deficit of below-normal precipitation was recorded between June 2012 and March 2014. December 2013 was the fifth driest month in Kosovo's recorded history. The drought continued throughout 2021–2022. Since 2015, the Hydrometeorological Institute of Kosovo has established a drought monitoring program based on the Standardization Precipitation Index (SPI) calculated from precipitation amounts monitored at 31 monitoring sites. Since a technically severe drought only begins when SPI = -1.5, droughts in Kosovo up to date have been classified as moderate droughts. Water shortages mainly affect low-lying areas in the central and eastern parts of the country (10).

Future scenarios project the entire SEE region (including Kosovo) to experience warming higher than the global average, especially for mountainous areas, a decrease in total annual precipitation, with the largest decrease in summer, and an increase in winter precipitation, especially in the mountains, resulting in more frequent spring floods (11).

Climate change projections for Kosovo indicate a further increase in average air temperatures and a decrease in precipitation. The increase in temperature is expected to significantly affect Kosovo's climate, which will be classified as sub-temperate in most of the territory by the end of this century. The decrease in precipitation is expected to cause more droughts, with only the northeastern and northern parts of the country still experiencing a dry season (12).

According to the RCP 4.5 scenario: in the period 2021-2030 in the region of Kosovo there is an increase in temperature compared to the base period (1986-2005) by 1.20^{0}C annually with the highest increase in the summer period (up to 1.70) but also in the period December-February (up to 1.30 ^{0}C). For the mid-century period (2036-2065) according to this scenario, the temperature in Kosovo will increase on average by 1.6^{0}C throughout the country, most of all in the summer period June July August (JJA) by 2.30^{0}C, but again surprisingly in the second place is for the winter period December January February (DJF) with an average increase of 1.70^{0}C about the base period. Finally, the RCP 4.5 scenario for the period 2071-2100 predicts an average increase in temperature throughout Kosovo by 2.00^{0}C with the highest average in the summer JJA period (2.5^{0}C) and somewhat less in the winter DJF period (2.30^{0}C). The number of tropical days and days with heat waves will also increase significantly. Precipitation amounts are stabilizing, but especially in the summer period, a period of exceptionally low precipitation amounts will intensify, especially in the already mentioned risk zones in the southeast. Greater precipitation is expected in the western part (Map 3.RCP 4.5 and 8.5).

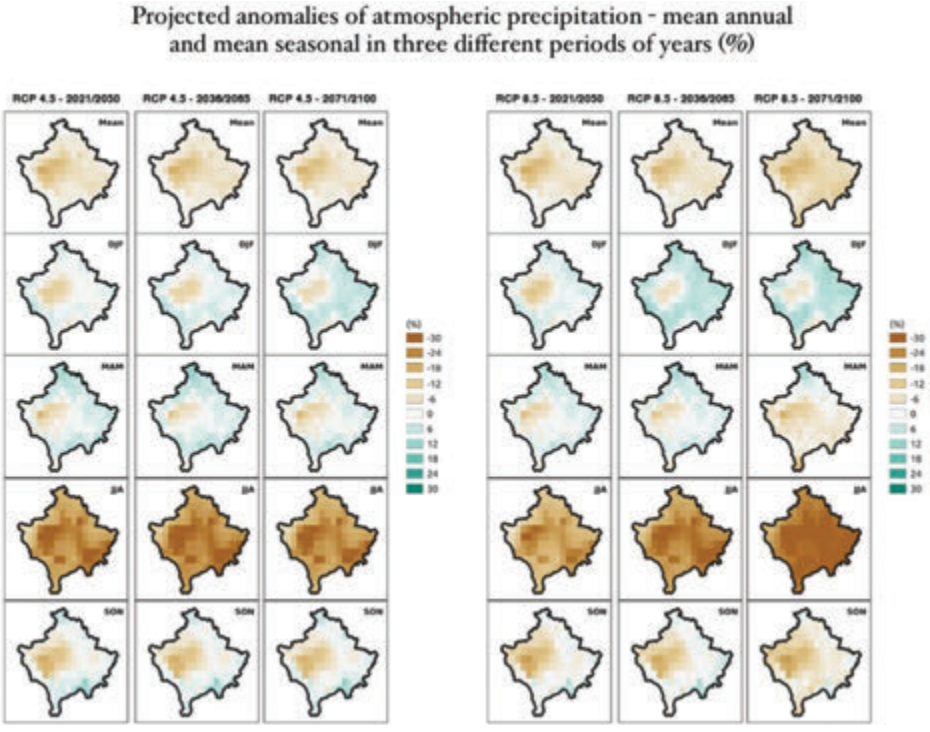


Map 3. Future Climate Scenario RCP 4.5 for temperature increase (variations) (left) and RCP 8.5 (right) at annual and seasonal levels in Kosovo in the period 2021-2100.

Seasons: Mean: annual average; DJF: December-January-February; MAM: March-April-May; JJA: June-July-August; SON: September-October-November.

Source: Simulated climate projections within the framework of the project: Climate proofing for sustainable development in the Western Balkans - https://www.entwicklung.at/en/projects/detail-en/climate-proofing-for-sustainable-development-in-the-western-balkans

The RCP 8.5 scenario predicts an average temperature increase on the entire territory of Kosovo by 0.9^0C in the period 2021, an increase of 1.6^0C in the period 2036-2065 and finally as much as 3.4^0C at the end of the century (2071-2100) with a 4^0C increase in the summer period but also a 3.7^0C increased average temperature in the winter DJF period. Of course, the number of tropical days and nights, as well as periods with heat waves will be even more frequent. The areas in the western part of the country will be somewhat more affected. In terms of precipitation amounts, they will also show a slight downward trend in the summer (JJA) period in this scenario, when in places precipitation will fall by as much as 30% compared to the base period (Map 4. RCP 4.5 and 8.5).



Map 4. Future Climate Scenario RCP 4.5 variations of atmospheric precipitation (left) and RCP 8.5 (right) at annual and seasonal levels in Kosovo in the period 2021-2100.

Seasons: Mean: annual average; DJF: December-January-February; MAM: March-April-May; JJA: June-July-August SON: September-October-November.

Source: simulation climate projections within the framework of the project: Climate proofing for sustainable development in the Western Balkans - https://www.entwicklung.at/en/projects/detail-en/climate-proofing-for-sustainable-development-in-the-western-balkans.

The elderly population is certainly the most vulnerable population group to all environmental hazards, including climate change. According to forecasts, the share of the population aged 65+ will increase to 13% by 2031 and reach 27% by 2061. In a 2013 survey, 42% of older people in Kosovo were unable to access medical care, 88% of whom were unable to afford it due to high costs. About 83% of older people reported at least one chronic condition (63% cardiovascular disease), and 45% had at least two chronic conditions. The most common chronic conditions were cardiovascular disease, followed by stomach and liver diseases, diabetes and lung diseases, with 63%, 21%, 18% and 16%, respectively (13).

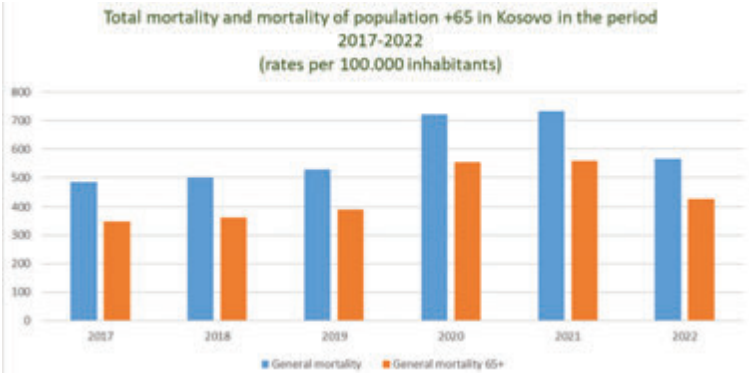
From a public health perspective, the country's geographical-regional inequalities mean that people in the north and rural areas face multiple aspects of exclusion and vulnerability. There are fewer economic opportunities, higher poverty rates, greater distances to health centers and fewer services available. These structural factors thus further compromise the existing poor situation in which the ageing population, including their long-term care, remains subject to lower quality care in rural and more northern areas.

Gross National Income per capita (GNI per capita, according to the Atlas method) in 2019 was $4,640 in Kosovo, which was the lowest in the region. Based on household income surveys in 2019, it is estimated that 18.0% (approximately 1 in 5 people) of the population of Kosovo lives

below the poverty line (1.85 euros per day), with 5.1% of the population living below the extreme poverty line (approximately 1 in 20 people) (1.31 euros per day) in 2017 (14). The poverty rate in rural areas is higher than that in urban areas, and the gap between urban and rural areas continues to grow.

The latest data shows that the total number of deaths in Kosovo in 2021 is 14,900, while the mortality rate is 8.4 deaths per 1,000 inhabitants. This figure is the lowest compared to countries in the region - where Serbia has the highest mortality rate of 17‰ - and European Union countries with an average of 12‰. Circulatory diseases and tumors are among the most common causes of death in Kosovo for the period 2016-2020 (15).

The highest mortality rate is expected to be registered among the most vulnerable population over 65 years of age (over 70% of total mortality) (Graphic 3).



Graphic 3. Total mortality and mortality of population +65 in Kosovo in the period 2017-2022 (per 100,000 people).

Source: Kosovo Agency of Statistics, Statistical Yearbook 2022.

In Kosovo, 81.4% of the population can access the nearest primary health facility within 30 minutes on foot or by public transport, and 76.5% can access a pharmacy within 30 minutes. On the other hand, 54.8% of the population can reach a General Hospital within 30 minutes on foot or by public transport, and 87.3% within an hour (16).

However, there are some cities that take longer to access a health facility. Only 3.3% of the population at the central level needs an hour or more to travel to primary health facilities. Meanwhile, for Novo Brdo and Zubin Potok this percentage is 57.3% and 58.9%, respectively. Moreover, the percentage of residents who need an hour or more to access general hospitals is 81.2% for Novo Brdo, 60% for Zubin Potok and 55.1% for Strpce.

In terms of chronic non-communicable diseases in Kosovo in the period 2015-2021, among the ten non-communicable chronic diseases, the highest number of cases is dominated by: Primary arterial hypertension with 46.5%, followed by non-insulin-dependent diabetes with 36.9%, Insulin-dependent diabetes with 6.35% and Schizophrenia with 2.95% (17).

Cases of acute diarrhea and salmonellosis can be linked to poorly regulated infrastructure such as drinking water supply from uncontrolled sources, long water supply interruptions, lack of basic sanitation, irregular waste disposal, unsafe food, poor economic and hygienic conditions that

are evident in Kosovo. Of the vector-borne diseases, Lyme disease, West Nile virus and malaria occasionally occurred in Kosovo during the observation period (2018-2022) (18).

Among the environmental factors that may, in synergy with climate change, affect the health of the population of Kosovo, the state of air quality and the safety of drinking water are worth highlighting.

Ambient air quality is particularly poor in Prishtina, the Obilic area, the Drenas area and the Mitrovica area. Besides the domestic heating, the two coal-fired power plants Kosovo A and B can be considered the main source of particulate matter in the Prishtina region. The Kosovo A power plant, which pollutes 3 times more than the newer Kosovo B in terms of particulate matter, will still be closed (19,20).

Rising temperatures, changes in precipitation patterns, floods and extreme droughts can have a serious impact on drinking water supply systems. Exposure to a large number of pathogens in water and food increases, is often accompanied by diarrheal diseases (intestinal infections) that can be a major risk to public health during climate extremes.

The analysis of the demographic, socio-economic, health and climate profile of Kosovo confirmed that there is a health risk to the population from climate change, especially from certain climate extremes and especially in future climate scenarios if mitigation and adaptation measures are not taken.

The risk matrix contains the main elements:

- A climate extreme that is occurring or is expected to occur in the future ;
- Expected health risk;
- Vulnerable population groups;
- Vulnerable regions;
- Expert assessment (of the actuality of the risk) or proven risk;
- Effect/ consequences on the health sector;
- Indicators for monitoring risk/ consequences.

Although for the needs of this research, sufficient quality health data covering a longer historical period have not been obtained, nor specific studies have been conducted or developed to assess the direct connection between climate change and health, indirect indicators and existing models - forecasts confirm that the occurrence of high temperatures and heat waves, especially in the summer period, is the greatest risk from current and especially future climate change for the population in Kosovo. Of course, not all population groups are equally at risk, with the focus of risk being on the elderly, the chronically ill, workers who work outdoors (which primarily include agricultural and communal workers) and socially marginalized groups living in substandard conditions and most often in rural areas of Kosovo. In terms of geographical region, the risk is in urban settlements (due to the occurrence of heat wave islands but also due to summer air pollution), as well as settlements in the southwestern part of the country which seem to be most at risk from this climate extreme.

In conditions of such health risk, a special burden on the health system is expected with a focus on certain services (adult and elderly treatment services and emergency medical care) whose

strengthening must be among the first priorities to enable appropriate climate adaptation and resilience. Cardio-respiratory diseases and mortality are the main health consequences as a result of exposure to extremely high temperatures and heat waves. Their monitoring will be among the main indicators for evaluating the risks and dealing with them.

In the absence of authentic studies investigating the direct impact of climate extremes on health, data from existing strategic documents and available manuscripts (including those for neighboring countries) indicate that increased atmospheric precipitation, floods, droughts and forest fires pose mainly moderate risks to health and the health system in Kosovo. The health risk is mainly indirect through health threats but also damage to basic infrastructure, the availability of safe water and food (floods and droughts), or air pollution (from fires).

Geographically, the greatest risk from these floods is in regions where these extremes have historically been reported with the highest frequency and those that are projected to be at higher risk in national climate scenarios. Particularly vulnerable population groups include the elderly, the chronically ill and socially marginalized groups, including the population living in remote rural settlements in the threatened areas. In these regions, access to health services will be more difficult, and a particular burden on the health system will be the overloading of primary healthcare facilities and emergency medical services. Injuries, drowning, impaired mental health or an increased number of vector-borne and infectious diseases transmitted through contaminated drinking water and food are also expected to be more common.

The simultaneous occurrence of high temperatures and floods or high rainfall can be assumed to be a moderate health risk for the population in the affected regions. Increased incidence of some enteric infectious diseases from unsafe water and food (especially during floods) or vector-borne infectious diseases (during high temperatures and increased rainfall), with deterioration of drinking water quality, are among the main health risks and impacts. From a geographical perspective, a more serious effect is expected in regions with historically the highest risk of floods and high precipitation and those with predominantly rural unsafe water supply systems, as well as regions suitable for the emergence of the Asian tiger mosquito (Aedes albopictus) and West Nile virus.

The effects on the agricultural sector can also be considered as a threat to public health. Namely, as concluded from this task, increased temperature, more frequent and prolonged heat waves, reduced rainfall in some regions and the increased number of hot and tropical days will have a very negative impact on agricultural crops and livestock and increase heat stress. These conditions reduce productivity in agriculture and especially affect the health of livestock. All this, in regions that rely mainly on locally produced food, can also result in a risk of malnutrition, especially among vulnerable population groups.

Discussion

According to the 2018 Regional Cooperation Council (RCC) Study on Climate Change in the South-Eastern Europe (SEE) region, the priority recommendation for the SEE region is to ensure human health, safety and quality of life, including the development of warning systems, information dissemination and public preparedness, for disaster risk management. In the presented climate period, the temperature in the region increased by 1.2°C compared to the previous climate period (21). Precipitation decreased during the 1980s and 1990s, then started to increase

and returned to the current climate, to the values of the period defined as the past climate. The intensity of extreme heat waves described by the Heat Wave Magnitude Index (HWMI) has increased across the Western Balkans region, particularly along the eastern Adriatic coast (22, 23). The largest increases have been observed in southern Bosnia and Herzegovina, Montenegro and northern Albania. Other significant increases have been observed in northern Serbia, Kosovo and the Republic of North Macedonia. On average, the magnitude of extreme heat waves over the Western Balkans has doubled in the last two decades compared to the period 1981–2000. According to the same RCC study, climate change shows that the Western Balkans is moving towards a subtropical climate further north, leaving coastal and southern areas very hot and dry during the summer season, which is expected to last longer from the near future to the end of the century. The most important climate-related risks to human health in the region are the following: an increase in the frequency and intensity of heat waves, a very likely decrease in the quality of drinking water, and a very likely wider spread and emergence of new vector-borne diseases (24). Since 2000, there has also been an increase in the number of forest fires in Kosovo (25). Although no direct health effects have been recorded, between 2001 and 2023, Kosovo lost 2.25kha of forest cover to fires and 15.1kha to all other causes of loss (13% of the total forest cover lost during that period). The year with the highest forest cover loss due to fires during this period was 2012, with 575 hectares lost to fires, which is 33% of the total forest cover loss for that year (26).

To predict future scenarios, the possible future impact of high temperatures on population mortality in European countries was measured in 2017. In this, the period 1971-2000 was considered as the basic climate baseline and meteorological projections refer to future periods 2036-2064 and 2071-2099, and in terms of model scenarios the focus was on Representative Concentration Pathways (RCP) 4.5 and 8.5 (27).

Increased flooding and stagnant water, increase the availability of habitat for mosquito larvae, thus supporting the spread of the Asian tiger mosquito. The Asian tiger mosquito (Aedes albopictus) is an invasive mosquito species that is considered a potential vector of about 22 arboviruses, including Dengue, Chikungunya and Zika. The first record of Aedes albopictus in Kosovo was made in July 2020, when a seven-weeks field survey confirmed the presence of adult mosquitoes in a village near Prizren. This discovery shows that the tiger mosquito is expanding its geographical range to the Balkans and southeastern Europe (28).

Judging by existing strategic documents, Kosovo's climate change-related vulnerability can be summarized in six key issues: air pollution, water scarcity, water quality, land degradation (soil contamination by heavy metals, soot drift, irregular waste disposal, hazardous material and chemical disposal), environmental degradation and basic services (e.g., food quality, forest maintenance, waste management, meteorological forecasts), and forest degradation (irregular logging, soil erosion) (29).

Conclusions

Floods and droughts are the most common climate extremes after heat waves that characterize the current and indicate the future climate profile of Kosovo.

Analyses of the future climate scenarios for two climate extremes (temperature and precipitation amounts), confirmed the forecasts that in the period until the end of this century in Kosovo

there will be a further increase in average air temperature and a decrease in precipitation (especially in summer).

The occurrence of high temperatures and heat waves, especially in the summer period, is the greatest risk from current and especially future climate change to the health of the population in Kosovo. The risk from an increase (in winter) or decrease in precipitation (in summer) is more moderate.

Particularly vulnerable population groups are the elderly, the chronically ill, workers who work outdoors (primarily agricultural and communal workers), and socio-economically marginalized groups who live in substandard conditions, most often in the northern and rural areas of Kosovo.

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PREVALENCE AND IDENTIFICATION OF POTENTIAL PREDICTORS ASSOCIATED WITH GESTATIONAL DIABETES MELLITUS IN NORTH MACEDONIA

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Abstract

Introduction: Gestational diabetes mellitus (GDM) is defined as the occurrence of diabetes which is discovered during pregnancy. It is a widespread global condition with many maternal and fetal health risks.

Objective: The aim of this study was to identify the prevalence and potential predictors of GDM among a cohort of women from North Macedonia.

Patients and Method: A total number of 154 (143) participants were included in the study. The diagnosis of GDM was made using the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria. Patients with known diabetes prior to pregnancy, history of GDM, in vitro fertilization (IVF), multiple gestation and severe medical conditions were excluded from the study. The recorded variables were age, nationality, religion, education, parity, family history of diabetes (FHD), pre-pregnancy body mass index (BMI), weight gain, smoking and oral contraceptive use. The statistical analysis was done calculating exact logistic regression in "R".

Results: Significant predictors: For every one-unit increase in BMI, the odds of developing GDM increased by 8.6% (coefficient=0.086, p=0.026). Women with family history of diabetes had 2.74 times higher odds of developing GDM (coefficient=1.008, p=0.011). The Orthodox participants had significantly lower odds of developing GDM compared to the Muslim ones (coefficient=-2.528, p=0.011). Two prior pregnancies raised the odds to 4.70 times higher compared to no prior pregnancies (coefficient=1.547, p=0.042).

Conclusion: The study emphasizes the importance of addressing pre-pregnancy BMI and screening individuals with family history of diabetes. The high prevalence of GDM suggests a need for public health strategies focusing on preconception care, lifestyle interventions and regular screening during pregnancy.

Key Words: *Gestational diabetes mellitus; prevalence; risk factor.*

Introduction

Gestational Diabetes Mellitus (GDM) is a common pregnancy complication that affects a significant number of women, with serious short and long-term health implications, including an increased risk of preeclampsia, preterm birth and macrosomia, as well as the future development of type 2 diabetes in both mothers and children.

Worldwide, the prevalence of GDM ranges from 5% to 25.5% and is dependent on many socio-demographic factors, as well as screening and diagnostic criteria. According to the International Diabetes Federation (IDF), the prevalence of GDM is expected to be on the rise year by year (1).

