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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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WHEN EARLY RECOVERY REALLY MATTERS

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FARMA TREJD

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While efforts have been made to ensure their accuracy and integrity, readers are advised that they have not been subjected to the rigorous scrutiny typically applied in peer-re-viewed scientific literature.

CONTENT

REVIEW ARTICLE *UDK: 616.831-001:616.152*

WATER-ELECTROLYTE IMBALANCE IN PATIENTS WITH TRAUMATIC BRAIN INJURY: CLINICAL MANIFESTATION AND TREATMENT

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Abstract

Traumatic brain injuries constitute a direct injury to the central nervous system. The presentation depends on the location, type, and severity of the injury. Fluid and electrolyte imbalance are common after traumatic brain injury and may manifest as abnormalities in sodium, potassium, chloride, and calcium levels. Changes in serum sodium levels are the most common and critical electrolyte abnormality. Plasma sodium concentration is a primary determinant of plasma osmolality and is regulated by the secretion of antidiuretic hormone or arginine vasopressin, followed by a sensation of thirst. For decades, disturbances in salt and water balance due to impaired secretion of arginine vasopressin have been observed after traumatic brain injury. This occurrence can manifest as arginine vasopressin deficiency, formerly called central diabetes insipidus, leading to hypernatremia, or arginine vasopressin excess, leading to the syndrome of inappropriate antidiuretic hormone secretion and hyponatremia. Dysnatremia is associated with an increased risk of secondary brain injury due to the resulting changes in brain fluid levels, as well as greater morbidity, and longer hospital stays. Posterior pituitary dysfunction following traumatic brain injury, including alterations in arginine vasopressin release and dysnatremia, most commonly occurs in the acute phase, as it is often transient, and resolves in most patients after recovery from the initial injury. Most importantly, in both hypo and hypernatremia, early detection and prompt appropriate treatment often save lives.

Key words: *traumatic brain injury, water-electrolyte imbalance, diabetes insipidus, SIADH, CSWS*

Introduction

Traumatic brain injury is one of the most common causes of death among individuals between the of 1 to 35 years that leads to various disabilities with a high socioeconomic burden. The total incidence of traumatic injuries is estimated to be 538.3 per 100,000 population (1).

Traumatic brain injury is classified into primary and secondary injuries. The usual mechanisms of primary traumatic brain injury include direct impact, rapid acceleration/deceleration, penetrating injury, and blast-related injury. Although these mechanisms are heterogeneous, their common trait is externally applied mechanical forces to the brain. The resulting trauma includes focal cerebral contusions, hematomas, and diffuse axonal lesion, all of which are associated with cerebral edema. Secondary brain injury develops as a result of complex molecular mechanisms initi-

ated at the time of the primary trauma and evolve over hours or days. Some of these mechanisms include excessive glutamate-mediated stimulation, free radical-induced cell membrane damage, mitochondrial dysfunction, damage to the vascular wall, inflammatory reactions, apoptosis, ischemia due to vasospasm, local microcirculatory occlusion, and electrolyte abnormalities (2,3).

Serum electrolyte imbalances in patients with traumatic brain injury are considered preventable secondary complications. They may result directly from brain injury, iatrogenic factors, or other coexisting conditions such as renal insufficiency, cirrhosis, and congestive heart failure (4,5). The risk of electrolyte imbalance in patients with traumatic brain injury depends on the severity of the injury, the presence or absence of comorbidities, the patient's age, and the initial treatment strategies, such as adequate choice of fluids for resuscitation, administration of mannitol or diuretics and hyperventilation (6). Early recognition of serum electrolyte disturbances may reduce mortality and morbidity rates associated with primary and secondary brain trauma.

The aim of this paper is to present the common serum electrolyte imbalances and their clinical manifestations in patients with traumatic brain injury.

Material and methods

In this review article, a comprehensive literature research was performed using PubMed and Google Scholar databases. The following key words or medical subject headings were used: "traumatic brain injury", "water-electrolyte imbalance", "diabetes insipidus", "SIADH", "CSWS". The most relevant and recent literature, was analyzed and summarized.

Discussion

Patients with traumatic brain injury frequently develop electrolyte imbalances that may manifest as abnormalities in the levels of sodium, potassium, chloride, and calcium. Among these, serum sodium disorders are the most common and clinically significant electrolyte abnormalities (7).