Since 2013 GDM has been defined as the **development** of diabetes during pregnancy (2). The Scientific Association of Endocrinologist and Diabetologists of Macedonia has accepted the International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria (2) shown in Table 1, which are based on the 2008 Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study findings (3).

Table 1. IADSPG criteria:

Glucose measurement	Plasma glucose concentration (mmol/l)
Fasting	≥5.1
1 h	≥10
2 h	≥8.5

GDM is diagnosed if one or more of the following glucose values exceed the threshold during a 75g Oral Glucose Tolerance Test (OGTT) at 24–28 weeks of gestation.

Despite increasing awareness of GDM, studies exploring the predictors of its occurrence, particularly in specific populations, remain limited. Few studies have investigated the role of socio-cultural factors in non-Western populations, leaving a gap in understanding the predictors of GDM in other regions, particularly in Eastern Europe. The majority of the non-Western studies are done among the Asian, African and Middle Eastern population (4–7). This is especially true for North Macedonia (8).

This study seeks to identify the prevalence and some of the predictors of GDM in a cohort of women from Republic of North Macedonia, with an emphasis on demographic, clinical, and socio-cultural factors.

Materials and Method

This cross-sectional study was performed at the Obstetrics & Gynecology office "INA" in Skopje from 01.01. to 31.12.2022. From a total number of 154 consecutive pregnant patients, the ones with a history of GDM in previous pregnancies, IVF, multiple gestation and severe medical conditions were excluded from the study, which left 143 women. The diagnosis of GDM was made using the criteria of the IADPSG after a 75mg OGTT from 24-28 gestational weeks (2).

Their demographic data, past medical, obstetrical and family history, obtained by semi-structured one-on-one, face-to-face interviews included: age, nationality, religion, education, parity, family history of diabetes, pre-pregnancy BMI, smoking, and use of oral contraceptives. The OGTT was done at the "Biotek" laboratory in Skopje. The statistical analysis was done by calculating exact logistic regression in R statistical software.

Results

Out of 143 women who participated in the study, 56 (39.1%) had GDM. The median age was 31 years, with an interquartile range of 7 years. The majority were Macedonian Christian Orthodox (118; 82.5%). More than half of the participants (64.9%) had university education or higher. More than half had none or one child (46.2% and 39.2%, respectively). The family history of diabetes was present in 39.2% and more than half had normal pre-pregnancy BMI (65%). Only 22.4% were still smoking and 45.5% had never smoked. The absolute majority (96.5%) had never used oral contraceptives.

Table 2. Analyzed variables and GDM.

Characteristic	Subjects (total 143)	GDM n=56 (39.1 %)	No GDM N=87 (60.8%)	Exact logistic regression analysis (95%CI) p value
Age				
<30	55 (38.5%)	22 (40%)	33 (60%)	
30-35	59 (41.3%)	24 (40.7%)	35 (59.3%)	
>35	29 (20.2%)	10 (34.5%)	19 (65.5%)	p = 0.962
Nationality				
Macedonian	118(82.5%)	43 (36.4%)	75 (63.6%)	
Roma	11 (7.7%)	7 (63.6%)	4 (36.4%)	
Albanian	7 (4.9%)	3 (42.9 %)	4 (57.1%)	p > 0.05
Other	7 (4.9%)	3 (42.9%)	4 (57.1%)	
Religion				
Orthodox Cristian	118 (82.5%)	46 (39%)	72 (61%)	
Muslim	20 (14.0%)	10 (50%)	10 (50%)	
Atheist	2 (1.4%)	0	2 (100%)	p = 0.011
Other	3 (2.1%)	0	3 (100%)	
Education				
MSc/Doc.	22 (15.4%)	8 (36.4%)	14 (63.6%)	
University	70 (49%)	24 (34.3%)	46 (65.7%)	
Secondary school	43 (30.1%)	18 (41.9%)	25 (58.1%)	p > 0.05
Primary school	8 (5.6%)	6 (75%)	2 (25%)	
Parity				
0	66 (46.2%)	21 (31.8%)	45 (68.2%)	
1	56 (39.2%)	21 (37.5%)	35 (62.5%)	p = 0.042
2	15 (10.5%)	11 (73.3%)	4 (26.7%)	
≥3	6 (4.1%)	3 (50.0%)	3 (50%)	
Family history of diabetes type2				
Yes	56 (39.2%)	30 (53.6%)	26 (46.4%)	p = 0.011
No	87 (60.8%)	26 (29.9%)	61 (70.1%)	

Characteristic	Subjects (total 143)	GDM n=56 (39.1 %)	No GDM N=87 (60.8%)	Exact logistic regression analysis (95%CI) p value
Pre-pregnancy BMI				
Underweight	8 (5.6%)	2 (25%)	6 (75%)	
Normal	93 (65.0%)	33 (35.5%)	60 (64.5%)	p = 0.026
Overweight	31 (21.7%)	14 (45.2%)	17 (54.8%)	
Obese	11 (7.7%)	7 (63.6%)	4 (36.4%)	
Smoking				
Never	65 (45.5%)	26 (40%)	39 (60%)	
Quit	46 (32.2%)	18 (39%)	28 (61%)	p = 0.82
Yes	32 (22.4%)	12 (37.5%)	20 (62.5%)	
Use of oral contraceptives				
Never	138 (96.5%)	53 (38.4%)	85 (61.6%)	
Occasionally	3 (2.1%)	2 (66.7%)	1 (33.3%)	p > 0.05
>2 years	2 (1.4%)	1 (50%)	1 (50%)	

Socio-demographic data, past medical, obstetrical and family history of the participants.

The key findings of the exact logistic regression analysis are as follows:

Significant predictors:

- BMI before pregnancy: Coefficient: 0.086 (p=0.026). This means that a one-unit increase in BMI before pregnancy increases the odds of GDM by ~8.6%.
- Family history of diabetes type 2: Coefficient: 1.008 (p=0.011), which means that the participants with a family history of diabetes have ~2.74 times higher odds of developing GDM.
- Religion: Coefficient: -2.528 (p=0.011). The analysis showed that the Orthodox participants have significantly lower odds of GDM compared to the others.
- Parity: Coefficient: 1.547 (p=0.042). This means that participants with two previous pregnancies have ~4.70 times higher odds of GDM compared to no prior pregnancies.

The following were non-significant predictors:

- Age, nationality, education, smoking and use of oral contraceptives.

The prevalence of GDM in this cohort was 39.2% (95% CI: 31.6% – 47.3%).

Model Fit Interpretation: Likelihood Ratio Test (LRT) p-value: 0.0138; Wald Test p-value: 0.0284 (both are <0.05, thus this logistic regression model has statistical validity).

Discussion

A systematic review and meta-analysis published by Saeedi et al. in 2021 (9) states that worldwide, the prevalence of GDM varies from 1 to 28 %. This is because even when the same diagnostic criteria are used, there are differences depending on population characteristics. Data about the prevalence in the region is very limited. Paulo et al. in 2021 did a meta-analysis and

systematic review of GDM prevalence studies in Europe (10) and reported 10.9%. However, in Eastern Europe it was 31.5%. Data about Republic of North Macedonia is very scarce. Papers from Katerniakova et al., Ahmeti et al. and Recica et al., published 2019-2024 have reported data about diabetes type 2 (11–13), but there is no mention of GDM. In 2016 Krstevska et al., analyzed the maternal OGTT levels in relation to large-for-gestational-age newborns and reported a prevalence of 66.1% (14).

In our study the prevalence of GDM was 39.2% (95% CI: 31.6% – 47.3%), which is higher compared to global and regional average. We believe that this is not due to the screening criteria, as the studies we have compared use the same ones. It could be a result of the population characteristics, or the lifestyle factors specific to this region, although we are aware of the fact that because of the sample size, the CI is wider, which suggests that the true prevalence lies in this range. We could not compare our results with similar studies done in our country, except the one by Krstevska et al. which shows even a higher prevalence (14).

Numerous studies have looked for potential predictors of GDM. The most commonly identified predictors are pre-pregnancy BMI (5,15,16). Pre-pregnancy BMI was identified as a significant predictor in our study, as we expected. It is especially worrying that 28.4% of the participants fell into the category of obesity. The percentage of women with a normal BMI was only 37.8%, which shows the necessity for education of women in the reproductive period about the risks of having high pre-pregnancy BMI. The observation that a one-unit increase in BMI before pregnancy increases the odds of GDM by ~8.6%, highlights the need for pre-conception counseling and weight management programs in the general population of women.

The family history of diabetes type 2 (FHD) is the other variable which has been associated with GDM worldwide. In our study it also emerged as a significant predictor of GDM (p=0.011). The patients with positive family history had 2.74 times higher odds of developing GDM compared to those without such a history. This is comparable with many international studies (5,6,17). In 2008 Robitaille and Grant published a review about the genetics of GDM (18).

In our group we found 4.7 times higher odds of developing GDM in women with two previous pregnancies, compared to those with no prior pregnancies. The reports in the literature are not consistent, although there are studies suggesting that increased parity may elevate metabolic stress and insulin resistance, thereby increasing GDM risk (19–21).

Orthodox participants had significantly lower odds of developing GDM compared to others (Coefficient: -2.528). The intersection of religion and GDM has been explored in some studies. Haigh et al. performed a systematic review in 2023 (23) and concluded that women from culturally and linguistically diverse backgrounds (CALD) experienced varying cultural beliefs surrounding food, exercise and pregnancy. In 2021 a study done in Australia with South Asian women (24) found that religious and cultural dietary practices influenced adhering to medical advice. Our findings may reflect unmeasured cultural or lifestyle differences, such as dietary patterns or physical activity, which warrant further investigation. However, we have to acknowledge that 82.5% of our patients were Christian Orthodox. We believe that there is a need for a wider analysis of the differences between the dominant religion groups in our country.

Age was not a significant predictor in our group, which is different from data reported in literature (25). This may be due to the fact that most of the participants fall within a relatively narrow range (IQR = 7 years). Regarding the use of oral contraceptives, we cannot rely on the data about

their prediction strength as only 3 participants reported their use.

Data in the literature about the association of maternal education level and GDM are not consistent (25–27). In our study we did not find any association between maternal education level and GDM.

The relationship between smoking and GDM has been the subject of various studies, with mixed results. Bar-Zeev et al. found that prenatal smoking is associated with higher odds of GDM, even after adjusting for known risk factors (28). On the contrary, a systematic review and meta-analysis by Athanasiadou et al. in 2023 found no association of smoking and GDM. In our study smoking was not identified as a predictor for GDM ($p>0.05$).

The exact logistic regression model used in our study demonstrated statistical validity, as evidenced by the Likelihood Ratio Test ($p=0.0138$) and Wald Test ($p=0.0284$). This is one of the strengths of our study, as well as the diverse set of predictors. The limitations are the size of the sample, which is relatively small, as well as the fact that there are confounding factors which are not measured (cultural, dietary, physical activity habits) that can influence some of the predictors (i.e. religion).

Conclusion

This study emphasizes the importance of addressing pre-pregnancy BMI and screening individuals with FHD. The high prevalence of GDM suggests a need for public health strategies focusing on preconception care, lifestyle interventions, and regular screening during pregnancy. Subsequently, identification of high-risk women before pregnancy can be very beneficial for the prevention of potential maternal and neonatal complications resulting from GDM. The results of this initial analysis show the need for further larger studies.

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RIGHT VENTRICULAR PERFORMANCE IN MECHANICALLY VENTILATED POLYTRAUMATIZED PATIENTS BASED ON ASSESSMENT OF TRICUSPID ANNULAR PLANE SYSTOLIC EXCURSION AND RIGHT VENTRICULAR FRACTIONAL AREA CHANGE

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Abstract

Even in terms of using lung protective strategies, mechanical ventilation could lead to different types of lung injury with severe consequences over systemic and pulmonary hemodynamics, showing deleterious properties over the right ventricular performance as well. Fifty polytraumatized patients admitted in the ICU were included in this prospective study. They were divided into two groups regarding the need for mechanical ventilation. In all patients we have examined Right heart function by measuring Tricuspid Annular Plane Systolic Excursion (TAPSE) and Fractional Area Change (FAC) 24 hours, 7 and 14 days after admission in the ICU. Statistical analysis was done with calculating the mean value of TAPSE and FAC, as well as with using Mann Whitney U Test. In both groups, mechanically ventilated and spontaneously breathing patients, values for TAPSE were not significantly different at all examination points. The values for FAC were significantly lower in the group of mechanically ventilated patients after 7 and 14 days of mechanical ventilation initiation (U=275; 163,5; 86,5 and z= 0,7; 2,02; 1,96 for p value of 0,47; 0,04 and 0,04 respectively). TAPSE as a surrogate for the assessment of longitudinal systolic function of the right ventricle, has been intact in both groups regardless the usage of mechanical ventilation, but radial systolic function of the right ventricle was significantly lower 7 and 14 days after starting mechanical ventilation. Impairment of the radial systolic function of the right ventricle with preserved longitudinal systolic function was previously reported in patients with high pulmonary pressures and elevated right ventricular afterload. The mechanical ventilation is associated with radial right ventricular systolic dysfunction and with lower values for FAC in mechanically ventilated compared to spontaneously breathing polytraumatized patients.

Key Words: *Fractional Area Change; Right Ventricular Systolic Function; TAPSE.*

Introduction

Many life-threatening conditions demand mechanical ventilation characterized by Positive End Expiratory Pressure (PEEP) changing the normal physiology in order to achieve better gas ex-

change. Application of PEEP implies changes in the respiratory pressures that inevitably will have an impact over the pulmonary circulation altering right ventricular preload, afterload and finally right ventricular performance and function [1]. It is already well known that applying PEEP could possibly alleviate left ventricular performance in patients with cardiac compromise but also can worsen right ventricular function. Spontaneous breathing generates negative pleural pressure at the end of inspiration associated with greater right ventricular preload and better right ventricular perfusion, in contrast, positive pressure ventilation implies creating greater right ventricular afterload due to positive pressure ventilation [2]. The positive pressure ventilation by itself could lead to alveolar overdistension resulting in alveolar vessels compression while creating greater pulmonary vascular resistance, which implies elevation of right ventricular afterload. The elevation of right ventricular afterload has well known deleterious effects over the right sided myocardium with possibility of right ventricular disfunction development.

Aim of the Study

According to the above-discussed effects of positive pressure ventilation, right ventricular performance and function in polytraumatized patients demanding mechanical ventilation, will be examined and compared to spontaneously breathing patients not needing mechanical ventilation. The aim of this study is to evaluate the effect of positive pressure ventilation over the right ventricle and to explore possible existence of association of mechanical ventilation with right ventricular dysfunction. Conduction of this study was approved by the Ethical Committee for Human Research of Medical Faculty – Skopje at "Ss. Cyril and Methodius" University – Skopje on 1st of February 2023 with number of approval 03-300/3.

Material and Methods

In this study we have included 50 patients admitted to the Department of Anesthesia, Reanimation and Intensive Care at the University Clinic for Traumatology, Orthopedics, Anesthesia, Reanimation, Intensive Care and Emergency Department in Skopje. All patients included in the study were polytraumatized adults with more than 18 years of age and had signed informed consent by their family member, since some of the admitted patients were unconscious. All patients that have not fulfilled the criteria for having polytrauma, patients younger than 18 years of age, pregnant women and already resuscitated patients, as well as those whose families did not provide informed consent for participation have not been included in the study. Regarding the need for mechanical ventilation, all patients included in the study were divided into two groups, a group of mechanically ventilated patients and spontaneously breathing patients not needing mechanical ventilation. We performed an echocardiography exam focusing on the right heart function in all patients that have fulfilled the inclusion criteria in three time points. The first echocardiographic examination was performed 24 hours after ICU admission, second exam was performed on day 7 of admission, while the third examination was done 14 days after admission. Right ventricular function was examined with measuring Tricuspid Annular Plane Systolic Excursion (TAPSE) and Right Ventricular Fractional Area Change (RV FAC). TAPSE is a surrogate for assessment of longitudinal systolic function of the right sided myocardium, while FAC is representing radial systolic function [3]. According to the European Recommendations for Cardiac Chamber Quantification in Adults, values for TAPSE and RV-FAC were measured in 4 chambers apical view of the heart [3]. TAPSE was measured using M-mode echocardiog-

raphy (Figure No.1A) referring to the systolic longitudinal displacement of the lateral tricuspid annulus towards the apex, since the septal annulus movements are relatively limited, and its value represents longitudinal systolic function of the right ventricle [4]. Values for TAPSE less than 17mm were considered as systolic dysfunction [3,4]. RV-FAC was measured in four chambers view with measuring Right Ventricular End Diastolic Area (RVEDA) at the end diastole and Right Ventricular End Systolic Area (RVESA) during the systole (Figure No.1B). RVEDA and RVESA values were used to calculate RV-FAC according to the following equitation: RVEDA-RVESA/RVEDA x100 [3]. RV-FAC values lower than 35% were considered as a sign for radial right ventricular systolic dysfunction. Statistical analysis was done with calculating the mean value of TAPSE and FAC, as well as with using Mann Whitney U Test.

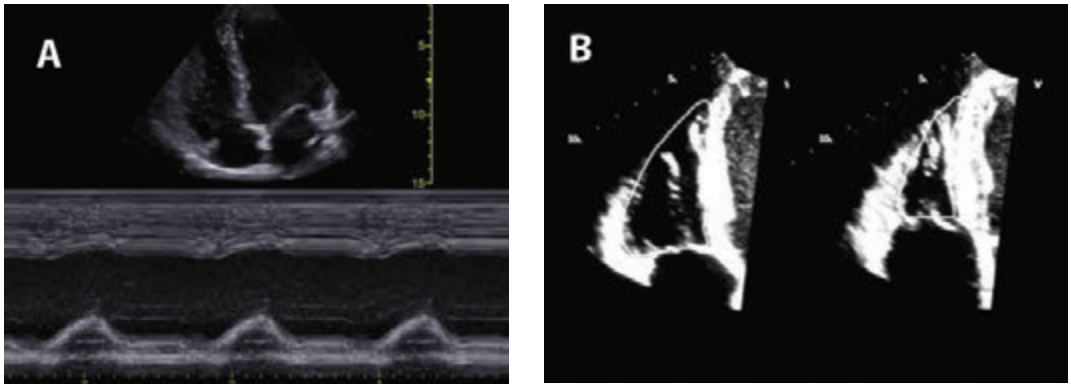

Figure 1. (A) M-mode measurement of TAPSE in four chamber view and (B) measurement of RVEDA and RVESA in order to calculate RV FAC.

Results

In total, 50 polytraumatized patients were included in the study where 26 of them (52%) were mechanically ventilated, while 24 (48%) were in the spontaneously breathing patients' group not needing mechanical ventilation. In the group of mechanically ventilated patients 80.7% were males in comparison to the group of spontaneously breathing patients, where 79.1% were males without statistically significant difference in between groups (Chart No.1). Regarding the longitudinal systolic function, mean values for TAPSE were 20, 19.1 and 19.9 in mechanically ventilated patients 24 hours, on the 7th day and at the 14th day of admission respectively in comparison to 21.9, 20.57 and 20.08 in spontaneously breathing patients at the same examination points (Chart 2). Nevertheless, that at all measuring points the values for TAPSE were higher in the spontaneously breathing patients when compared to mechanically ventilated patients, using Mann-Whitney U Test, we did not found statistically significant difference in between both groups (p 0.07; p 0.123 and p 0.77) 24 hours after admission, on 7th day and on 14th day after admission in the ICU (Table 1). Mean values for RV-FAC 24 hours after admission were 39.8 in mechanically ventilated patients versus 41 in spontaneously breathing patients without any statistically significant difference between both groups (Mann-Whitney U test: p 0.47). On 7th day and on day 14 after admission in the ICU, the mean values for FAC were 38.9 and 39.6 in mechanically ventilated patients, respectively, versus 44.9 and 47.5 measured in spontaneously breathing patients, confirming that RV-FAC was significantly lower in the group of patients demanding mechanical ventilation (Mann-Whitney U test: p 0.04 and p 0.03) (Table 2 and Chart 3).

Table1. Mann-Whitney U Test values for TAPSE in mechanically ventilated versus spontaneously breathing patients.

Mann-Whitney U Test	TAPSE 24 hours after admission	TAPSE on 7th day	TAPSE on 14th day
U	216	184.5	161
Z	-1.79	1.5	-0.28
p	0.07	0.123	0.77

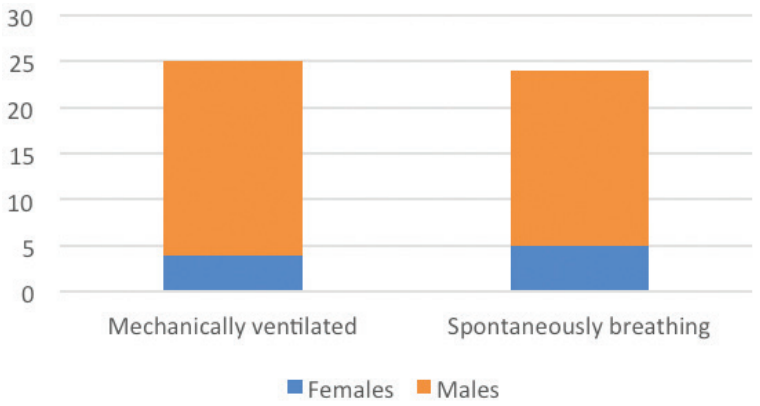

Chart 1. Distribution of patients by number and gender in both study groups: mechanically ventilated versus spontaneously breathing.

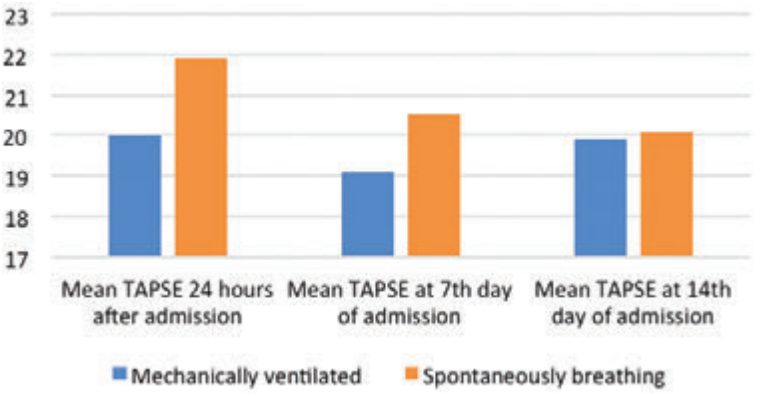

Chart 2. Mean values for TAPSE in both groups measured 24 hours after admission, 7 days after admission and 14 days after admission.

Table 2. Mann-Whitney U Test values for RV FAC in mechanically ventilated versus spontaneously breathing patients.

Mann-Whitney U Test	RV FAC 24 hours after admission	RV FAC on 7th day	RV FAC on 14th day
U	275	163.5	99.5
Z	-0.7	2.02	-2.1
P	0.47	0.04	0.03

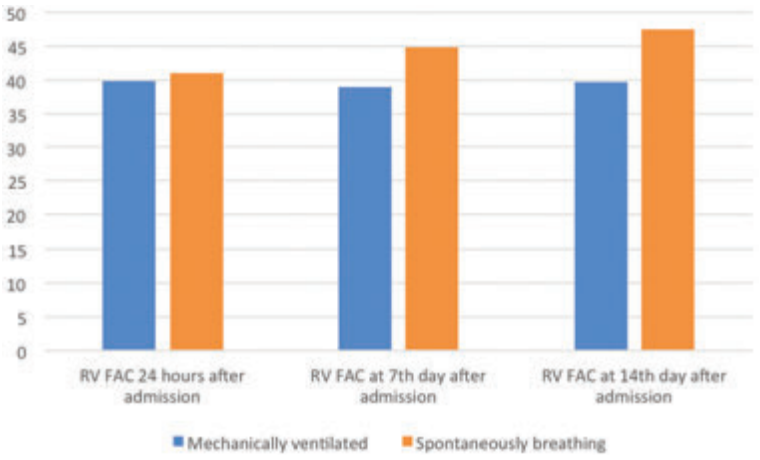

Chart 3. Mean values for RV FAC in mechanically ventilated patients versus spontaneously breathing patients 24 hours after admission, 7 days and 14 days after admission.

Discussion

Among all patients included in the study we could not found any gender related association with mechanical ventilation since regardless the need of respiratory support, the male to female ratio were similar in both groups where around 20% of polytraumatized patients were female. Similar results were found in the retrospective study of Weihs V. et al., where among 980 polytraumatized patients 30% were females which is confirmative that polytrauma in general is related with male gender [5], as presented in our results. Another study confirms the finding that polytrauma is more frequently met in males [6]. Regarding the gender representation among polytraumatized patients with chest trauma, Jayle CP et al. found exactly the same male to female ratio where only 20% of patients experiencing flail chest were females [7], which is in accordance to our results.

Right ventricular disfunction (RVD) has been observed in severely injured patients and has been related to higher mortality, especially when it was found to happen in the early stages of polytrauma [8]. Therefore, we have examined right ventricular performance and function with measurement of TAPSE and RV FAC as surrogates of longitudinal and radial systolic function of the right ventricle in mechanically ventilated, versus spontaneously breathing polytraumatized patients. Until now, TAPSE was considered as a "gold standard" in detection of right ventricular dysfunction and lower than normal values have been associated with bad outcome in mechanically ventilated patients [9]. TAPSE lower than 17mm was considered as a cut off value for diagnosis of Right Ventricular Dysfunction [3]. Since TAPSE is marker for longitudinal systolic function, we measured RV-FAC as a marker of radial systolic function. In our study, values for RV-FAC lower than 35% were considered as evidence for RVD existence which has been previously already stated and widely accepted [3,9]. In the study of Simmons J. et al., TAPSE and RV-FAC were used to detect the right ventricular dysfunction in patients exhibiting respiratory failure and needing mechanical ventilation while in our study we use them to examine the effect of mechanical ventilation over the right ventricle in polytraumatized patients and its association with RVD, dividing the patients into two groups regarding the need for mechanical ventilation. Usage of mechanical ventilation was previously recognized as potentially hazardous for right ventricular performance and was considered as a risk factor for dysfunction development [10]. Regardless of the previously discussed statement by Paternot A. et al. that mechanical ventila-

tion could worsen the right ventricular systolic function, thus, when using TAPSE as a marker of longitudinal systolic dysfunction in our study, we found that mechanically ventilated patients exhibited lower values for TAPSE than spontaneously breathing patients, but those differences were not statistically significant in none of the examining points. Contrary, we have found that at all examining points mechanically ventilated patients have had lower values for RV-FAC which were significantly lower (p 0.04 and p 0.03) on the 7th day and 14th day of admission and commencement of mechanical ventilation. According to these findings, exposure of the patients to mechanical ventilation for at least 7 days leads to impairment of radial RV systolic function. Therefore, our findings confirm the existence of association between the usage of mechanical ventilation and de novo development of RVD in patients with previously intact right ventricle. The impact of positive pressure ventilation over the right ventricle and its relationship with RVD development was discussed and highlighted in the study of Oweis J. et al., where right ventricular function in COVID patients was examined using the same tools as we did in our study. Same as we found association of mechanical ventilation with RVD occurrence, they found positive correlation between usage of mechanical ventilation and existence of right ventricular dysfunction and/ or dilatation [11]. Despite the same conclusion regarding the usage of mechanical ventilation and development of RVD, unlike in our study, in the study of Oweis J. et al., it was not specified which type of right ventricular systolic function was more affected, either longitudinal or radial. Positive pressure ventilation installation has been associated with worsening of right ventricular systolic function according to Magunia H. et al., where right ventricular function was examined with echocardiography in patients prior to and after positive pressure ventilation initiation [12]. They found significantly lower values for TAPSE (p 0.0013) after initiation of positive pressure ventilation when compared to spontaneous ventilation in the same patients, suggesting that longitudinal systolic function could be altered in mechanically ventilated patients which was present in our study as well, because values for TAPSE were lower in the group of mechanically ventilated patients but still not statistically significant as in the study of Magunia H. et al. Nevertheless, we found significantly lower values for RV FAC in mechanically ventilated patients after 7 days of mechanical ventilation that have become even more significant after 14 days of mechanical ventilation, but that was not met in the study of Magunia H. et al. We believe that the difference between ours and theirs results could be explained by the difference in the study protocols, since they have assessed RV function in spontaneously breathing patients prior to induction in anesthesia and positive pressure ventilation initiation and immediately after that, while in our study those patients which were mechanically ventilated were sedated with continuous sedation not exhibiting strong effects over the hemodynamics as it does regular induction in anesthesia. Positive pressure ventilation initiation is related to increasement of the right ventricular afterload, while RV is extremely sensitive when changes in inspiration arise [13], therefore changes of function are more than expected especially in patients exposed to long lasting mechanical ventilation as it was seen in our study. Chu A. et al. recently have published a study where they evaluated the right ventricular performance in patients with obstructive sleep apnea that needed positive pressure ventilation in comparison to healthy subject group. Since in this study they have examined the effect of positive pressure ventilation over the RV, we consider that the results are worth and relevant to mention and compare to our results despite the differences in the study design. Therefore, they have found no significant differences in values for TAPSE, but significantly lower values for right ventricular end diastolic volume (RVEDV) and right ventricular end systolic volume (RVESV) were found in the group of patients that were exposed on mechanical ventilation [14]. Those findings are in complete accordance with our findings, despite the fact that we were measuring RVEDA and RVESA instead of RVEDV and RVESV where both are surrogates for assessment of the radial

right ventricular function. Obviously, in absence of significant difference in TAPSE found in our study as in the study of Chu A. et al. but detecting significantly lower values for RV FAC confirms that patients exposed to positive pressure ventilation are prone to suffer of right ventricular dysfunction where radial systolic function is affected, but longitudinal systolic function stays preserved even in terms of elevated right ventricular afterload. Lower values for RV FAC were associated with longer period of mechanical ventilation [15], which is confirmed in our study as well, since we met significantly lower values for RV FAC after 7 days of mechanical ventilation initiation which became even more significant after 14 days of mechanical ventilation commencement. We strongly believe that even more detailed analysis of the right ventricular function, as well as its morphology, could bring us even more useful data that could help in understanding the effect of mechanical ventilation over the right sided myocardium. We consider our results could serve as an initiator for further research on this topic where a greater group of patients will be assessed in order to provide even stronger conclusions. Modern echocardiography offers even more precise analysis of the right ventricle with use of Right Ventricle Speckle Tracking Echocardiography with right heart strain evaluation which could be helpful for further research. We mustmention that this study has its own limitations as well, since it is a single center study where a small sample size of patients were prospectively evaluated. The larger cohort of patients could be needed in order to provide more detailed results.

Conclusion

The usage of mechanical ventilation is associated with significantly lower RV FAC when compared to spontaneously breathing patients. Our findings imply association of radial right ventricular systolic dysfunction with positive pressure mechanical ventilation, while longitudinal right ventricular systolic function stays unaffected. Longer duration of mechanical ventilation has been related to worsening of already affected radial systolic function of the right ventricle.

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NON-CARDIAC SURGERY IN CARDIAC PATIENTS: KEY INSIGHTS

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Abstract

The growing elderly population leads to a higher proportion of primarily non-cardiac surgeries being performed on patients with cardiac conditions. This highlights the necessity to review and update protocols for ensuring safe surgery in the patient group mentioned above. The cardiovascular complications are especially prevalent in patients with documented or asymptomatic coronary heart disease, left ventricular (LV) dysfunction, valvular heart disease (VHD) and arrhythmias, particularly when undergoing surgeries that place prolonged strain on the heart and hemodynamics. Preoperative N-terminal fragment of proBNP (NT-proBNP) measurement is the stronger predictor for postoperative complications. We should not initiate beta blockers, alpha-2 agonists, calcium channel blockers and statins, but rather continue them during the preoperative period. The risk of postoperative bleeding should not be the main reason for delaying non-cardiac surgery.

Key Words: *anesthesia management; cardiac patient; non-cardiac surgery.*

Introduction

Global estimates indicate that over 300 million major surgeries take place annually, representing approximately 5% of the world population, a figure that is steadily increasing. Around 74% of these procedures occur in countries with substantial healthcare investments (1).

Cardiovascular risk factors and conditions are common among adults undergoing non-cardiac surgery (NCS), and perioperative cardiovascular complications play a significant role in causing morbidity and mortality. The risk of perioperative complications is influenced by factors such as the presence of comorbidities, the patient's pre-surgery health status, and the urgency, scale, type, and length of the surgical procedure. Cardiovascular complications are especially prevalent in patients with documented or asymptomatic coronary heart disease, left ventricular (LV) dysfunction, valvular heart disease (VHD) and arrhythmias, particularly when undergoing surgeries that place prolonged strain on the heart and hemodynamics (1,2). Perioperative myocardial ischemia can be result of three main mechanisms: an imbalance between oxygen supply

and demand due to coronary artery stenosis, which may become flow-limiting during perioperative hemodynamic fluctuations; acute coronary syndrome (ACS) caused by stress-induced rupture or erosion of vulnerable atherosclerotic plaques, combined with the pro-inflammatory and hypercoagulable states triggered by surgery, as well as hemodynamic stress from fluid shifts and anesthesia; and increased bleeding risks during surgery, which may necessitate halting antiplatelet therapy and potentially cause stent thrombosis in patients who have had recent coronary stent placements before non-cardiac surgery (3). Left ventricular dysfunction and arrhythmias can develop for various reasons across all age groups. As the incidence of coronary artery disease (CAD), VHD, heart failure and arrhythmias rises with age, the risk of perioperative cardiovascular mortality and morbidity becomes especially concerning in adults undergoing major non-cardiac surgeries (1,3,4).

Methods and Aims

We conducted a thorough literature search to identify clinical studies, reviews and other evidence involving human subjects, published in English. The search included MEDLINE (via PubMed), EMBASE, the Cochrane Library and other relevant databases pertinent to this guidelines review, with the goal of helping healthcare professionals to determine the most effective management strategies for each patient based on their specific condition. Guidelines and their recommendations should support healthcare providers in making informed decisions in their everyday practice.

Preoperative and Operative Assessment

The American Society of Anesthesiologists (ASA) Physical Status Classification System categorizes patients based on their overall health (5). The Revised Cardiac Risk Index (RCRI) is a straightforward, validated and widely used tool for assessing the perioperative risk of major cardiac complications, using six risk factors: ischemic heart disease, cerebrovascular disease, history of HF, insulin therapy for diabetes, serum creatinine ≥2.0mg/dL, and planned high-risk procedure (intraperitoneal, intrathoracic or vascular surgery) (with one point assigned for each) (6). The RCRI provides moderate risk discrimination for cardiac events in patients undergoing non-cardiac surgery, although there is inconsistency among different risk-prediction tools in accurately identifying low-risk patients. Despite the patient's condition, another important factor is the time of surgery (6). In elective surgery, preoperative management involves optimizing medical therapy and considering revascularization through minimally invasive percutaneous coronary intervention or coronary artery bypass grafting when indicated. However, in emergency procedures, only medical management remains a viable option (7). Generally, acute procedures are associated with a higher risk of complications compared to elective procedures. Several factors influence outcomes when comparing acute or time-sensitive surgery to elective surgery, including the patient's overall condition versus the stage and progression of the acute illness. If emergency surgery for a life-threatening condition is needed, it is believed that most of the patients would prioritize the potential benefits of the surgery over the risks. Consequently, surgery should not be delayed unless there is a legitimate reason (1,7). The patient's best interests should be prioritized when making treatment decisions, informed consent should be obtained whenever possible, and all decisions should be clearly documented (8). The optimal timing for non-cardiac surgery (NCS) should be determined through discussions within a multidisciplinary team, in-

cluding an anesthesiologist, to ensure tailored and optimized anesthesia for each patient.

Several prospective observational studies have investigated the ability of N-terminal fragment of proBNP (NT-proBNP) and BNP to predict major cardiovascular events following non-cardiac surgery. Brain natriuretic peptides (BNPs) and the NT-proBNP are released by the myocardium in response to stimuli like myocardial stretch and ischemia (9,10). A low ejection fraction, measured by echocardiography during rest, was found to be a significant borderline independent predictor of major cardiovascular complications occurring within 30 days following non-cardiac surgery. However, a preoperative NT-proBNP measurement was a much stronger independent predictor (11). The patients with pre-existing heart conditions are typically managed with appropriate drug therapy. The recommendations for discontinuing or maintaining treatment differ depending on the class of medication. The advice goes against starting beta-blockers, alpha-2 agonists, and calcium channel blockers therapy within 24 hours prior to non-cardiac surgery, but the chronic therapy should be continued. (Strong Recommendation; High-Quality Evidence) (12,13). ACEi/ARB blockers, as well as statins, should be continued preoperatively and postoperatively due to the minimized risk of uneventful events after non-cardiac surgery.

The type of surgery, the patients' hemostasis values, and the anticipated bleeding all influence blood management during surgery. Tranexamic acid should be promptly considered for patients experiencing significant surgical bleeding (Class IIa, LOE A). The use of washed cell salvage is also recommended for surgeries where expected blood loss exceeds 500mL (Class I, LOE A) (14).

Perioperative Assessment

Both major bleeding and thrombosis (such as stroke and venous thromboembolism) are significant surgical outcomes and major contributors to mortality in non-cardiac surgery (NCS). Managing these perioperative risks is especially challenging in patients on long-term oral anticoagulation (OAC), including vitamin K antagonists (VKA) and direct oral anticoagulants (DOAC). Developing a perioperative plan for elective NCS should involve assessing patient-specific factors (e.g., age, thrombotic risk, renal function, history of bleeding), procedural factors (e.g., timing of surgery, bleeding risk) and medication characteristics (e.g., dosing, drug interactions, onset/offset) (13). In general, it is considered safe to perform surgeries with minimal bleeding risk without stopping OAC therapy for non-cardiac surgeries with higher bleeding risks; a time-based interruption ("time reversal") of OAC therapy is recommended. Procedures with higher bleeding risks, such as neuraxial anesthesia, should be conducted with a complete interruption of OAC. To achieve minimal drug effects, anticoagulants should be withheld for at least 5 half-lives with a minimum of 3 days for factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and at least 4 days for dabigatran (or 5-6 days if creatinine clearance is <50mL/min) (15). If resuming full-dose anticoagulation in the postoperative period presents a bleeding risk greater than the risk of thromboembolic events, it may be appropriate to delay full anticoagulation until 48-72 hours post-surgery, using interim thromboprophylaxis until it is deemed safe to restart full anticoagulation (Class IIb, LOE C). The use of reduced-dose NOACs is not recommended to minimize the risk of postoperative bleeding. Recommendations go to perioperative measurement of NT proBNP/BNP, monitoring of ECG, and against use of pulmonary artery catheters (1).

Hemodynamic monitoring is essential in these patients due to their increased risk of cardiovascular instability. Continuous ECG monitoring is recommended intraoperatively, especially in

patients with a history of coronary artery disease (CAD) or heart failure (HF), to detect ischemia or arrhythmias. Non-invasive blood pressure (NIBP) monitoring is standard, but in high-risk cases, invasive arterial blood pressure monitoring provides more precise hemodynamic control and facilitates blood sampling for arterial blood gas analysis and coagulation parameters. Central venous pressure (CVP) monitoring may be considered in patients with significant cardiac dysfunction, volume status uncertainty, or the ones requiring vasoactive therapy. Advanced hemodynamic monitoring, such as pulse contour analysis or esophageal Doppler, can be useful for guiding fluid management in patients with significant cardiovascular risk. Pulmonary artery catheters are not routinely recommended due to a lack of proven benefit in most of the perioperative settings. Perioperative measurement of NT-proBNP/BNP is recommended to assess cardiovascular risk and predict postoperative complications. Maintaining normovolemia and avoiding hypotension are key goals to reduce the risk of perioperative myocardial injury, with careful titration of fluids and vasopressors to balance perfusion without exacerbating bleeding risk (16).

When selecting anesthetic techniques for cardiac patients undergoing non-cardiac surgery, both general and regional anesthesia have distinct considerations. General anesthesia provides controlled airway management and stable hemodynamics but may suppress myocardial function. Regional anesthesia, such as neuraxial or peripheral nerve blocks, can attenuate the surgical stress response and offer superior postoperative analgesia, potentially benefiting patients with cardiovascular disease. However, in the patients receiving anticoagulant therapy, regional anesthesia carries an increased risk of hemorrhagic complications, including vertebral canal hematoma, which can lead to permanent neurological deficits if not promptly addressed. Therefore, the decision to employ regional anesthesia in anticoagulated patients requires careful evaluation of bleeding risks and adherence to established guidelines. For instance, the American Society of Regional Anesthesia and Pain Medicine provides evidence-based recommendations to mitigate these risks. For general anesthesia, maintaining hemodynamic stability is crucial. The choice of induction agents should prioritize minimal cardiovascular depression, while maintenance should involve anesthetics that support cardiac function and provide adequate depth of anesthesia without compromising myocardial performance. Close intraoperative monitoring, including invasive blood pressure measurement and cardiac output assessment, is recommended to ensure optimal perioperative management (17,18). Ultimately, the choice between general and regional anesthesia should be individualized, taking into account multiple factors, including the patient's cardiac status, anticoagulation regimen, urgency and timing of surgery, overall physical status, presence of comorbidities, and the type and extent of the surgical procedure. These considerations help optimize perioperative management, balancing the risks of anesthesia-related complications with the benefits of maintaining hemodynamic stability and minimizing bleeding risks.