Serum sodium concentration is the principal determinant of plasma osmolality, and is maintained in a close physiological range by central osmoregulation through the secretion of antidiuretic hormone or arginine vasopressin (AVP) and thirst mechanisms. Arginine vasopressin is released in response to increased plasma osmolality (8). Traumatic brain injury is defined as any brain injury caused by an external force and can lead to dysfunction of hypothalamic-pituitary axis.

By examining autopsy samples after fatal head injury, Kibayashi et al. identified infarction or hemorrhage of the pituitary gland in 40.9% of cases, as well as hypothalamic infarction (9). The supraoptic and paraventricular nuclei were most commonly affected sites of injury, leading to denervation of the posterior hypophysis and impaired arginine vasopressin release (9,10). For decades, salt and water imbalance due to altered secretion of arginine vasopressin have been observed following traumatic brain injury, and they may manifest as arginine vasopressin deficiency (formerly known as central diabetes insipidus). It leads to hypernatremia, or excess arginine vasopressin, resulting in the syndrome of inappropriate diuresis (SAID) and hyponatremia (11). Dysfunction of the posterior hypophysis most often occurs after acute traumatic brain injury and resolves in the majority of cases (12).

The pattern of water-electrolyte and endocrine abnormalities after brain trauma vary depending on the site of the injury. Hypothalamic injury may cause anterior hypopituitarism, diabetes insipidus, or inappropriate secretion of antidiuretic hormone (13). Damage to the posterior hypophysis alone does not usually lead to permanent diabetes insipidus, as ADH synthesized in the hypothalamic nuclei may still be found into the peripheral circulation. After transection of the pituitary stalk, a three-phase response has been described (initially DI, followed a few days later by transient SIADH and later recurrence of DI, either transient or permanent) (14).

Post-traumatic Diabetes Insipidus

Diabetes insipidus (DI) is a hormonal disorder caused by reduced secretion or impaired action of antidiuretic hormone (ADH, vasopressin). It is classified into central and nephrogenic diabetes insipidus. Central diabetes insipidus occurs following damages to vasopressinergic neurons due to trauma, neoplasms, neurosurgical procedures, or autoimmune inflammations that involve neurons secreting vasopressin (15).

Diabetes insipidus is a rare disorder with a prevalence of 1 per 25,000 individuals considering all causes. However, its incidence reaches up to 20% in patients with moderate or severe traumatic brain injury. The onset of diabetes insipidus is associated with brain death, and is present in 80% of brain-dead patients (16). No clear age or sex predisposition has been identified. It is noteworthy that post-traumatic diabetes insipidus may persist from several days to several weeks and is associated with high mortality rates (57%-69%), particularly when it develops very early after traumatic injury (86%-90%) (17).

Many reports confirm diabetes insipidus, often diagnosed according to the criteria proposed by Seckl and Dunger (polyuria >3l, urine osmolality below 300 mOsm/kg, hypernatremia >145 mmol/L) (18).

Patients with DI lose the ability to concentrate urine and excrete large volumes of dilute urine (polyuria) resulting in polydipsia. Predominant manifestations of diabetes include hypotonic polyuria with diuresis exceeding 50 mL/kg within 24 hours and polydipsia with fluid intake greater than 3 L/day. Most patients with diabetes insipidus are in a poor health condition and frequently have impaired consciousness (due to the direct traumatic effect, cerebral edema, intracranial hemorrhage or sedative medications used in intensive care units) on their admission to the intensive care unit. They may be unable to express their feeling of thirst or to maintain adequate oral intake. In such cases, the excessive volume of inadequately dilute urine output and hypernatremia are key indicators for establishing the diagnosis. Inadequate fluid intake combined with rapid renal water loss may lead to severe dehydration and hypovolemic hypernatremia (with hypotension and reduced cerebral perfusion pressure) (19).

The diagnosis of PTDI is not always simple. Patients in intensive care units often require interventions such as shock management, blood product transfusion, and volume correction, as well as treatment of the increased intracranial pressure with hyperosmolar substances or barbiturate administration. These therapeutic procedures may impact the diagnosis of DI.

Once polyuria is identified, it is necessary to exclude other causes of large urine output (often encountered in patients with trauma as a result of hypercatabolic condition and medications), administration of hyperosmolar agents (e.g., mannitol or hypertonic saline solution), or diuretic therapy (20).