Postoperative Care

The postoperative period is a high-risk phase for cardiac patients recovering from non-cardiac surgery, demanding meticulous monitoring and targeted interventions to prevent complications such as myocardial infarction, arrhythmias, heart failure exacerbation and thromboembolic events. Continuous telemetry is essential for at least 48 hours in high-risk patients—particularly those with prior coronary artery disease, reduced ejection fraction, or a history of arrhythmias—to detect silent ischemia or unstable rhythms. Serial 12-lead ECGs should be performed

immediately after surgery and daily for 48–72 hours in these patients, while invasive hemodynamic monitoring (e.g., arterial lines or pulse contour analysis) may be warranted in those with hemodynamic instability or cardiogenic shock (1,16,19,20).

The biomarker evaluation plays a central role in early detection of adverse events. High-sensitivity troponin levels should be measured at 24 and 48 hours postoperatively, as asymptomatic elevations often indicate perioperative myocardial injury and correlate with poor outcomes. Concurrently, serial BNP or NT-proBNP measurements help to identify subclinical heart failure, guiding judicious diuretic use and volume management. Medication optimization is equally critical: beta-blockers should be continued to avoid rebound tachycardia, with doses adjusted to maintain a heart rate of 60–80 bpm without inducing hypotension. Statins must be resumed promptly to stabilize endothelial function, while anticoagulants and antiplatelet agents (e.g., aspirin) should be restarted as soon as surgically safe, balancing thrombotic and bleeding risks (9,10).

The volume management requires a nuanced approach, prioritizing goal-directed fluid therapy using dynamic parameters like stroke volume variation to prevent both hypovolemia and overload. In patients with heart failure, cautious diuresis may be needed to avert pulmonary edema, while respiratory care,including early extubating, incentive spirometry, and opioid-sparing analgesia, reduces the risk of hypoxia-induced ischemia. Postoperative arrhythmias, particularly atrial fibrillation, are common and managed initially with rate control (beta-blockers, calcium channel blockers) or amiodarone for rhythm stabilization, with anticoagulation initiated if arrhythmias persist beyond 48 hours. Heart failure exacerbations demand prompt recognition of signs like jugular venous distension or crackles, treated with IV diuretics, nitrates, or inotropes as needed (19,20).

Enhanced Recovery After Surgery (ERAS) protocols, emphasizing early mobilization within 24 hours improve cardiopulmonary function and reduce thromboembolic risks. Pain management should prioritize regional techniques or non-opioid analgesics (e.g., acetaminophen, NSAIDs) to minimize delirium and respiratory depression. Multidisciplinary collaboration is vital: cardiology input is mandatory for troponin-positive patients or those with hemodynamic instability, while thromboembolic prophylaxis with low-molecular-weight heparin or mechanical compression devices should continue until full mobility is restored. Prior to discharge, it should be ensured that the patients meet criteria such as stable vitals, adequate pain control and baseline functional capacity, with structured follow-up plans involving cardiac rehabilitation and medication adherence counseling. Patient education on symptom recognition (e.g., chest pain, dyspnea) and dietary modifications (e.g., sodium restriction in heart failure), further support the recovery (21-24).

Seamless coordination between surgeons, anesthesiologists, cardiologists and rehabilitation teams ensures optimal transitions from acute care to outpatient management, prioritizing both cardiac stability and surgical recovery.

Conclusion

Despite ongoing advancements in perioperative cardiovascular risk assessment and management, optimizing outcomes for cardiac patients undergoing non-cardiac surgery remains a complex challenge. A multidisciplinary, evidence-based approach incorporating NT-proBNP

measurement, individualized medication management and vigilant perioperative monitoring is essential for reducing morbidity and mortality. For postoperative care, the most significant role is a vigilant, protocol-driven approach—integrating continuous monitoring, biomarker-guided therapy and ERAS principles. Further research is warranted to refine risk prediction models and develop tailored perioperative strategies for high-risk cardiovascular patients.

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TWO CASE REPORTS ON THE EFFECT OF SEVOFLURANE EXPOSURE DURATION ON SERUM LEVELS OF NEURON-SPECIFIC ENOLASE (NSE) AND S100 PROTEIN IN CHILDREN

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Abstract

The length of sevoflurane exposure may raise the risk of neuron-specific enolase (NSE) and S100 protein alterations in blood, which might thereafter result in postoperative cognitive dysfunction (POCD). The pathophysiology of POCD caused by the volatile anesthetic sevoflurane has been the subject of extensive research in recent years. This case study looks at preliminary findings about the effects of different sevoflurane anesthetic exposure durations on the levels of S100 protein and NSE in children's blood. Additionally, it looks into how sevoflurane affects children's early cognitive performance following surgery. To detect neurological effects during general anesthesia and ascertain the length of sevoflurane exposure, we employ the particular markers such as S100 protein and NSE.

In this case study, we present two pediatric patients who underwent general anesthesia with sevoflurane for different durations. The aim was to observe potential postoperative changes in NSE and S100 protein levels, which are biomarkers associated with neuronal injury and cognitive function. After the surgery, we utilize these levels to assess any cognitive problems. The parents or guardians gave their informed consent.

Key Words: *General anesthesia for children; sevoflurane, neuron-specific enolase, S100 protein, postoperative cognitive dysfunction in children.*

Introduction

Sevoflurane (1,1,1,3,3,3-hexafluoro-2-[fluoromethoxy]propane ether) is one of the most commonly used volatile anesthetics for both induction and maintenance of general anesthesia, particularly in pediatric patients. Its favorable pharmacokinetics, including rapid onset and offset, minimal airway irritation and hemodynamic stability, make it an ideal choice for children. However, concerns have emerged regarding its potential neurotoxic effects, particularly in the developing brain. Studies suggest that prolonged or repeated exposure to sevoflurane may contribute to postoperative cognitive dysfunction (POCD), manifesting as impairments in memory, attention and learning (1).

The exact pathophysiological mechanisms underlying sevoflurane-induced cognitive dysfunction remain unclear, but several hypotheses have been proposed. These include neuroinflammation, mitochondrial oxidative stress, disruptions in neurotransmitter signaling, and increased blood-brain barrier permeability. Notably, the role of specific biomarkers such as S100β and neuron-specific enolase (NSE) has been investigated as potential indicators of neuronal injury. Elevated levels of these biomarkers have been correlated with cognitive impairment, suggesting that they may serve as valuable tools for assessing perioperative neurocognitive changes.

Despite conflicting findings, emerging evidence suggests that young children, whose brains are still developing, may be particularly vulnerable to sevoflurane-induced neurotoxicity. This raises concerns regarding the long-term neurodevelopmental consequences of general anesthesia in pediatric patients, making it crucial to identify risk factors, implement preventive strategies, and establish monitoring protocols for cognitive assessment (2-4).

In this report, we present two pediatric cases in which POCD was observed following sevoflurane anesthesia. We discuss potential contributing factors, the role of neuro-biomarkers, and the importance of early detection and intervention in mitigating the risk of cognitive impairment in young patients.

Case Presentation 1.

The first case we present is a two-year-old patient with 13kg body weight, ASA 1, admitted to the Clinic for Pediatric Surgery for elective surgery with a diagnosis of contracture of digits in the left hand after combustion. The patient was preoperatively prepared with Midazolam syrup (0.5mg/kg), after which he was introduced into general endotracheal anesthesia with Propofol, Fentanyl, Lidocaine and Rocuronium. Intraoperatively, he was administered with Sevoflurane with a MAC of 0.8 for a duration of 80 minutes, and one dose of Paracetamol was also administered. Preoperatively measured values of NSE were 1.96ng/ml and S100 0.134μg/L, while one hour postoperatively the values of NSE were 0.156ng/ml and S100 18.28μg/L. The following tables present all findings.

Table 1. Intraoperative information about OP and anesthesia.

Variables		**Short duration**	**Long duration**
Duration of surgical intervention			70 min.
Duration of exposure to sevoflurane			80 min.
ANESTHESIA		**Medication**	**mg/kg**
Premedication		Sir. Midazolam	0.5mg/kg
Induction:	Hypnotic	Propofol	4.5mg/kg
	Relaxing agent	Rocuronium	0.4mg/kg
	Opioid analgesic	Fentanyl	0.004mg/kg
Anesthesia maintenance		Sevoflurane	MAC 0.8
Additional therapy		Paracetamol	15mg/kg
		Lidocaine 1%	0.5mg/kg

Table 2. Perioperative monitoring.

Variables	Before induction	10 min. after induction	30 min. after induction
BP (mmHg)	110/53	117/60	118/65
Pulse/min	116	112	111
SpO2 %	99	99	99
EtCO2	49	42	41

Table 3. Laboratory values of examined biomarkers.

Variables	Preoperatively	After 1 hour
S100	0.134	0.156
NSE	1.96	18.28

Table 4. Postoperative pain and anxiety.

Variables	PACU	After 1 hour
VAS	6	5
Anxious scale	2 – medium anxious	3 - calm
RASS - scale	3 – sedated easily agitated	3 - sedated easily agitated

Case Presentation 2.

The second case was a twelve-year-old 56kg body weight patient, ASA 1, admitted to the Clinic of Pediatric Surgery for elective surgery with a diagnosis of pyogenic granuloma on the hand. The patient was preoperatively prepared with Midazolam syrup (0.5mg/kg), after which he was introduced into general endotracheal anesthesia with Propofol, Fentanyl and Lidocaine. Intraoperatively, he was administered Sevoflurane with a MAC of 0.8 for 12 minutes. Preoperatively measured values were NSE 20.29ng/ml, and S100 0.064μg/L, while one hour postoperatively the NSE values were 19.89ng/ml and S100 0.100μg/L. All findings are presented in the following tables.

Table 5. Intraoperative information about OP and anesthesia.

Variables		Short duration	Long duration
Duration of surgical intervention		10 min.	
Duration of exposure to sevoflurane		12 min.	
ANESTHESIA		**Medication**	**mg/kg**
Premedication		Sir. Midazolam	0.5 mg/kg
Induction:	Hypnotic	Propofol	4.5mg/kg
	Opioid analgesic	Fentanyl	0.004mg/kg
Anesthesia maintenance		Sevoflurane	MAC 0.8
Additional therapy		Lidocaine 1%	1mg/kg

Table 6. Perioperative monitoring.

Variables	Before induction	10 min. after induction	30 min. after induction
BP (mmHg)	120/80	110/65	
Pulse/min	80	66	
SpO2 %	99	100	
EtCO2	34	34	

Table 7. Laboratory values of examined biomarkers.

Variables	Preoperatively	After 1 hour
S100	0.064	0.100
NSE	20.29	19.89

Table 8. Postoperative pain and anxiety.

Variables	PACU	After 1 hour
VAS	4	3
Anxious scale	3 - calm	3 - calm
RASS - scale	2- sedated not agitated	0 - calm

Discussion

Anesthetic agents, including sevoflurane, are widely recognized for their neuroprotective properties, primarily through their ability to reduce cerebral metabolic demand and oxygen consumption. This effect helps maintain the balance between brain energy supply and demand, thereby increasing neuronal tolerance to hypoxic and ischemic injury. However, emerging evidence suggests that certain anesthetics, particularly volatile agents such as sevoflurane, may also exert neurotoxic effects, especially with prolonged exposure. This paradoxical effect has been linked to neuroinflammation, oxidative stress, and alterations in neurotransmitter function, ultimately leading to neuronal damage and cognitive dysfunction (5,6). In our presented cases, the potential for sevoflurane-induced neurotoxicity was evaluated using two well-established biomarkers of neuronal injury: neuron-specific enolase (NSE) and S100 protein. Both biomarkers serve as indicators of blood-brain barrier integrity and neuronal distress. NSE, an enzyme found in neurons and neuroendocrine cells, is widely used as a marker of neuronal damage. S100 protein, primarily found in astrocytes and Schwann cells, plays a role in calcium homeostasis, inflammatory regulation and cellular proliferation. Under normal physiological conditions, both biomarkers are present in the serum at very low levels. However, disruption of the blood-brain barrier due to ischemic, traumatic, or toxic insults can result in their elevated serum concentrations.

The findings from the two cases provide valuable insight into the potential impact of sevoflurane exposure on neurological integrity. In the first case, the patient was exposed to sevoflurane for 80 minutes, resulting in a significant postoperative increase in NSE levels. However, S100

protein levels remained unchanged. The selective increase in NSE suggests a primary neuronal injury rather than a widespread disruption of the blood-brain barrier. The lack of S100 elevation could indicate that astrocytic and glial responses were either delayed or less pronounced in this scenario. The second patient was exposed to sevoflurane for only 12 minutes, with no significant increase in NSE or S100 levels. This suggests that brief exposure to sevoflurane may not lead to measurable neuronal or astrocytic damage, reinforcing the hypothesis that anesthetic duration plays a critical role in neurotoxicity. Several factors could explain the observed discrepancy between NSE and S100 levels in Case 1: Selective neuronal vulnerability**:** Neurons may be more susceptible to direct anesthetic-induced injury than astrocytes, leading to an increase in NSE without a concurrent rise in S100; Delayed astrocytic response**:** S100 protein release may occur later in the neuroinflammatory cascade, potentially manifesting at later time points beyond the immediate postoperative period; Different pathways of cellular injury**:** NSE elevation may result from direct neuronal stress, while S100 release typically occurs in conditions involving more extensive blood-brain barrier disruption (7).

These findings underscore the potential risks of prolonged sevoflurane administration, particularly in pediatric patients with developing brains. Several studies have suggested that repeated or prolonged exposure to volatile anesthetics may contribute to postoperative cognitive dysfunction (POCD), neuroinflammation and long-term neurodevelopmental deficits. This is particularly concerning in children, as their immature blood-brain barrier and ongoing synaptic development may render them more vulnerable to anesthetic-induced toxicity (8).

Given the lack of definitive evidence regarding the long-term impact of anesthetic-induced biomarker changes, further studies are warranted to: Investigate the time course of NSE and S100 changes postoperatively to determine whether delayed elevations occur. Assess additional biomarkers such as glial fibrillary acidic protein (GFAP) and tau protein for a more comprehensive evaluation of neuronal injury. Explore potential neuroprotective strategies, including pharmacological interventions and anesthetic technique modifications, to minimize neurotoxicity in pediatric populations (8).

Those cases highlight the differential effects of sevoflurane exposure duration on neuronal injury biomarkers, with a significant increase in NSE following prolonged exposure but no changes in S100 levels. These findings suggest that sevoflurane-induced neurotoxicity may primarily affect neurons rather than astrocytes in the early postoperative period. While brief exposure appears to be well tolerated, prolonged administration may contribute to neuronal stress, warranting further research into protective strategies and long-term neurocognitive outcomes.

Conclusion

This article discusses the pathophysiology and etiology of postoperative cognitive dysfunction (POCD) following general anesthesia, as well as the timely identification and assessment of individuals with this critical clinical condition. This study shows that postoperative levels of biomarkers of cerebral damage and postoperative agitation are significantly influenced by the length of sevoflurane exposure.

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PRE-OPERATIVE ASSESSMENT ON A PATIENT FOR LAPAROSCOPIC CHOLECYSTECTOMY WITH B12 ANEMIA

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Abstract

The pre-operative assessment is an opportunity to identify co-morbidities that may lead to patients' complications during the anesthesia, surgical or postoperative period. Patients scheduled for elective procedures will generally attend a pre-operative assessment 2-4 weeks before the date of their surgery. A woman at the age of 57 years was admitted to the hospital planned for the elective laparoscopic cholecystectomy. On the preoperative assessment on laboratory analysis, we found presence of anemia with MCV levels above normal and low levels of vitamin B12. She was never treated for anemia before. Peripheral blood smear showed presence of macrocytosis. The patient was put on treatment with intramuscular injections of vitamin B12. The operation was delayed for two months. She was admitted to the hospital after two months of treatment and blood analysis were made that showed Hb levels of 115g/l, hematocrit 35%, MCV was 92. She was operated after she had been hospitalized, and laparoscopic cholecystectomy was made without complications. She was released from hospital two days after surgery. The purpose of a preoperative evaluation is not to "clear" patients for elective surgery, but rather to evaluate, and if necessary, implement measures to prepare higher risk patients for surgery. By diagnosing anemia in the preoperative assessment, we reduced the risk of complications during the surgery and during the postoperative period. Early identification and effective treatment of anemia has the potential to improve clinical outcomes in surgical patients.

Key Words: *anemia; B12 deficiency; cholecystectomy; laparoscopy; pre-operative assessment.*

Introduction

The pre-operative assessment is an opportunity to identify co-morbidities that may lead to patients' complications during the anesthesia, surgical or postoperative period. Patients scheduled for elective procedures will generally attend a pre-operative assessment 2-4 weeks before the date of their surgery. A history and physical examination, focusing on risk factors for cardiac and pulmonary complications and a determination of the patient's functional capacity are essential to any preoperative evaluation (1).

Laparoscopic cholecystectomy has become a gold standard procedure since its introduction in the late 1980s and is now used worldwide as a treatment for cholelithiasis. Elective laparoscopic cholecystectomy is performed routinely as day-case surgery and is generally considered safe op-

eration. However, despite the advances in technology, the complications associated with laparoscopic cholecystectomy remain the same. Iatrogenic perforations of a gallbladder was the most common complication, and postoperative complications are bleeding from abdominal cavity, biliary duct leaks and infection of surgical wounds (2-4).

The perioperative anemia has been associated with increased risk of red blood cell transfusion and increased morbidity and mortality after surgery. In patients with pre-operative B12 anemia perioperative treatment with vitamin B12 injection reduces the need for intra and postoperative blood product transfusion. Laboratory examinations such as full blood count and MCV together with periphery blood smear are necessary for distinguishing types of anemia and implementing the right treatment. The optimal time frame to begin treating preoperative anemia before surgery is scheduled, ideally at least 3 to 4 weeks in advance (5).

Case report

A woman at the age of 57 years was admitted to the hospital planned for the elective laparoscopic cholecystectomy. At the admission, a new abdomen ultrasound was made that showed her gallbladder was filled with concrements and intrahepatic and extrahepatic bile ducts weren't dilated. She had acute cholecystitis attacks two times in the last five years, and she was treated with conservative treatment. Laboratory findings showed anemia with hemoglobin levels of 83g/l, hematocrit level of 26%, MCV 119, other laboratory parameters including transaminase levels and bilirubin levels were normal. We found that previous laboratory analysis that were made in 2023 also showed low hemoglobin levels of 95g/L, hematocrit levels of 26%, MCV 117fl, and she was not treated for anemia. She was only talking pills for hypothyroidism. We took blood levels of B12 vitamin and they came back low 104.6pg/ml. We also sent peripheral blood smear to the Clinic of Hematology, and the result showed presence of macrocytosis. In consultation with the hematologist we put the patient on a treatment with B12 1000mcg IM once daily for 10 days, then three times a week for three weeks and then once a month together with Folic Acid tablets 5mg once a day. The operation was delayed for two months. She was admitted to the hospital after two months. Blood analysis was made that showed Hb levels of 115g/l, hematocrit 35%, MCV was 92fl. She was operated next after she had been hospitalized, and laparoscopic cholecystectomy was made without complications under general anesthesia with the use of induction agents such as propofol and benzodiazepine. Muscle relaxant was also added. She was released from hospital two days after the surgery.

Discussion

The purpose of a preoperative evaluation is not to "clear" patients for elective surgery, but rather to evaluate and, if necessary, implement measures to prepare higher risk patients for surgery. Pre-operative outpatient medical evaluations can decrease the length of hospital stay, as well as minimize postponed or cancelled surgeries. A patient presenting without an established medical diagnosis is not necessarily healthy (6,7). Preoperative evaluation should seek to determine absolute contraindications to laparoscopy, such as inability to tolerate pneumoperitoneum and complications associated with anesthesia. Vitamin B12–deficiency anemia, also known as cobalamin deficiency, is a condition that develops when the body can't make enough healthy red blood cells because it doesn't have enough vitamin B12. Symptoms may include tingling feel-

ings or pain, trouble walking, feeling tired, uncontrollable muscle movement, confusion, slower thinking, mood or mental changes such as depression or irritability, problem with smell or taste, mouth ulcers diarrhea and weight loss, glossitis. The causes of B12 anemia are lack of intrinsic factor, drinking too much alcohol, stomach surgery, ulcerative colitis, Crohn disease, vegetarian diet, atrophic gastritis, drug induced megaloblastic anemia such as anemia caused by hydroxyurea, metformin, methotrexate. Treatment of B12 anemia is based on intramuscular treatment with B12 injection (8-10).

Conclusion

The perioperative assessment is important for reducing the postoperative complications in abdominal surgery. Clinical history, preoperative questionnaires, physical examination, routine tests, individual risk-assessment are necessary for reducing the postoperative complications. All the necessary examinations and evaluations were done on our patient and that was important because we discovered medical conditions for which the patient was not treated before. Operation was delayed and then was performed when the patient's comorbidities were adequately treated. In that way we reduced the complications during the surgery and during the postoperative period. Early identification and effective treatment of anemia has the potential to improve clinical outcomes in surgical patients.

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ULTRASOUND GUIDED SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK FOR UPPER LIMB SURGERY IN CARDIOVASCULAR COMPROMISED PATIENT

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Abstract

Introduction: We can use the supraclavicular block as a postoperative pain management approach, as an addition to general anesthesia, or as the sole form of anesthesia for upper limb surgery. For upper limb surgery, this block is a fantastic substitute for general anesthesia in patients with pulmonary and cardiac comorbidities.

Case Presentation: In order to undergo surgery for a fracture of the proximal portion of his upper arm, a 66-years-old male AA was brought to the Clinic for Orthopedic Diseases in Skopje. The anesthesiologic examination revealed that the patient had diabetes mellitus type II, cardiomyopathy, untreated ischemic heart disease and wheezing and crepitations in the distal portions of his lungs. We planned the open fixation of the fracture for the patient. A supraclavicular brachial plexus block was performed as the most non-invasive procedure for perioperative treatment, taking into consideration the patient's health. The patient's vital indicators were normal and stable during the procedure. After receiving therapy for two days, the postoperative course was uneventful, leading to the patient's discharge. **Conclusion**: If not addressed earlier, preoperative pulmonary and cardiac comorbidity increases the risk of perioperative and postoperative problems. With no postoperative problems, peripheral nerve block - in our case, supraclavicular brachial plexus block - proved to be a safe option for anesthesia management used for upper limb surgery.

Key Words: *Brachial plexus block; supraclavicular block; fracture of upper arm; anesthesia; postoperative complications.*

Introduction

Patients with pre-existing pulmonary and cardiac conditions have an increased risk for perioperative complications and an increased mortality rate.[1] High-risk pulmonary patients, in particular, who undergo general anesthesia may be more prone to risks of barotrauma, postoperative hypoxemia, pneumonia and respiratory failure after surgery.[1,16] Patients with pre-existing cardiac conditions are also at risk for experiencing perioperative complications and increased morbidity.[1] High cardiac risk patients are those with previously diagnosed coronary artery disease - CAD (as indicated by previous myocardial infarction, typical angina, atypical angina with

positive stress test results or angiography), or were at high risk for CAD stratified according to ACC/AHA - American College of Cardiology /American Heart Association criteria.[2]

The functional capacity examination covers the estimated energy requirement for various activities. It is defined as MET = metabolic equivalent, which is measure for heart metabolic demand during different daily activates, shown in Table 1. [3]

Table 1. Functional capacity.

1 MET	Self-care?
	Eating, dressing, or using the toilet?
	Walking indoors and around the house?
	Walking one to two blocks on level ground at 2 to 3 mph?
4 METs	Light housework (e.g., dusting, washing dishes)?
	Climbing a flight of stairs or walking up a hill?
	Walking on level ground at 4 mph?
	Running a short distance?
	Heavy housework (e.g., scrubbing floors, moving heavy furniture)?
	Moderate recreational activities (e.g., golf, dancing, doubles tennis, throwing a baseball or football)?
>10 METs	Strenuous sports (e.g., swimming, singles tennis, football, basketball, skiing)?
MET - metabolic equivalent; mph = miles per hour	

The persons with major predictors and 1- 3 MET-s have high postoperative cardiac risk while these with MET≥ 4 have low postoperative cardiac risk.[3]

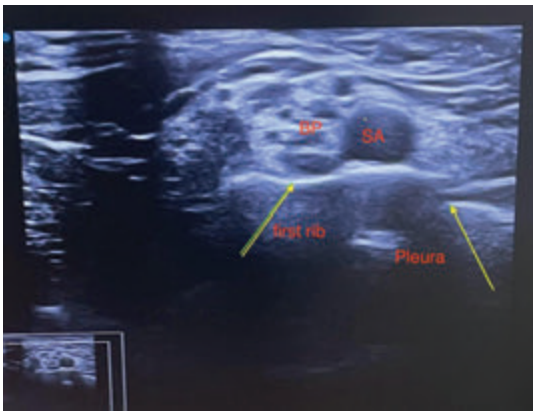
General anesthesia is traditionally used for upper extremity surgery. Perioperative complications can be minimized with careful management.

However, regional techniques are increasingly being used as stand-alone anesthesia techniques, as an adjunct to general anesthesia, or for the treatment and control of postoperative pain.[5,6] The traditional regional anesthesia techniques for shoulder surgery are associated with high rates of phrenic nerve paralysis which significantly impairs pulmonary function.[7] Newer regional anesthesia techniques, such as using ultrasound visualization with a high-frequency linear probe and lower amount of local anesthetic, provide effective analgesia and surgical anesthesia while having much lower rates of phrenic nerve paralysis, thereby preserving pulmonary function.[8,9,10,11]

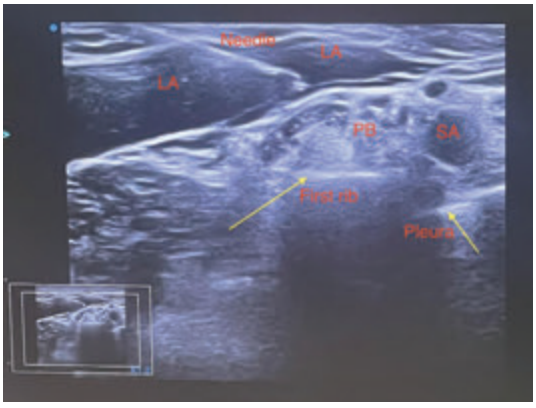
The brachial plexus is formed by ventral (anterior) rami of nerve roots C5, C6, C7, C8 and T1. As these roots course distally, they rearrange to form trunks, divisions, cords and lastly branches. The supraclavicular approach to blocking the brachial plexus is thought to occur at the level of the nerve trunks. The brachial plexus is the most compact at the level of the trunks and so injecting local anesthetics here gives the greatest likelihood of blocking all the branches of the brachial plexus.[8,9]

The ultrasound probe is placed in the supraclavicular fossa in the transverse orientation parallel to the clavicle, and behind the sternocleidomastoid muscle, and aimed inferior toward the ipsilateral thorax. The brachial plexus and the subclavian artery are visualized (Picture 1). The

first rib appears as a hyper echoic line with the lung pleura deeper to this bony border. Utilizing the in-plane approach, the needle is advanced from lateral to medial, aimed for near the main neural cluster of the brachial plexus. After negative aspiration, local anesthetic (about 10mL) is injected (Picture 2). Subsequently, smaller aliquots of local anesthetic are deposited near the surrounding satellite neural clusters.[8] Injection should be stopped if the patient experiences paresthesia or pain.



Picture 1. BP-Brachial plexus, SA- Subclavian artery



Picture 2. BP-Brachial plexus, SA- Subclavian artery, LA-local anesthetic

Another approach is "the corner pocket technique," first described by Soares and colleagues in 2007.[9] This involves a needle trajectory aimed towards the deeper portion of the brachial plexus with the goal of local anesthetic solution raising the brachial plexus off from the first rib. Then, the needle is retracted and advanced at a shallower angle, aiming towards the superficial brachial plexus. After negative aspiration, a local anesthetic is injected (about 10 mL).[9] This technique may have higher potential for pleural puncture.

The neurostimulator can be used as an additional technique to the ultrasound.[10] When using a direct current of 0.5mA, contraction of the corresponding muscles of the arm occurs. By reducing the current to 0.3mA, the contractions stop, which indicates that the needle is far enough from the nerve plexus and the local anesthetic can be safely applied without risking nerve damage. Neurostimulator provides additional safety when performing the block using ultrasound and reduces the risk of intraneural application of local anesthetic.[10]

Complications that occur when performing supraclavicular block include the risk of infection, hematoma, neuropathy and systemic toxicity when intravascular application of local anesthetic happened.[10] Other complications may include hoarseness due to ipsilateral laryngeal nerve block, Horner's syndrome due to stellate ganglion block, and hemi diaphragmatic paresis due to phrenic nerve block. However, with ultrasound-assisted supraclavicular block, these complications are very rare.[7,10,11,12]

Contraindications for supraclavicular block include patient's refusal, allergy to local anesthetic, infection at the puncture site, neurological deficit and coagulopathy.[10,13]

Despite the possible side effects, supraclavicular brachial plexus block has been shown to be a safe choice over general anesthesia in patients with pulmonary and cardiac comorbidities, providing excellent 24-hours postoperative analgesia, shorter hospital stays and significant patient's satisfaction with this type of anesthesia.[14-26]

Case Report

A 66-years-old male AA (height 180cm, weight 110kg) was admitted to the Clinic for Orthopedic Diseases in Skopje for surgical treatment of a fracture of the proximal part of the upper limb. The initial assessment upon admission revealed respiratory status with wheezing and crepitation in the basal parts of the lungs, but without recent coughing episodes, absence of dyspnea, and no edema. Chest X-ray was with signs of congestive changes, aggravated bronchovascular pattern and enlarged cardio-thoracic (CT) ratio. SpO2 - 95%. The patient reported being a smoker, 30 cigarettes per day. The ECG showed a widened QRS segment, supraventricular tachyarrhythmia and pronounced depression of the ST segment. Complete laboratory analysis and hemostasis were without significant changes except for elevated values of glycaemia, total lipids and cholesterol. The patient did not provide information about any health problems, claiming that he felt completely well, but functional capacity examination revealed that he felt tired when climbing stairs and uphill and did not practice walking for long distances at all. He did not engage in heavy physical work. He was a professional driver. There were no results from previous cardiological, pulmonary and general internal medical tests, nor any information about previous surgical interventions. He only was taking regular oral therapy for hypertension (calcium channel blocker), statins and diabetes. He was classified as ASA III status. Preoperatively, he was referred to the cardiologist, and he was put on oral bisoprolol (beta blocker) 5mg once daily.

After 2 days, the patient was scheduled for an open fixation of the upper arm fracture. The choice for perioperative management was to perform a supraclavicular brachial plexus block, as the most non-invasive technique, taking into account the patient's health condition.

After explaining the technique of performing the block, the feeling of arm numbness for a longer period of 16-20 hours and the risks associated with supraclavicular block and the growing evidence about the safety of this form of anesthesia in relation to the underlying condition, the patient accepted the technique and signed the informed consent.

The supraclavicular block was performed 30 minutes before the start of the surgical intervention, at the recovery room. Basic monitoring, ECG, non-invasive blood pressure, pulse oximetry was set up and he was sedated with iv. diazepam 5mg. The block was performed using ultrasound and a neurostimulator at the same time. After ultrasound identification of the plexus

(Figure 1), with an 50mm, 18 G neurostimulator needle and an "in plane" lateral-to-medial approach technique in which the entire length of the needle is followed, local anesthetic 0.5% bupivacaine 20ml, 2% lidocaine 9ml and dexasone 4mg was applied by aspiration of every 5ml. 20ml in the upper part of the plexus (Figure 2) and 10ml in the lateral and distal parts. The patient's hand began to become numb after a few minutes and complete numbness and inability to lift it occurred after 15 minutes.

Preoperatively, basic monitoring was set such as ECG, non-invasive blood pressure and pulse oximetry. Initial parameters were: NIBP 150/90mmHg, HR 75b/min and SpO2 96%. The patient was managed on an oxygen mask with a flow rate of 4L/min and 1500ml saline 0.9%. The surgical intervention lasted 2 hours and the patient was stable throughout the entire period with normal vital parameters. ECG was monitored at 12 drains and during the intervention there was no worsening of the already existing ST depression, nor any other changes compared to the previously diagnosed ones. During the surgical intervention the patient did not feel pain and did not need additional sedation besides diazepam which was given before the block performance. The block lasted 18 hours and after its discharge the patient had a normal motor and sensory status of his upper limb.

In the postoperative period the patient was treated with antibiotics and anticoagulant therapy. Pain relief drugs were given after 24 hours, such as acetaminophen and NSAIDS. He was discharged from the surgical clinic after 2 days in good general condition with the same previously established cardiac and respiratory changes and advised undergo complete analyses in order to obtain appropriate cardiac and health treatment.

Discussion

Peripheral nerve blocks are routinely performed in our institution for upper limb surgery. In the referred case, the patient's cardiac and pulmonary findings were an additional reason for performing a regional technique in order to provide better perioperative stability and satisfactory analgesia, without the use of opioid and non-opioid analgesics. The patient had stable vital parameters during the surgical intervention and was discharged after 2 days in good general condition.

The decision to use regional anesthesia can be a complex medical choice. Preexisting medical conditions, type of surgery, anesthetic risks, and patient's characteristics all may have a profound impact on anesthetic choice and perioperative management. In patients with cardiovascular disease, regional anesthesia techniques (either alone or in conjunction with general anesthesia) can offer the potential perioperative benefits of stress response attenuation, cardiac sympathectomy, earlier extubating, shorter hospital stay and intense postoperative analgesia.[10]

Lee et al. investigated the use of peripheral nerve blocks for orthopedic shoulder surgery in patients with asthma and chronic obstructive pulmonary disease (COPD). These patients, under general anesthesia, may develop respiratory failure and require mechanical ventilation in the postoperative period, which further increases the risk of postoperative morbidity and mortality. The authors examined several combinations of regional anesthesia, including a supraclavicular block - the application of local anesthetic in the area of the upper pole of the plexus where the upper trunk is localized. In addition to the regional anesthetic technique, the volume of local anesthetic is an important factor that may influence the risk of potential Horner's syndrome

or even hemi-diaphragmatic paresis. A certain minimum dose of local anesthetic is necessary to provide either surgical anesthesia or analgesia. For example, the superior trunk block has demonstrated efficacy using 15mL of bupivacaine 0.5% and 20mL of levobupivacaine 0.5%, respectively. By limiting the volume of local anesthetic, the risk of proximal spread of local anesthetic to the phrenic nerve and resulting diaphragmatic paresis is reduced. With newer techniques and greater clinician experience, regional anesthesia may offer important benefits for patients undergoing shoulder surgery while minimizing the side effects associated with this technique.[16]

Ozen in his case report study used ultrasound guided selective supraclavicular nerve and low-dose interscalene brachial plexus block in a 67-years-old patient with coronary artery disease and chronic obstructive pulmonary disorder (COPD) who was scheduled for open fixation of the fracture of his right clavicle. The supraclavicular block was performed with 4ml of bupivacaine 0.5%, in order to provide intra- and postoperative analgesia in the area around the acromioclavicular joint. To provide a block of the interscalene plexus, 10ml of bupivacaine 0.5% were applied. With this dose of local anesthetic, complete motor and sensory block was achieved. Surgery was performed without any hemodynamic instability or complications. According to this study, low dose peripheral nerve block is an alternative option at high-risk patients due to heart and lung disease.[17]

Kim et al., and Mardirosoff and Dumont in their studies refer to possible complications of semi diaphragmatic paresis[11] and convulsions[12] associated with the large amount of anesthetic administered during interscalene block. In the study by Kim et al., interscalene block was performed as an adjunct to general anesthesia to achieve postoperative analgesia and it is recommended to compare a dose of 5ml versus a dose of 15ml. The conclusion of this study is that a 5ml dose of local anesthetic provides the same analgesia as a 15ml dose.[11] In the study by Mardirosoff and Dumont, convulsions appeared because 80ml of ropivacaine 0.5% was administered by mistake instead of the planned 40ml while performing interscalene block with a neurostimulator. Both studies report that adrenaline or dexamethasone as an adjunct to local anesthetic could prolong block duration. Dexamethasone also reduces nausea and vomiting.[12]

The findings in these studies are consistent with our referred case, in which the patient was administered a total of 30ml local anesthetic (0.5% bupivacaine 20ml, 2% lidocaine 9ml and dexasone 4mg) for supraclavicular brachial plexus block as a stand-alone anesthetic technique. The patient had no side effects, no transient Horner's syndrome or dizziness at the peak anesthetic absorption that occurs after 30 - 45 minutes.

Peripheral nerve blocks are of significant interest not only for anesthesiologists, but also for surgeons, considering the benefit to the patient, especially good pain relief and thus patient's satisfaction with the type of anesthesia and surgical intervention, as well as the possibility of early discharge from the hospital. Some studies referred performing supraclavicular block by the orthopedic surgeons themselves in 20 patients undergoing upper limb orthopedic surgery. The time required to perform the block, the duration of the surgical procedure, and the duration of the block itself, which lasted an average of 7 hours, were measured. All patients experienced transient Horner's syndrome immediately after the block, but there were no other complications or side effects. 97% of the patients were satisfied with the type of anesthesia.[14]

Bilateral use of peripheral nerve blocks is controversial. Holborow et al., in their study investigated the possibility of performing a bilateral brachial plexus block for bilateral upper limb sur-

gery. Bilateral blocks represent a great challenge, although traditionally they have been avoided by anesthesiologists due to concerns about systemic toxicity from the local anesthetic, phrenic nerve block and pneumothorax. Research of Medline and EMBASE, from 1966 to January 2009, was conducted using multiple search terms to identify techniques of providing anesthesia or analgesia for bilateral upper limb surgery and potential side effects. The use of ultrasound and catheter techniques for continuous analgesia also reduce the risk of local anesthetic toxicity, as does performing the block at different times which allows avoiding local anesthetic simultaneous peak absorption. Regional anesthesia has been shown to be beneficial for bilateral upper limb surgery but only as a continuous technique, except for interscalene brachial plexus block, due to the risk of phrenic nerve block, even with low doses of anesthetic.[15]

In the case referred above, the supraclavicular block was performed in a conscious patient, previously sedated with diazepam 5mg. Peripheral nerve block performed in a deeply sedated or already anesthetized patient is still controversial. The conscious patient may cooperate and complain of severe pain during the application of the anesthetic, which is very important if the needle is not in the right place. However, peripheral blocks in children and sometimes in adult patients must be performed under anesthesia or deep sedation. The recommendations of Bernards et al., for the safe and effective performance of these blocks, are the introduction of ultrasound guidance, new modes of electrical nerve stimulation, and injection pressure monitoring.[22]

Of course, peripheral nerve blocks are particularly suitable and safe for outpatient interventions such as shoulder and knee arthroscopy, hand contractures and other short interventions. Klein et al. in 2005 determined that the use of peripheral nerve blocks for outpatient interventions provides patients with excellent postoperative analgesia, a short stay and discharge from the hospital the next day, which reduces financial costs for both patients and hospitals. This increases not only the satisfaction of patients, but also of the surgeons themselves.[19]

Among the listed contraindications for performing a peripheral nerve block is neuromuscular weakness. However, peripheral blocks were performed in patients with Charcot-Marie-Tooth disease, which is a hereditary peripheral neuropathy characterized by progressive peripheral muscle atrophy and muscle-sensory impairment, especially in the extremities. There is concern about the application of peripheral nerve blocks, which could be associated with peripheral nerve denervation. It has been thought that peripheral nerve blocks could worsen pre-existing nerve deficits. Three studies have demonstrated the safe and successfully performed continuous or sole distal sciatic nerve block for foot surgery[24,25,26] combined with epidural or spinal anesthesia. In all three subjects, local anesthetic was successfully applied through the placed catheter or through the needle without complications and worsening of the previously determined neurological deficit.[24,25,26]

Single-injection regional blocks and continuous peripheral catheters play a valuable role in a multimodal approach to pain management in peri and post-operative period in all patients, especially in those with comorbidities, providing excellent patients' comfort while reducing the physiologic stress response.[5,6,10] However, compared to neuraxial and general anesthesia, success with peripheral nerve blocks is undoubtedly more anesthesiologist-dependent. Technical skills and determination are required for the successful implementation of peripheral nerve blocks. Factors such as accurate identification of surface landmarks and an adequate number of supervised, successful attempts at each block are necessary for safe and effective peripheral nerve block implementation.[21]

Conclusion

When managing patients with compromised cardiovascular function, anesthesiologists need to select an appropriate anesthesia technique and carefully monitor vital signs to maintain hemodynamic stability during the perioperative period. Pulmonary and cardiac preoperative comorbidity, especially if previously untreated, represents a high risk for peri- and postoperative complications. Peripheral nerve block, in our case supraclavicular brachial plexus block, provides excellent anesthesia, maintains hemodynamic stability during the perioperative period, excellent postoperative pain relief, reduced postoperative complications and facilitates early physical activity and early hospital discharge in patients for upper limb surgery.