However, to confirm the diagnosis of DI, we must include a 24-hour urine collection with urine volume measurement, urine and plasma osmolality, as well as serum sodium concentration, and copeptin levels. Plasma osmolality > 280 mOsm/kg and sodium levels > 147 mEq/L support the diagnosis of diabetes insipidus. The water deprivation test has been used as a standard method for diagnosing DI for years, although its diagnostic accuracy is approximately 70%. Following the water deprivation test no increased ADH release has been identified, and hypotonic urine continues to be excreted. For definitive diagnosis of diabetes insipidus, additional tests may be necessary, such as hypertonic saline infusion or arginine stimulation testing. The hypertonic physiological solution test can be used for differentiation between patients with primary polydipsia and patients with central diabetes insipidus, with 93% sensitivity and 100% specificity. This test is performed by infusing 250 mL 3% hypertonic physiological saline within 15 minutes, followed by copeptin and sodium level measurements every 30 minutes. The infusion is stopped once the plasma sodium concentration reaches ≥147–150 mmol/L, at which point the final copeptin sample is taken, while a value above 4.9 pmol/L indicates a condition of primary polydipsia (PP). Regarding the arginine test, if the copeptin serum is <3.8 pmol/L after a 60-minute arginine infusion, then the diagnosis is central diabetes insipidus. Intravenous infusion of arginine demonstrated a diagnostic accuracy of 93% in differentiating CDI from PP. In situations where it is necessary to make a distinction between central and nephrogenic diabetes insipidus, copeptin values ≤ 4.9 pmol/L are specific for central diabetes insipidus, while levels ≥ 21.4 pmol/L indicate nephrogenic diabetes insipidus. Also, magnetic resonance (MRI) has been applied as diagnostic tool. Pituitary stalk hematoma or loss of the posterior pituitary bright signal on T1-weighted scans is occasionally observed An ectopic bright spot in cases with stalk transection has been rarely described. In some cases, cerebral CT/MRI do not show any abnormal findings, meaning that a certain hypoxic damage or diffuse axonal injury has occurred (21,22).

Treatment of patients with diabetes insipidus in intensive care units follows the same general intensive care principles as for the other critically ill patients, including careful monitoring of vital signs, blood pressure, pulse, diuresis, cerebral perfusion pressure, intracranial pressure, GCS, oxygenation status, hydration status, standard laboratory parameters, urine specific weight, plasma and urine osmolality, and serum sodium levels monitoring (23,24).

After diagnosing DI, the initial approach aims to avoid dehydration by fluids compensation (related to negative outcome in patients with acute injury to the head) (25). In conscious patients, with preserved thirst mechanisms and good general physical condition, oral fluid intake may adequately compensate for renal water losses. In patients with impaired consciousness, which is most commonly seen in patients in intensive care units with associated neurological deficit, dysphagia or changes in the thirst mechanism, or hypotonic polyuria may rapidly lead to hypovolemia and hypernatremia. Initially, hypovolemia should be managed by intravenous fluids' administration , while evaluation of the volume status is mandatory. Five percent dextrose solution is recommended for free water replacement (26).

Fluid correction must be made with close clinical monitoring and CVP measurement to avoid both under-resuscitation (related to hypovolemia and reduced CPP) or over-resuscitation (that can exacerbate cerebral edema, increase intracranial pressure and may cause lung edema). The free water deficit may be calculated using the following formula:

(0.6[weight in kilograms])x(serum sodium-140):140=body water deficit (in liters) (27).

With fluid correction, serum sodium levels would be reduced. In cases of severe hypernatremia (>150 mmol/L), the correction should be carefully managed as the brain tissue is too sensitive to rapid osmotic changes that lead to aggravation of cerebral edema. The recommended rate of sodium reduction should not exceed 0.5 mmol/h or 10-12 mmol/L/24 hours. The treatment should include hormone substitution with desmopressin, particularly in patients with urine output exceeding >250 mL/hour (28,29).

Desmopressin is the treatment of choice for central diabetes insipidus and may be administered orally, intranasally, subcutaneously, or intravenously. Oral doses of desmopressin range from 0.05 mg to 0.8 mg (in divided doses) daily. The oral form is weaker than the nasal one since only 5% is reabsorbed by the intestines. Intranasal dosing typically ranges from 10 mcg to 20 mcg per day. Intravenous or subcutaneous administration is used for acute diabetes insipidus (30).