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CASE REPORT *UDK: 616-005.4:616.75-089.87*

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UNLOCKING TENSIONS: THE SYNERGY OF POINT OF CARE ULTRASOUND AND FASCIOTOMY

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Abstract

Compartment syndrome is an agonizing state arising from excessive pressure buildup within muscles, hindering blood circulation and depriving nerve and muscle cells of vital oxygen and nutrients. Usually, this condition arises following injury-induced bleeding or swelling. The elevated pressure characteristic of compartment syndrome impedes the circulation of blood, oxygen and essential nutrients to and from the impacted tissues. In some cases, it necessitates immediate surgical intervention to avert lasting damage. Consensus holds that prompt intervention offers the greatest opportunity for full recovery and for averting additional tissue necrosis. Treatment primarily relies on clinical presentation, supported by corroborative measurements of compartmental pressure. A fasciotomy is an emergency procedure used to treat acute compartment syndrome. We describe a scenario involving a 19-years-old male, where in the diagnosis and postoperative outcome was swiftly facilitated by point-of-care ultrasound (POCUS), revealing a substantial thigh hematoma within the anterior compartment with vascular compromise before fasciotomy revealed by color and pulse wave doppler. Using POCUS, restorage of circulation and local hemodynamics after fasciotomy were assured by detecting normal doppler signal of previously involved peripheral arteries. Although POCUS should not serve as the sole method for evaluating potential compartment syndrome, it can significantly contribute as a supplementary tool in the diagnostic process and especially when following up patients where therapeutic actions have been done.

Key Words: *compartment syndrome; fasciotomy; POCUS.*

Introduction

Compartment syndrome arises when an enclosed muscle space in the body experiences an excessive pressure buildup, often triggered by bleeding or swelling following an injury. The relatively fixed volume inside the fascial compartments means that any introduction of excess fluid or external constriction can elevate the pressure within the compartment, subsequently impeding circulation and reducing tissue perfusion. This heightened pressure restricts blood flow

and delivery of oxygen and nutrients to and from the affected tissues. Compartment syndrome manifests as an intense pain due to elevated pressure within muscles, impeding blood flow and thereby depriving nerve and muscle cells of essential oxygen and nutrients delivery. This condition is typically diagnosed clinically, often identified by the classic presentation of the 5 'P's: pain, pulselessness, pallor, paresthesia and paralysis (1). Compartment syndrome may present as either acute, characterized by severe symptoms over a brief duration, or chronic, persisting over an extended period. The acute compartment syndrome stands as the predominant form of the condition, with approximately three-quarters of cases stemming from a fractured leg or arm (2). This variant swiftly progresses over hours or days until permanent damage is done, and it is considered as the most severe form. Without timely intervention, it can lead to functional impairment or necessitate amputation of the affected region. Chronic compartment syndrome, also referred to as exertional compartment syndrome, typically does not present as a medical emergency which is frequently triggered by athletic activity and is reversible through rest and relaxation (3).

Case Presentation

We present a case of 19 years old male, 75kg by weight and 180cm height, without history of chronic diseases and no therapy in use. Four hours before admission, he had a motorcycle accident in which he got an injury to his right lower leg, resulting with compartment syndrome. He was admitted to the University Clinic for Traumatology, Orthopedics, Anesthesia, Reanimation, Intensive Care and Emergency Department in Skopje for an urgent fasciotomy in order to prevent further damage of muscles, nerves and soft tissue due to impaired blood flow. Surgery has been conducted 4 hours and 45 minutes after injury under spinal anesthesia, a choice made with consideration of the local anesthetic vasodilatory properties on the vessels and circulation. This decision aimed to enhance post-fasciotomy perfusion, contributing to better tissue oxygenation, since preoperatively we did a color and pulse wave doppler examination where significantly low velocity with poor, nearly absent flow and retrograde diastolic blood flow were registered at arteria dorsalis pedis as shown in Figure 1A and 1B. Surgery has lasted 45 minutes. Postoperatively, in the operating room, immediately after fasciotomy, we did a Point of Care Ultrasound examination of arteria dorsalis pedis and arteria retro-malleolar using Color Doppler and Pulse Wave Doppler modalities to assure if there was present adequate blood flow and assess vascular patience. A perfect pulsation and a Doppler signal on both examined arteries has been registered with Color Doppler, as well as with Pulse wave Doppler confirming restorage of blood flow followed by elevated values for blood flow velocity with disappearance of the retrograde diastolic blood flow compared to the preoperative findings as shown at Figure 1C. Clinical examination as well has shown palpable pulses on both arteries, while warming of the injured leg has been observed too, after fasciotomy was performed. The patient has been discharged 2 days after surgery and at 1st, 3rd and 6th month of follow up after surgery had signs of complete recovery from the injury without any consequences.

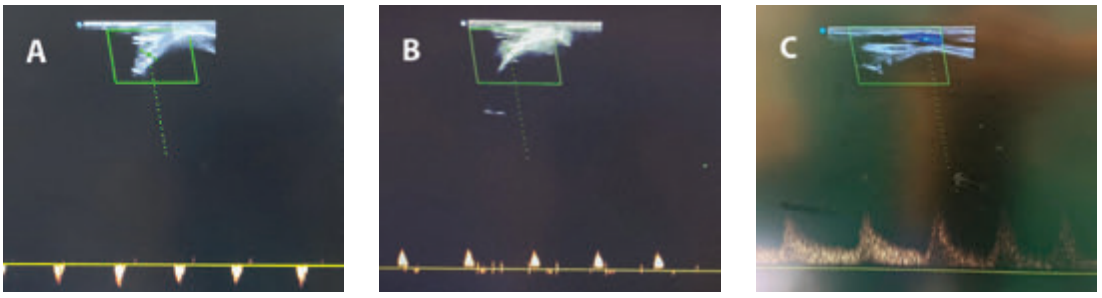

Figure 1. Presence of Diastolic reverse arterial flow of arteria dorsalis pedis before fasciotomy (A) with low systolic velocity before fasciotomy (B) and restoring of blood flow with normal pulse wave signal of arteria dorsalis pedis after fasciotomy (C).

Discussion

The aim of treating compartment syndrome is to alleviate the dangerous pressure within the affected body compartment. This often involves removing any constricting dressings, casts, or splints from the affected body part. In alert patients with acute compartment syndrome, surgical intervention is typically guided by clinical assessment (2,3). The four classic signs and symptoms, often referred as the four Ps, include: pain that is out of proportion to clinical findings, pain with passive stretch of involved muscles, pain associated with palpation of involved compartment resulting from the pressure increase within the compartment (4). Absolutely, it's essential to recognize that not all these signs may be present in cases of acute compartment syndrome. Moreover, the absence of a pulse or weak pulsation of the lower extremity arteries is more indicative for presence of significant vessel injury (5), typically occurring as a very late manifestation of compartment syndrome, as was previously presented in our case report. Since blood flow is more than essential for tissue metabolic needs of oxygen, glucose and nutrients, early recognition of blood flow impairment and vascular patency involvement may be crucial regarding establishing an on-time indication for fasciotomy (6,7) and performing fasciotomy as soon as possible in order to provide better outcome. Complete recovery without any consequences have been associated with early recognition of acute compartment syndrome and performing fasciotomy within 6 hours of injury as it was presented in our case, while catastrophic complications were met in cases where fasciotomy was delayed up to 12 hours (8). In those patients who are unable to communicate pain or paresthesia, clinical examination alongside compartment pressure monitoring assumes greater significance in aiding diagnosis which could be simplified if vascular patency and current blood flow examination with doppler ultrasonography is done as well. The utilization of Point of Care Ultrasound (POCUS) needle guidance has enhanced the assessment of compartment pressures, offering a more precise approach compared to the traditional method, which relies on blind palpation and landmarks. That has been clearly described and discussed in the case report of Daniel L. et al. where needle guidance for measurement of intra-compartmental pressure was done under ultrasound guidance (9). The occurrence of limb compartment syndrome could be associated with limb fracture, or without bone fracture at all, but with significant soft tissue injury. Since clinical examination of patients with complex trauma has a low sensitivity in detecting compartment syndrome, adding complementary methods in diagnosis is recommended. Direct needle measurement of intra-compartmental pressure has been strongly recommended by the American College of Surgeons, Trauma Committee. In the study of Mc Loughlin S. et al., Pulse Wave examination of the brachial artery in patients where different levels of external pressure were added in order to mimic compart-

ment syndrome, mean velocity and blood flow were lowered and diastolic retrograde arterial flow were observed in all groups (10). All assessed parameters have shown correlation with the grade of severity of the compartment syndrome exhibiting the worst results in the group where the pressure was the highest (10). Therefore, mean velocity, blood flow and diastolic retrograde arterial flow should be examined in all patients where compartment syndrome is suspected in order to facilitate on time diagnosis. According to Fukuda I. et al. contemporary approach of limb viability assessment implies examination of motor and sensory functions combined with interrogating Doppler flow signals at the level of the pedal arteries as categorized by Rutherford (11). Another case report of acute compartment syndrome of the limb because of burns was published by Mahmoud O. et al., where the role of doppler ultrasound examination in decision making was highlighted. In their article they had described presence of impaired blood flow and impaired doppler signals at the arteries located proximally of the compartment syndrome (12) which are identical to our findings before performing fasciotomy. Compared to their case, we have examined the patient prior to operating room entrance and immediately after fasciotomy was performed which has brought us clear information about the blood flow and limb hemodynamic after performing fasciotomy showing totally different velocities and blood flow at the second examination where the ultrasound signs of altered circulation have disappeared. In another case report published by Smith A. et al., point of care ultrasound was used in diagnosis of acute compartment syndrome of the limb in a patient where the cause was a snake envenomation. They have reported that frequent ultrasound examinations in conjunction with clinical examination have aided significant data for diagnosis, following up and making a decision for fasciotomy in order to rescue the limb (13). Another study had evaluated the importance of POCUS when diagnosing acute compartment syndrome in a group of snakebite patients, where 27 patients were examined with ultrasound for locating soft tissue swelling and presence of diastolic retrograde artery flow as a sign of acute compartment syndrome. When soft tissue swelling is present, the space inside the compartment becomes reduced and at some point, leads to an artery compression exhibiting diastolic retrograde artery flow as a sign suggestive for acute compartment syndrome (14), which has been found in our patient before fasciotomy and have disappeared following surgical intervention. Eicken J. had published a case report where usage of bedside ultrasound has led to rapid diagnosis of compartment syndrome of the lower extremity in a patient taking anticoagulant therapy and experiencing symptoms of tightness of the right thigh. According to the authors immediate point of care ultrasound has led to decision for ordering further examination with CT in order to confirm the diagnosis of compartment syndrome since using ultrasound has shown a presence of right thigh hematoma with vascular compromise detected using color doppler mode, highlighting the significance of recognizing the findings associated with acute compartment syndrome (15).

Not many case reports were published nowadays, but the very few of them that were accessible at Pub Med were cited in the discussion of this article where systematic comparison of ours and their findings was done in order to provide conclusion about the usefulness of the point of care ultrasound as a diagnostic tool, but as well as an available tool for following up patients after taking therapeutic actions. If we consider the fact that in short time framework, we have performed doppler examination at two different points, through the valuable ultrasound data we could follow the evolution of the hemodynamic changes in patients with compartment syndrome. Although doppler ultrasound is still not considered as a sole diagnostic technique when establishing diagnosis of acute compartment syndrome, however it can be helpful in many ways, either for diagnosis of injured limb hemodynamic disturbances or for postoperative follow up of the vascular patency.

Conclusion

The assessment of compartment pressures benefited from POCUS needle guidance making this procedure more precise than blind intra-compartmental pressure measurement. Point of Care assessment of doppler signals of arteries located proximately to the compartment syndrome could provide significant information for the local perfusion and hemodynamics and according to us should become a standard procedure, since it is widely available and easy to perform. While it's not advisable to rely solely on POCUS for diagnosing compartment syndrome, it can serve as a valuable adjunct in the diagnostic process, and it can also give us information for postoperative outcome. Obviously, the usage of POCUS instantly providing valuable information in critical moments could overcome the expectations of many and facilitate many aspects of treatment.

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SEPTIC SHOCK IN POLYTRAUMATIZED PATIENT: A CASE STUDY AND MANAGEMENT CHALLENGES

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Abstract

Septic shock is a life-threatening condition that represents the final stage of sepsis, where infection leads to widespread systemic inflammation, tissue hypoperfusion and multi-organ dysfunction. The management of septic shock becomes even more complicated in polytraumatized patients, where multiple severe injuries often contribute to both the patient's clinical deterioration and the risk of infection. We present the case of a 55-years-old male with multiple traumatic injuries including thoracic contusion, fractures of the cervical and rib bones and bilateral extremity fractures, who developed severe septic shock during his hospitalization. His medical history included type II diabetes mellitus and chronic gastritis.

Upon admission, the patient was intubated and mechanically ventilated, started on broad- spectrum antibiotics, anticoagulants and fluid resuscitation. Initial microbiological tests revealed no pathogens, but by day 10, Methicillin-resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa and Acinetobacter species were identified. Despite aggressive antibiotic therapy, the patient developed worsening sepsis marked by hyperthermia, elevated inflammatory markers and oliguria by day 12. As his condition deteriorated, Cytosorb therapy was initiated on day 13, followed by hemodialysis on day 15 for acute kidney injury. On day 20, blood cultures revealed Vancomycin-resistant Enterococcus (VRE). As the infection evolved, additional pathogens including Klebsiella pneumoniae, Pseudomonas aeruginosa and Candida glabrata, were identified. Antifungal therapy with caspofungin was introduced on day 33. Despite the complexity of multiple infections and resistance patterns, the patient responded to tailored therapy, with negative blood cultures achieved by day 42.

This case highlights the challenges in managing septic shock in polytraumatized patients, particularly with the emergence of multidrug-resistant organisms. A multidisciplinary approach, involving timely microbiological testing, antibiotic stewardship and supportive therapies such as Cytosorb and renal replacement was essential for improving patient's outcome. The case also underscores the importance of vigilant management of fungal infections such as Candida glabrata in critically ill, immunocompromised patients.

Key Words: *Cytosorb; polytraumatized patients; replacement therapy; septic shock.*

Introduction

Septic shock is characterized by persistent hypotension despite adequate fluid resuscitation and is associated with high mortality rates, particularly in polytraumatized critically ill patients (1). It is often complicated by the presence of multidrug-resistant pathogens which further complicate the treatment. The management of septic shock in polytraumatized patients requires a multidisciplinary approach to treat both the underlying trauma and the associated infection (2). This case shows the challenges and management strategies in treating septic shock in a polytraumatized patient with multiple comorbidities and evolving microbial resistance. Infections are a major cause of morbidity and mortality in critically ill patients, often associated with a complex multi-organ involvement and an impaired immune response. While bacterial pathogens have traditionally been the primary focus of infection control in intensive care units (ICUs), fungal infections particularly co-infections with fungal organisms are increasingly recognized as a significant clinical concern (3). Fungal co-infections complicate the management of critically ill patients, exacerbating the severity of the underlying condition, prolonging hospital stay and worsening patients' outcome (4). Intensive care units are a critical environment for the management of patients facing life-threatening conditions, including those with acute kidney injury (AKI), sepsis and other complex multisystem failures (5). Advance therapeutic interventions used in ICU have increased significance among patients with sepsis induced organ failure, severe inflammatory responses and kidney failure, using renal replacement therapy (RRT) and Cytosorb therapy. Renal replacement therapy, which includes hemodialysis, hemofiltration and hemodiafiltration, is an important part in the administration of critically ill patients with respect to fluid balance, electrolyte disturbance and toxin removal. Meanwhile, Cytosorb is an extracorporeal cytokine adsorption therapy that addresses the overwhelming systemic inflammation that often accompanies conditions like septic shock (6).

Case Presentation

A 55-years-old male was admitted to the Intensive Care Unit (ICU) after a high-energy trauma resulting in multiple fractures: thoracic contusion, fracture of the transverse process of the first thoracic vertebra (Th1), a left pertrochanteric femoral fracture, right humeral neck fracture, right clavicular fracture, and serial fractures of ribs I-X. The patient's past medical history included type II diabetes mellitus on insulin therapy and chronic gastritis. Upon admission, the patient was intubated, placed on mechanical ventilation, and received fluid resuscitation with both crystalloids and colloids. A central venous catheter (CVC) was placed for central venous pressure monitoring and for the administration of medications and fluids. Empiric antibiotic therapy (carbapenems and polymyxins) was started based on the suspicion of infection, given the severity of trauma and signs of systemic inflammation. Gastroprotective agents and anticoagulation therapy were also initiated as part of standard critical care management. Initial microbiological testing, including blood cultures and tracheal aspirates, revealed no significant growth. Over the following days, however, the patient developed increasing signs of infection.

On the 10th day of hospitalization, microbiological testing revealed the presence of Methicillin-resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa from tracheal aspirates, and Acinetobacter species from blood cultures. Based on these findings, the antibiotic regimen was adjusted to include MRSA-targeted therapy:

- Vancomycin (MRSA-targeted): 1g IV every 12 hours,

- Meropenem (for *Pseudomonas* and *Acinetobacter* species): 2g IV every 8 hours,
- Polymyxin B (for multidrug-resistant organisms): 2.5mg/kg IV every 12 hours.

On the 12th day, the patient developed an increase in inflammatory markers (CRP, IL-6, procalcitonin), oliguria and persistent hyperthermia. The clinical picture was suggestive of progression to septic shock. Despite adequate fluid resuscitation, the patient remained hypotensive, requiring escalating doses of vasopressors to maintain a mean arterial pressure (MAP) >65mmHg. The patient's fluid balance and renal function continued to deteriorate, prompting the initiation of **Cytosorb therapy.**

On day 13, after consulting with a nephrologist, Cytosorb (cytokine adsorption therapy), to address the patient's persistent inflammatory state, a blood purification therapy for the removal of inflammatory mediators was initiated for 24 hours.

On day 15, due to the patient's progressive renal failure, it was likely secondary to sepsis-related acute kidney injury (AKI) leading to the decision to start hemodialysis. Hemodialysis was administered for 4-hours sessions, 3 times per week. Antibiotic dosing was adjusted during dialysis to account for changes in drug clearance:

- Vancomycin: Reduced to 500mg IV every 12 hours,
- Meropenem: Administered after each dialysis session (2g IV after each session),
- Polymyxin B: Maintained at 2.5mg/kg IV every 12 hours, with careful monitoring of renal function.

On day 20, Enterococcus faecium resistant to vancomycin (VRE) was isolated from blood cultures. This led to the escalation of the antibiotic regimen, including the addition of linezolid (an oxazolidinone) for VRE coverage:

- **Linezolid:** 600mg IV every 12 hours.

Throughout the hospitalization, the patient's infection profile evolved.

On day 29, microbiological tests revealed Klebsiella pneumoniae and Pseudomonas aeruginosa in tracheal aspirates. Blood cultures grew Candida glabrata, a resistant fungal pathogen, on the same day.

Given the risk of fungal sepsis in an immunocompromised patient, echinocandin therapy (caspofungin) was initiated on day 33, according to the antifungal susceptibility profile:

- **Caspofungin:** 70mg IV on day 1, followed by 50mg IV once daily thereafter.

Despite the frequent emergence of new infections and resistant organisms, targeted antibiotic therapy was adjusted based on the evolving microbiological results and antibiograms. The patient received a broad-spectrum approach, initially with carbapenems, polymyxins, oxazolidines, and later including antifungal therapy, which was critical in controlling the infection.

By day 42, blood cultures were negative, signaling the resolution of the bacterial sepsis.

Discussion

Septic shock often occurs in patients with multiple traumatic injuries, where the initial trauma serves as a precipitating factor for both local and systemic infections (7). This case can show several important challenges in the management of septic shock in polytraumatized patients.

Challenges of Managing MDR Organisms

The emergence of multidrug-resistant (MDR) organisms, such as MRSA, VRE and **Candida glabrata,** posed significant therapeutic challenges. Resistance mechanisms in this case, including beta-lactamase production and altered penicillin-binding proteins, required careful selection of antibiotics and frequent adjustments. The patient's treatment regimen, which included **vancomycin, meropenem, polymyxin B, linezolid** and **caspofungin**, demonstrated the need for combination therapy to address diverse resistant pathogens. A key challenge was adjusting dosing due to the patient's progressive renal failure and the impact of hemodialysis on drug clearance.

Role of Fungal Infections in Septic Shock

Fungal infections, especially Candida species, are increasingly recognized as a major concern in critically ill patients (8). The identification of Candida glabrata in this case highlights the risk of opportunistic fungal infections in patients with complex comorbidities and prolonged ICU stays. Candida glabrata is known for its resistance to commonly used antifungal agents, making early identification and targeted antifungal therapy essential. Early use of caspofungin, as demonstrated in this case, has been shown to improve survival rates in critically ill patients with suspected fungal co-infections.

Sepsis-Induced Acute Kidney Injury (AKI) Mechanisms

Sepsis-induced AKI is a multifactorial condition characterized by renal hypoperfusion, direct tubular injury, and inflammation. In this case, the patient's septic shock led to reduced renal blood flow and ischemic injury, exacerbating AKI. Pro-inflammatory cytokines, such as TNF-alpha and IL-6, contribute to endothelial dysfunction and glomerular filtration impairment (9).

Efficacy of Innovative Therapies (Cytosorb and RRT)

Renal replacement therapy (RRT) was essential in managing fluid balance, electrolyte disturbances, and toxin removal (10). Antibiotic dosing was carefully adjusted during hemodialysis sessions to avoid underdosing and drug accumulation. The use of Cytosorb therapy and hemodialysis was critical in addressing the systemic inflammatory response and managing acute kidney injury in this patient. While Cytosorb therapy remains a controversial and evolving area, it was considered in this case due to the patient's persistent inflammatory state and poor response to standard therapies.

Multidisciplinary Approach Management involved coordinated work between trauma surgeons, intensivists, infectious disease specialists, nephrologists and pharmacists. Early identification of septic shock coupled with aggressive resuscitation and targeted therapy was critical in preventing further deterioration. Recent studies showed an increase in fungal co-infections in critically ill patients, and indicated the need of improving the strategies of diagnosis as well as therapy. A study by **Wang et al. (2020)** in *Clinical Infectious Diseases* found that co-infection with **Candida species** and **Pseudomonas aeruginosa** in ICU patients with ventilator-associated pneumonia was associated with significantly higher mortality than bacterial infections alone (11). Furthermore, a study in *The Lancet Infectious Diseases* (2021) concluded that early use of echinocandins in septic patients with suspected fungal co-infections resulted in improved survival outcomes suggesting the need for early antifungal therapy in high-risk patients (12).

Conclusion

This case underscores the complexity of managing septic shock in polytraumatized patients, particularly in the presence of multidrug-resistant infections and evolving pathogens. Understanding the infection and physiological aspects at the patient level is vital to a multidisciplinary individualized approach to sepsis therapy. Timely microbiological testing and appropriate antibiotic treatment, renal support and innovative strategies such as Cytosorb were indispensable in improving prognosis and patient's recovery. The emergence of pathogens such as Candida glabrata and other resistant pathogens emphasizes the need for continuous monitoring and appropriate use of antifungal agents in critically ill patients. Renal replacement therapy together with Cytosorb represents two of the most crucial interventions in intensive care, particularly for patients suffering from severe sepsis, AKI and other complex critical illnesses. RRT plays a key part in controlling kidney dysfunction and fluid imbalance, while Cytosorb treatment offers an innovative method to mitigate the hyper-inflammatory response which causes organ failure. Therefore, when the two therapies are combined the benefits become relevant in the intensive care unit setting for critically ill patients. Future research is needed to define optimal indications for these therapies, evaluate their long-term effectiveness, and integrate them into clinical guidelines for managing sepsis in critically ill patients.

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BARDET-BIEDL SYNDROME

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Abstract

Bardet-Biedl syndrome (BBS) is a genetic and multisystem disease that affects the genitourinary tract, locomotory system, causes eye anomalies, cognitive disorders and characteristic truncal obesity. It is caused by mutations in certain genes, namely: BBS1 to BBS21 gene. The approach to this disease is multidisciplinary.

Material and Methods: We present a 3-years-old female child who was referred to the Clinic for Pediatric Surgery due to supernumerary toes on both feet. This is postaxial polydactyly. Intrauterine lobulated kidney structure was observed. The child had problems with her peers and avoids socializing with them. The following examinations were performed: cardiological, ophthalmological and genetic. Genetic examinations confirmed the BBS syndrome.

Results: The patient was operated at the clinic for pediatric surgery, the operative and postoperative period were without complications.

Conclusion: BBS is a rare autosomal disease that requires timely detection and appropriate multidisciplinary treatment. This allows complications to be reduced and the child to be included in everyday activities.

Key Words: *Bardet-Biedl syndromee; genetic disease; postaxial polydactyly.*

Introduction

Bardet-Biedl syndrome (BBS) is a rare multisystem autosomal genetic disorder that affects cells (ciliopathy). Patients with BBS have problems with obesity in which fat tissue being distributed around the abdomen. The patients also suffer in terms of intelligence. Renal, ocular and genital function disorders are known. The first description of this syndrome was done in 1920 by Bardet, and later in 1922 by Biedl.

Truncal obesity is a condition characterized by a disproportionate distribution of adipose tissue around the abdomen, and less commonly on the chest and extremities. This phenomenon is known as the "apple-shaped body". The child's weight is usually normal at birth, but a noticeable change occurs quickly in the first year of life. Patients with BBS suffer from non-insulin-dependent diabetes in 45% of the cases. Obesity in these patients is manifested in 72%-92% of the cases (1).

These patients may have changes in the cardiovascular system, such as defects in the heart muscle, valve stenosis, that result in arrhythmias.

Retinal changes in this syndrome may appear around the 7th and 8th year of life as "nail blindness", which progresses to varying degrees. Affected individuals first lose peripheral vision and look directly at a frontal point. Over time, retinal degeneration occurs. Additional eye changes in affected individuals include strabismus, cataracts and glaucoma (2).

Patients with BBS have abnormalities of hands and feet. Postaxial polydactyly, syndactyly (8% between the second and third fingers), brachydactyly (46%), clinodactyly, and sandal gap between the first and second fingers have been described. Approximately, these changes occur in about 63% - 81% of the patients. Polydactyly can be present in all four limbs (21%), only in the upper limbs (8%), or only in the lower limbs (21%) (3).

Other cardinal abnormalities in BBS are the following: reduced or poor gonadal function; Hypogonadism is present in 59% of the patients. In boys, it is characterized by undescended testicles, micropenis, recessive penis and reduced testicular volume. Undescended testicles are a high risk for testicular cancer. Affected girls may have genital and urinary abnormalities, such as: underdeveloped fallopian tubes, underdeveloped ovaries and uterus, irregular menstrual cycles and polycystic ovaries. Hydronephrosis involves frequent bacterial infections that can result in pyelonephritis, chronic kidney damage and dialysis, up to and including kidney transplantation (4).

Cognitive impairment is a characteristic of this syndrome. It is present in 60%-66% of the patients (5). It manifests as learning difficulties, dysfunction of brain development, neurological changes such as poor coordination, large and small motor tremors, inability to play with friends, etc.

Certain individuals with BBS also have liver problems, such as dilation or stricture of the bile ducts, which is present in 30% of the patients. Digestive problems such as Hirschsprung's disease, ciliary disorders, inflammatory changes, stenoses and other anatomical anomalies of the intestine are rare (6). The prognosis of this disease depends on the degree of kidney damage and progressive vision loss.

Incidence

BBS affects both males and females equally. The distribution of this disease is not homogeneous. It occurs in 1 in 120,000 to 1 in 160,000 births in the population of North America and Europe (7). In Sweden, it occurs in 1 in 160,000 births. A high frequency of this syndrome occurs in the Bedouins of Kuwait, 1 in 13,500 births (8).

Cause of BBS

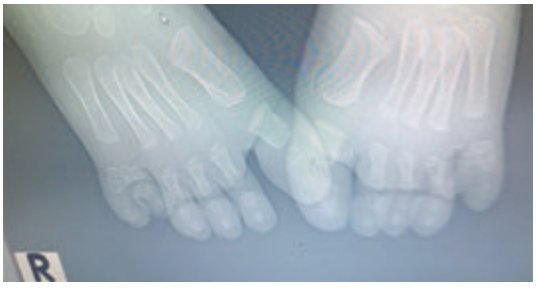
BBS can be caused by mutations in more than 20 different genes. It is an autosomal recessive disease. There are several gene mutations that lead to the development of BBS:

BBS1 gene, BBS2, BBS3, BBS4, BBS5 BBS6, BBS7, BBS8, BBS9, BBS10 to BBS 21 gene.

The risk of the disease occurring in a child of both parents carrying the gene is 25% for each pregnancy. The risk of the gene occurring in a child of both parents carrying the gene is 50% for each pregnancy (9).

Diagnosis

Diagnosis is based on clinical examinations and associated clinical manifestations. Some patients remain undiagnosed for years. Genetic testing may aid in diagnosis. Definitive diagnosis requires family history, clinical signs, neurological testing, ophthalmologic evaluation, audiometry, ECG and echocardiography, abdominal ultrasonography and renal function testing. Laboratory testing includes complete blood count, glucose tolerance test, liver enzymes, hormonal status and genetic testing. Cardinal diagnostic features include the following: retinal degeneration, obesity, postaxial polydactyly, renal anomalies, neurologic intellectual disability, hypogonadism and genitourinary abnormalities. Secondary features of BBS include musculoskeletal abnormalities, hearing loss, cutaneous dermatoses. The presence of four of the cardinal signs or three cardinal and two secondary signs is sufficient for a diagnosis of BBS. Genetic testing confirms the diagnosis.



Picture 1. Native radiography of both feet of a child with BBS.

Differential Diagnosis

Laurence-Moon syndrome (LMS) - LMS is a rare autosomal recessive disorder characterized by visual degeneration and pituitary dysfunction. Patients have neurological problems including loss of motor control, loss of peripheral nerve function and intellectual disability.

Alstrom syndrome - A rare autosomal recessive disorder characterized by hearing and visual abnormalities, obesity and progressive renal dysfunction. This syndrome also includes cardiac muscle dysfunction and intellectual disability.

Meckel syndrome - This syndrome is in a group of rare autosomal disorders characterized by protrusion of part of the brain, predominantly encephalocele, multiple renal cysts, polydactyly, hepatic fibrosis and genital abnormalities.

McKusick-Kaufman syndrome (MKKS) - It is an autosomal recessive genetic disorder characterized by postaxial polydactyly, congenital heart defects, hydrometrocolpos, gastrointestinal abnormalities, genitourinary anomalies and renal anomalies.

Biemond syndrome - This syndrome is an autosomal recessive genetic disorder. It is characterized by the absence of tissue in the eyes (iris coloboma), intellectual disability, obesity and genitourinary abnormalities.

Treatment for patients with BBS - The treatment is multidisciplinary and depends on the symptoms of the affected individuals. Some of the abnormalities can be corrected with surgical treatment (genitourinary abnormalities, congenital heart defects, polydactyly, kidney transplantation and

ophthalmological corrections). Obesity should be treated with specific diet programs, hobbies with athletics, and consultation with a nutritionist for the prevention of obesity. In 2022, the Food and Drug Administration (FDA) approved the drug setmelanotide for the treatment of chronic obesity.

Discussion

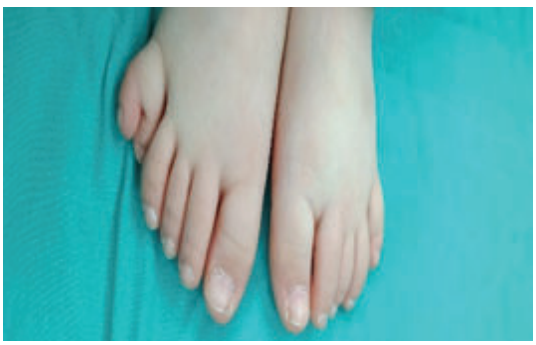
BBS is historically known as Laurence-Moon-Biedl-Bardet syndrome and was described by scientists as the first case of this syndrome. Cardinal signs of BBS are truncal obesity, intellectual disability, renal anomalies, polydactyly, retinal degeneration and hypogonadism.

Case report

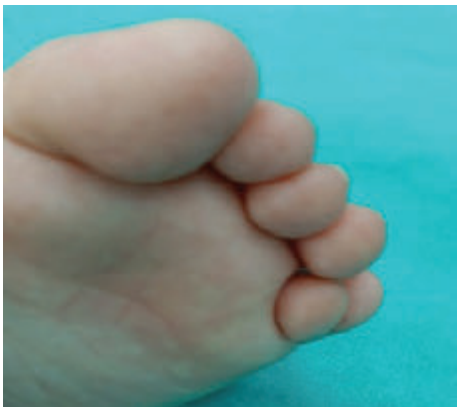
A 3-years-old female child was admitted to the Clinic for Pediatric Surgery due to polydactyly of both feet. From the family history, the mother has hypothyroidism and one grandmother died of pancreatic cancer. The change is congenital. The child was examined at the Clinic for Pediatric Diseases due to changes in both kidneys that were seen intrauterine. This is the second child from a second regular and properly controlled pregnancy. Born in the 38th week of gestation with a birth weight of 3,050 grams and a birth length of 48cm. Apgar was 9/10. Vaccination started regularly and established regularly according to the calendar. Examined in the nephrology outpatient clinic of the Clinic for Children's Diseases due to hyperechogenic kidneys with a granular structure. The remaining findings of abdominal ultrasonography were with normal parameters. The heart findings were normal, clear tones without systolic murmur and rhythmic action. The lung findings were within normal limits, mediastinal structures were properly positioned. Laboratory analyses: blood count, glycemia ionogram, hepatogram, proteinogram, AST and ALT, urea and creatinine were within normal limits.

Molecular genetic studies are compatible with the clinical diagnosis of autosomal recessive type BBS type 12 in our patient. Segregation analysis of variants confirmed the biallelic status in our patient with c8656>C inherited from the father (DNA ID 29101) and c 1658T> C from the mother (DNA ID 29100). These data were obtained from the Institute of Human Genetics - University Hospital Cologne.

Retinal echo was normal. Fundus examination with indirect biomicroscopy, PNO (optic nerve papilla) at the level of the retina with clear borders and normal color. Blood vessels were normal and Macula lutea (ML) was normal, without signs of retinopathy.

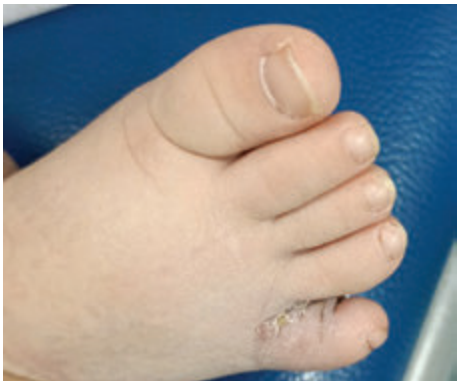


Picture 2. Before surgery.



Picture3. Before surgery.

A female child was admitted to the Clinic for Pediatric Surgery for surgical correction of axial polydactyly of both feet. X-ray in addition to postaxial polydactyly, Dg. Polidactilia Axial Ispedis bill. Based on the performed anesthesiologic examinations, surgical intervention was permitted. Laboratory examinations were within normal limits. The surgical intervention was performed under endotracheal anesthesia. Excision of the toes of both feet that were outside the axis was performed. On both feet, the accessory toes were located between the 4th and 5th toes. Local plastic surgery of the foot followed without the use of skin transplantation. Dressing was done with antibiotic gauze. Waking up was orderly. The postoperative course was orderly. Wounds were healed per primam. Finger movements were orderly.



Picture 4. Postoperative local finding.

Picture 5. Postoperative local finding.

Gene therapy research is an advance in BMS. Certain BMS mutations can be targeted with oligonucleotides. In vivo, potential therapeutic effects have also been demonstrated with fibroblasts. Over the past 10 to 15 years, studies have shown that loss of cilia at the cellular level or their dysfunction are numerous causes of BMS.

Pomeroy et al. observed an increase in sleep time that may be beneficial in alleviating obesity (10). Seo et al. published a study in 2009 on intravenous melanocortin receptor agonists for weight reduction and feeding (11). Mujahid describes pituitary abnormalities in 19.5% of the female population with BBS (12). Certain individuals with BBS may develop abnormalities in kidney structure and function. Renal anomalies include fetal lobulation of tissue, small kidneys, ectopic or duplex kidneys, tubular or interstitial nephritis, glomerulosclerosis, polyuria and others (13).

Setmelanotide is a melanocortin-4 receptor (MC4R) agonist that reduces weight and hunger. The Food and Drug Administration approved the treatment for chronic obesity in adults and pediatric patients of 6 years of age and older in 2022.

Ganawa et al. describe the success of using a GLP-1 agonist to reduce body mass index (BMI) (14). A mega-analysis was published by Niederlova et al. (15).

They analyzed the largest cohort study of BBS patients with a total of 889 patients, pooling data from 85 studies focusing on gene-phenotype correlations. Geno-phenotype correlations were used for disease severity. Patients with mutations and presumed loss of function had a higher syndromic score than the rest.

Prognosis

Depending on the symptoms, the survival rate varies. Moor and colleagues describe a median survival of about 63 years (16). Myocardial infarction results in mortality from 40 to 54 years. O'Dea describes in his study renal abnormalities from 19-60 years, then embolism with thrombosis from 32 to 34 years, gastrointestinal hemorrhages at 45 years (17).

Conclusion

BBS is a rare genetic disease due to ciliopathy. Due to the involvement of multiple systems, the approach to these patients is multidisciplinary. The diagnosis can be made even intrauterine. A multidisciplinary approach is mandatory in this disease due to multiorgan dysfunction. The role of cellular biology is important for the development of specific therapy.

Patient:	_____ (female)	Sample received	23.02.20
Date of birth:	03.02.2021	Request received	23.02.20
Ident. Sample Number:	29099	Sample processed	18.06.20
Sample type:	DNA	(date of sampling: unknown)	Payment Science

Reason for testing:

Diagnosis/assumption of autosomal recessive Bardet - Biedl Syndrome

Requested analisys

NGS analysis based on an exome for known genes for renal ciliopathy, using the Agilent SureSelectXT HS Human All Exon V8. Bioinformatical analysis of 520 genes related to renal pathology of genomic DNA. Alignment of the sequence with human hg38 reference genome. Analysis of coding gene regions and 20 bp of neighboring, non-coding regulatory sequence. The sequencing was done on the Illumina NovaSeq 6000 platform.

Clinical details and previous findings

Patient with bilateral hyperechoic kidneys with a status of previous polydactyly

Results

Filtering for potential complex heterozygosity in 520 genes related to kidney pathology produced a result of only two different heterozygotic BBS12 variants in the patient.

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OBESITY AND POSTOPERATIVE DELIRIUM IN A MIDDLE-AGE SURGICAL PATIENT

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Abstract:

The literature for bladder cancer patients outlines the role of malnutrition as one of the key factors for postoperative outcomes, including postoperative delirium (POD). However, there is still a debated question whether obesity has a protective, or etiology role in the process of occurrence of POD. Here, we present a case of a 56-years-old man with obese class 1 admitted to City General Hospital "8th of September", Skopje, Macedonia, for an elective major surgical procedure, radical cystectomy, presenting with postoperative delirium (POD). Anthropometric measurements (weight, high) and nutrition screening tools (body mass index, NRS-2002) verified his nutrition status. We additionally performed The Confusion Assessment Method and Mini-Mental Status Examination on admission and days 1, 2, 3, and 7 to evaluate signs of POD and his cognition level. Clinical presentation and radiographic imaging confirm the diagnosis of POD. We faced a few challenges writing this case report, including the impact of older age, selection of appropriate and available laboratory markers, examination of how body mass index affects POD, and identification of precipitated factors for POD.

We determined that hypoxia could be a key link that connects inflammation, nutrition status, and POD in our patient.

Key Words: *body mass index; delirium; middle age.*

Introduction

The literature for bladder cancer patients outlines the role of nutrition status as one of the key factors for postoperative outcomes (1). Considerable attention has focused on the role of malnutrition in the carcinogenic process and postoperative outcomes (2). Also, the effect of malnutrition on neurocognitive decline was reported (3). Malnourished bladder cancer patients who

undergo elective major surgery have been shown to have cognitive problems like postoperative delirium in addition to other adverse effects on the outcome (4). Unlike malnutrition, the role of obesity in the carcinogenic process of bladder cancer and its potential role in the development of POD is a subject of ongoing debate within literature. The main question is whether obesity has a protective or etiological role in the occurrence of POD (5). In this case report, we aimed to investigate the impact of BMI on POD and to test the possible mechanism for developing POD in middle-aged patients with obesity.

Case Report

In the presenting case, a 56-years-old man with a diagnosis of bladder cancer was admitted to City General Hospital "8th of September", Skopje, Macedonia, for an elective major surgical procedure, radical cystectomy. This case involved a patient who underwent aortic valve replacement with preexisting hypertension and an ongoing smoking habit of 25 cigarettes per day. The patient's respiratory function remained unaffected despite his preexisting conditions. We categorized our patient as an ASA 2 according to his condition. Upon admission, the patient's nutrition status and cognition were assessed. We employed a comprehensive range of tools, including the mini-mental status (MMSE) for basic cognitive evaluation, anthropometric measurements (weight, height), and nutrition screening tools (Body Mass Index, NRS-2002) for nutrition status evaluation. The confusion assessment method (CAM) was used for postoperative evaluation of cognition, and the C-reactive protein was used for inflammation; they were measured postoperatively on days 1-7.

The results of evaluations on admission day were negative for the CAM and MMSE tests, 32.4kg/m2 for BMI and low risk of malnutrition for NRS-2002, and 54.3mg/l for C-reactive protein, where the normal range is 0-10mg/l. Upon entering the operating room, routine monitoring was conducted, including electrocardiography, pulse, blood oxygen saturation monitoring, and noninvasive arterial pressure measuring device. The patient's condition was as follows: without an oxygen mask, his blood pressure was 130/70mmHg, heart rate 60/min, and saturation 98%. Total intravenous anesthesia (TIVA) was used in conjunction with epidural anesthesia to induce and maintain anesthesia. We skillfully placed an epidural catheter at the T10 vertebral level before the patient received general anesthesia. The patient received general anesthesia as follows: 2mg Midazolam, 0.1mcg Fentanyl and 150mg Propofol i.v. Bolus, followed by intubation with 50mg Rocuronium and ETT number 8. Continuous infusion of 0.05mg/kg/h of Propofol and 0.25% bupivacaine at 4-5ml/h through the epidural catheter was used to maintain anesthesia. Rocuronium was added intermittently every 40 minutes after induction and stopped 1 hour before surgery ended. Throughout the surgery, the patient's vital signs remained remarkably stable. The systolic pressure ranged from 90-130mmHg, the diastolic pressure from 60-90mmHg, the heart rate was maintained at 60-70 beats per minute, and blood oxygenation was consistently high at 99-100%. Capnography monitoring revealed an end-title CO2 level of 31, suggesting adequate ventilation. Intraoperatively, we administered gastroprotective therapy with Famotidine 20mg and Metoclopramide 10mg. The patient received 1000ml NaCl 0.9%, 500ml Dextrosa 5%, one blood transfusion, and 1000ml Ringer solution for fluid replacement. Seven hours after surgery successfully ended, the patient was extubated and mobilized to the intensive care unit for further monitoring and care. The postoperative pain management plan involved a continuous infusion of bupivacaine 0.5% at the rate of 4ml/h. It significantly reduced the patient's pain scores and opioid requirement postoperatively. During the first 24 hours after surgery, he

remained communicative, responsive to verbal commands, and oriented regarding time and space. He did not exhibit postoperative hemorrhage and had spontaneous diuresis and breathing, indicating a positive response to the treatment. We observed stable postoperative vital signs and laboratory analysis, with decreased oxygen saturation and increased heart and respiratory rates on the third day. The patient's vital signs on these 3 days were systolic pressure ranging from 90-130mmHg and diastolic pressure from 60-90mmHg. However, on the third day, we observed a significant decline in condition and oxygen saturation. The heart rate was 80-110 beats per minute, and blood oxygenation was consistently low at 85-90%. He manifested symptoms of agitation, including restlessness and anxiety, and displayed unwillingness to collaborate with medical staff. He went so far as to attempt to remove his nasogastric tube and urinal catheter. This disruptive behavior, coupled with ongoing attention disruption, hallucinations and insomnia, continued for the next 2 days. We performed cranial and chest computed tomography on the fifth postoperative day, followed by pulmonary angiography. The results indicated suspected thrombotic formation in arteries on the pulmonary angiography and mild-age-related cerebral atrophy on the cranial computed tomography. The patient received anxiolytic and antidepressant drugs as follows: risperidone 2mg twice a day and promazine 25mg daily until the seventh postoperative day, when he became completely asymptomatic. The control computer scanning on the 12th day was without changes. After 20 days, the patient was discharged from the hospital in a stable mental and urological status, indicating a successful recovery process.

Discussion

Postoperative delirium is an organic mental syndrome involving changes in thinking, cognition and perception unrelated to previous dementia (6). Postoperative delirium disproportionately affects older patients, especially those aged 65 and above, who represent a substantial portion of surgical patients, including those undergoing complex procedures like radical cystectomy (7). In this case, however, a 56-years-old man, who was not considered to be in the typical age range for postoperative delirium, developed POD on day 3 upon surgery. To assess the nutrition status of our patient, we used the Body Mass Index calculator and NRS-2002 screening toll, and the results were as follows: obesity class 1 after body mass index calculation and a low risk of malnutrition after nutrition screening. The relationship between nutritional status, including obesity and postoperative delirium, is still subject to ongoing debate. Current studies suggest that malnutrition is a significant risk factor for postoperative delirium, especially in vulnerable populations such as older cancer patients, including those with bladder cancer, where malnutrition is prevalent (8). Patients with a BMI between 30 and 34.9, classified as obesity class 1, may experience a reduced risk of postoperative delirium (POD) compared to those who are underweight or have more severe obesity (9). However, patients with obese class 1 may face a higher risk of POD if comorbidities are present (10). In our patient's medical history, we record cardiovascular disease among the comorbidities. Fat mass in obese patients leads to an inflammatory state characterized by sustained low-grade metabolic inflammation. While obesity-related inflammation is chronic, surgical interventions induce more acute inflammatory response. Both conditions lead to elevated CRP levels due to their activation of systemic inflammatory pathways (11). On the admission day, our patient's C-reactive protein level was 54.3mg/l, significantly higher than the standard 0-10mg/l range, indicating inflammation and inflammatory response. Elevated CRP levels cause blood-brain barrier disruption by increasing paracellular permeability, which allows leukocytes and inflammatory mediators to enter the brain parenchyma. This leads to brain edema and inflammation, impairing blood flow and oxygen delivery, and hypoxia in the end

(12). When delirium started, we observed a significant increase in the patient's C-reactive protein level from 54.3 to 130mg/l and a decrease in oxygen saturation while monitoring vital signs corresponding with blood-brain barrier disruption and hypoxia. The patient's oxygen saturation without oxygen supply before receiving anesthesia was 98%. His vital signs, including oxygen saturation, were stable until the third day when the oxygen saturation decreased to 85%. It has been shown that decreased oxygen saturation, whether systemic or cerebral, increases the risk of experiencing postoperative delirium during major surgeries (13). Additionally, a combination of respiratory dysfunction, increased carbon dioxide levels, and reduced breathing effort, which are frequently seen in obese patients, often leads to postoperative hypoxia and a decrease in oxygen saturation (14). Radiology investigation reported another possible reason for hypoxemia in our patient: pulmonary thromboembolism. Among the factors that increase the risk for pulmonary thromboembolism are a hypercoagulable state associated with obesity and Increased Operative Time (15). Our patient, in addition to being obese, was under a prolonged time of 7-hours surgery, a situation that corresponded to that risk.

Conclusion

In our case report, we determined that hypoxia is a key link between systemic inflammation, obesity, and POD. In addition to subjective tests like the CAM test, nutrition tools and inflammatory markers can help identify patients at risk for POD.

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MANAGING DUAL PATHOLOGIES: NEPHRECTOMY FOR RENAL CELL CARCINOMA IN A PATIENT WITH SEVERE TRICUSPID VALVE REGURGITATION

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Abstract

Renal cell carcinoma (RCC) is the most prevalent form of kidney cancer. Tricuspid regurgitation is a condition marked by the reverse flow of blood from the right ventricle into the right atrium and necessitates thorough assessment to ascertain its severity and effect on heart function. In this case, we present a 57-years-old male patient with symptomatic renal cell carcinoma and a severe tricuspid valve regurgitation. The performed open nephrectomy went uneventfully. While the patient was successfully and safely managed from an anesthesiology standpoint despite his comorbidities, performing the procedure in a resource-limited setting posed significant challenges. In such environments, the lack of immediate access to advanced hemodynamic monitoring, cardiothoracic surgical support and perioperative cardiac interventions increases the complexity of managing patients with dual pathologies. Ideally, conducting nephrectomy in an operating theater equipped for simultaneous surgical interventions, addressing both the renal pathology and potential worsening of tricuspid valve regurgitation, with a cardiothoracic team on standby, would have provided a safer approach. However, in settings with constrained resources, optimizing intraoperative management, ensuring rigorous hemodynamic monitoring, and coordinating multidisciplinary teams within the available infrastructure become critical for achieving favorable outcomes.

Key Words: *renal cell carcinoma; tricuspid valve regurgitation; simultaneous surgery.*

Introduction

Renal cell carcinoma (RCC) is the most prevalent form of kidney cancer, originating from the epithelial cells of the renal tubules. It accounts for approximately 85% of neoplasms arising from the kidney (1). RCC exhibits a variety of histological subtypes and may be presented with symptoms such as hematuria, flank pain and a palpable mass. A diagnosis is often made through imaging techniques and confirmed with a biopsy. Treatment options vary based on the tumor's stage and molecular features, and may include surgery, targeted therapy or immunotherapy (2). Surgical resection continues to be the main treatment for this condition. In cases where tumors are widespread, loco-regional therapies can still play an

important role in alleviating symptoms associated with the primary tumor or ectopic hormone production. Nevertheless, systemic treatments have demonstrated limited efficacy (3). Tricuspid regurgitation is condition which contributing factors may include valve degeneration, dilation of the annulus, or damage caused by conditions like pulmonary hypertension or infective endocarditis. The degree of tricuspid valve regurgitation (TR) indicates the extent of blood flow back from the right ventricle to the right atrium caused by inadequate closure of the tricuspid valve. Recent advancements in understanding the causes and impact of mitral regurgitation on patients' overall health have sparked renewed attention to the often "forgotten" tricuspid valve and tricuspid regurgitation (TR) (4). Although mild TR is commonly seen in healthy individuals, more severe forms of TR have been linked to significant morbidity and mortality, with up to one-third of patients with severe TR dying within a year of diagnosis.

Case Presentation

We present the case of a 57-years-old male patient, a smoker with a BMI of 26, classified as ASA class 3 and a Mallampati score of 3, without a medication or food allergies. He was admitted to the Urology Clinic for open nephrectomy due to renal cell carcinoma measuring 136x105mm revealed on a CT scan with macroscopic hematuria.

During pre-surgical preparations, the patient exhibited signs of right-sided heart failure, including neck pulsations from distended and pulsatile jugular veins and exercise intolerance. He has been receiving multiple medications, including a beta blocker, diuretics, antihyperlipidemic agents and an oral anticoagulant for an underlying condition, which will be discussed further.

Auscultation revealed vesicular breath sounds and a systolic murmur over the tricuspid valve. A cardiologist was consulted immediately, and appropriate investigations were carried out. An ECG revealed atrial fibrillation with a rapid ventricular response, while a chest X-ray showed cardiomegaly. Echocardiography revealed a 50% ejection fraction of the left ventricle without segmental wall-motion abnormalities, dominant right heart failure with enlarged right-sided chambers and severe tricuspid regurgitation. Additionally, the inferior vena cava was dilated to 25mm without inspiratory collapse, and pulmonary artery systolic pressure was 75mmHg.

The left ventricle was reduced in size to 47mm (the normal size for men is below 58mm), due to the septum being displaced by the enlarged right ventricle. On the other hand, the left atrium was enlarged to 50mm (normal is below 44mm), with moderate mitral regurgitation observed. The aortic and pulmonary valves were both structurally and functionally normal, consistent with the patient's age.

The patient was further referred to cardio-thoracic surgeon, who strongly advised that surgical intervention for the tricuspid valve is warranted. However, due to the high risk of bleeding and the necessity of anticoagulant therapy required for cardiopulmonary bypass during tricuspid valve surgery, it was decided that the primary renal condition should be treated first. This approach aimed to mitigate the risk of excessive perioperative bleeding while ensuring optimal timing for subsequent cardiac intervention. After recovery from the nephrectomy, the patient would undergo tricuspid valve replacement surgery at the Cardiothoracic Surgery Clinic. After comprehensive evaluation, the procedure was performed under general endotracheal anesthesia combined with epidural analgesia. Preoperative standard hemodynamic monitoring, which included electrocardiography, pulse oximetry and non-invasive blood pressure meas-

urement, was conducted prior to anesthesia induction. Subsequently, an epidural catheter was placed at the Th-12 to L1 intervertebral level. Following 2 minutes of preoxygenation with 8 liters of oxygen, the patient was pre-medicated with 2mg of Midazolam, 100mcg of Fentanyl, 60mg of Lidocaine, and anesthesia was induced with 150mg of Propofol and 40mg of Rocuronium. Due to the second attempt at intubation, necessitating the use of an endotracheal tube stylet, which was successful with endotracheal tube size 8F, a new-onset tachycardia occurred, and the heart rate escalated to 140 bpm. This was managed by administering 5mg of Presolol and 150mg of amiodarone, followed by an additional 150mg, which resulted in the heart rate returning to baseline. Magnesium sulfate was also administered to provide further stabilization. Anesthesia maintenance was achieved with Sevoflurane at 0.7 MAC. Mechanical ventilation was administered using a pressure-controlled, volume-guaranteed mode with a tidal volume of 6mL/kg. The respiratory rate was adjusted to maintain an end-tidal CO_2 level within the target range of 35–45mmHg, with an FiO_2 of 50% and PEEP of 5mmHg. Analgesia was provided via a continuous epidural infusion of Bupivacaine 0.125% and 100mcg of Fentanyl, delivered at a rate of 10ml/h, ensuring effective pain control without additional opioid use.

Throughout the procedure, except standard non-invasive monitoring, invasive monitoring was employed, including cannulation of the right radial artery, and a 7 French triple-lumen central venous catheter was inserted into the right internal jugular vein. Due to the severity of the condition and the patient's hemodynamic status, with a potential need for rapid therapeutic administration, a midline catheter of 5F was placed as well. Continuous hemodynamic monitoring was maintained throughout the procedure to promptly detect and manage any cardiovascular instability which was crucial, given the patient's significant comorbidities and the resource-limited setting.

In the absence of TEE, intraoperative hemodynamic management relied on central venous pressure (CVP) monitoring, invasive arterial blood pressure measurement and clinical assessments. However, due to the regurgitant flow into the right atrium, CVP is not a reliable indicator of intravascular volume status in patients with severe TR. We aimed to maintain a CVP range of 8–12mmHg with careful fluid titration to avoid excessive right ventricular (RV) volume overload, which could exacerbate systemic venous congestion and worsen hemodynamics. Additionally, systemic perfusion was optimized with a mean arterial pressure (MAP) >65mmHg while avoiding factors that could increase pulmonary vascular resistance (PVR), such as hypoxia, hypercapnia and acidosis. Given these hemodynamic challenges, our anesthesia plan was carefully tailored to minimize stress on the failing right heart.

On the other hand, balancing right ventricular function and renal perfusion was vital to ensure adequate vascular status to maintain perfusion of the remaining kidney, given the patient's nephrectomy. Careful fluid management, guided by all available parameters, allowed us to maintain an optimal balance between right ventricular function and renal perfusion.

Throughout the 3-hours procedure, the patient remained hemodynamically stable, eliminating the need for vasopressor or inotropic support, which was particularly advantageous given the resource-limited setting. Along with the hemodynamic advantages mentioned earlier, the regional anesthesia technique also facilitated successful early extubating and contributed to a reduction in positive end-expiratory pressure, which could otherwise worsen the pre-existing right heart failure. Following the extubating, the patient was transferred to the postoperative anesthesia care unit, where the early postoperative recovery was uneventful. Following a five-days hospital stay after the procedure, the patient was released in good health to receive treatment at home.

Discussion

Surgical resection remains the only established curative treatment for localized renal cell carcinoma and is also used to improve outcomes or provide palliation in cases of metastatic disease. Surgical options include partial nephrectomy, simple nephrectomy, and radical nephrectomy, which removes the entire kidney, the adrenal gland, surrounding tissue and usually nearby lymph nodes. In this case, a simple open nephrectomy was performed (5).

In contrast, the severity of tricuspid regurgitation (TR) is assessed using echocardiography, which evaluates factors such as the size of the regurgitant jet, enlargement of the right atrium or ventricle and clinical symptoms. Accurate grading of TR is crucial in determining the need for intervention and predicting outcomes. Tricuspid valve surgery is a viable treatment for symptomatic patients with progressive right ventricular (RV) dilation or dysfunction, as long as there is no severe left ventricular (LV) dysfunction and/ or significant pulmonary vascular disease or hypertension (6).

Given that there is no universally optimal anesthetic approach for a patient with severe tricuspid regurgitation requiring surgical intervention, and symptomatic renal cell carcinoma, the primary focus is placed on addressing the primary condition, in this case, nephrectomy for renal cancer, because of the increased risk of bleeding in accordance with the cardiac surgeon's recommendations. Our goal was to safely manage this patient, taking into account all the comorbidities and the associated risks. We utilized continuous epidural anesthesia combined with inhalational anesthesia while avoiding opioids except during induction. This multimodal approach provided excellent hemodynamic stability throughout the procedure, except during tracheal intubation, where transient tachycardia was observed. The choice of continuous epidural anesthesia was particularly advantageous in this patient, as it facilitated hemodynamic stability by preventing excessive sympathetic stimulation and abrupt hemodynamic shifts.

Considering the complexity of the patient's underlying conditions, the procedure would be conducted more safely in an operating theater, allowing for the potential simultaneous performance of both nephrectomy and eventual replacement of the deteriorated tricuspid valve, offering the capability for continuous cardiac output measurement and intraoperative transesophageal echocardiography. Lastly, the interventional options available in such a setting, including extracorporeal membrane oxygenation, if necessary, as well as the presence of a cardiac surgery team on standby, provide crucial support in the event of a deterioration in the patient's condition (7).

In patients with severe cardiac disease requiring surgical intervention, prioritizing cardiac surgery is often essential before addressing other organ pathologies. This approach is particularly relevant when managing patients with concomitant renal pathology requiring surgical treatment. Addressing the cardiac condition first, ensures hemodynamic stability, reducing perioperative risks associated with major non-cardiac surgery (8). However, in selected cases, performing both procedures simultaneously in an operating theater equipped for simultaneous concomitant procedures, along with the invasive monitoring and interventional capabilities described above, may provide the best clinical outcome, particularly in centers with appropriate expertise and resources (9). Performing a non-cardiac procedure, such as kidney surgery, in a patient with untreated severe cardiac disease poses significant risks, especially in settings without access to cardiopulmonary bypass (CPB) and cardiac surgery standby. In such cases, intraoperative hemodynamic instability could lead to life-threatening complications. Studies

have demonstrated that patients with advanced cardiac disease undergoing major non-cardiac surgery without prior cardiac optimization have increased mortality and morbidity (10,11). The European Society of Cardiology (ESC) guidelines recommend preoperative cardiac risk stratification and optimization to minimize perioperative complications (12).

Our case is from resource-limited settings in middle-income countries, where the ability to manage complex cases is highly dependent on the expertise of anesthesiologists and surgeons. In the absence of advanced perioperative monitoring tools and immediate access to extracorporeal support, anesthetic and surgical teams must rely on advanced clinical skills to navigate high-risk procedures safely. There are some previous reports similar to ours that have highlighted the role of experienced anesthesiologists in mitigating intraoperative cardiovascular instability through tailored anesthetic management strategies and fluid optimization (13). Despite the absence of advanced cardiac monitoring, our center, as the tertiary referral hospital, successfully managed this high-risk case with all available monitoring and expertise. This case highlights the feasibility of performing non-cardiac surgery in patients with severe TR when cardiac surgical intervention is not an option, provided that perioperative management is carefully optimized. Our experience underscores the need for a multidisciplinary approach in managing such complex cases, balancing surgical necessity with the patient's cardiovascular limitations.

Additionally, this case contributes valuable insight into the successful application of opioid reduced use in anesthesia with continuous epidural analgesia in a patient with severe TR, demonstrating that non-cardiac surgery can be safely performed even under constrained conditions (14).

Conclusion

A patient's total risk profile, institutional resources and available expertise, all must be considered when deciding whether to stage or combine procedures. In well-equipped centers, similar procedures can be performed safely, allowing for simultaneous cardiac and non-cardiac interventions. However, in resource-constrained environments, optimizing the management strategy based on available capabilities remains critical for improving patients' outcomes.

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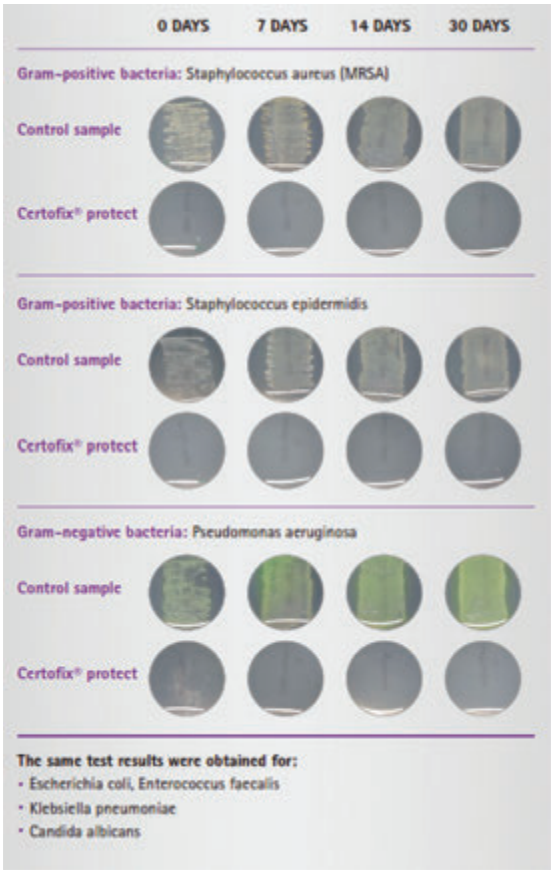

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