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a condition characterized by excessive release or action of antidiuretic hormone (ADH), which results in water retention and subsequent hyponatremia. SIADH is associated with various etiologies, and is most commonly combined with malignant lung tumors, surgical interventions, medications and central nervous system disorders. Traumatic brain injury is the cause of approximately 2.5% of SIADH cases (31). This disorder usually originates from injuries to the osmoreceptors or volume receptors of the hypothalamus and hypophysis, where ADH is produced and secreted. However, it may also result from changes in the renal tubules, specifically the collecting ducts, and their inappropriate reaction to ADH (32). Regarding traumatic brain injury, basically, there are limited data related to specific injury sites associated with SIADH and the mechanisms of its onset (33).

It is estimated that in 33% of patients with traumatic brain injury, hyponatremia and SIADH develop. The clinical presentation of SIADH in patients with TBI depends on the type of trauma and Na+ concentration. According to the study by Moro et al., the incidence of SIADH varies depending on the type of injury, where 47.9% of patients had cerebral contusions, 34.8% had acute subdural hematomas, 25% had acute epidural hematomas and 15.9% had chronic subdural hematomas (34). The majority of hyponatremia cases occur within the first four to ten days after injury, however, rare cases of persistent hyponatremia lasting for years have also been reported (35).

With regards to hyponatremia, the severity of symptoms correlates with the rapidity of its onset and its severity. As hyponatremia develops, all cells absorb water causing cellular swelling. This process is problematic to the brain, which is enclosed within an inextensible skull. Astrocytes are especially sensitive to osmotic stress, although the excretion of potassium and other electrolytes within 6 to 12 hours and organic osmolytes, including glutamine and taurine within 24 to 48 hours, reduce the content of cellular soluble substances and help in diminishing edema in case of hyponatremia. Taking into consideration the time course, acute hyponatremia is defined as a condition in which hyponatremia develops within 48 hours, whereas chronic hyponatremia persists for a longer period and develops in the majority of cases. In severe hyponatremia, Na+ <125 mEq/L, which develops within less than 48 hours, and water absorption in the brain over-

whelm compensatory mechanisms, therefore, symptoms are primarily neurological and progress to mild clinical presentation involving nausea, vomiting, lethargy, headaches, confusion and muscle spasms. Severe complications of acute deep hyponatremia involve cerebral edema, seizures, coma, brainstem herniation, and neurogenic pulmonary edema. It is considered that long-term hyponatremia may be symptomatic if severe, although many patients with chronic mild to moderate hyponatremia remain asymptomatic (36).

The diagnosis of SIADH is based on clinical signs and symptoms and laboratory findings. Laboratory findings include low serum sodium levels (<135 mEq/L), low plasma osmolality (<275 mOsm/L), increased urine sodium levels (>25 mEq/L), and increased urine osmolality (greater than serum osmolality) (37).

Osmotic demyelination syndrome (ODS) is associated with rapid correction of hyponatremia. In patients with acute hyponatremia, it develops within 24 to 48 hours, and in patients with initial sodium [Na+] levels >125 mEq/L, treatment is not associated with osmotic demyelination syndrome. On the other hand, chronic hypotonic hyponatremia and [Na+] serum levels of <105 mEq/L represent major risk factors for ODS.

In acute hyponatremia, Na+ normalization does not carry a risk of ODS; the correction rate does not need to be restricted when hyponatremia duration is less than 48 hours. In chronic hyponatremia, [Na+] levels should be increased to prevent the risk of severe complications such as seizures or brain herniation while minimizing the risk of ODS. Studies have shown that in patients with chronic hyponatremia no post-therapeutic neurological complications occurred when [Na+] correction was <12 mEq/L within 24 hours or <18 mEq/L within 48 hours. Also, no post-therapeutic neurological symptoms were observed in patients where [Na+] increased to <0.55 mEq/L per hour until a sodium concentration of 120 mEq/L was reached (38).

Initially, SIADH is treated by water intake restriction (<1000 mL/24 hours). Practical guidelines from Italian Society of Endocrinology (SIE) and U.S. guidelines indicate that urine osmolality greater than 500 mOsm/kg is a strong predictor of a poor response to fluid restriction. According to SIE Practice Guidelines, U.S. and British guidelines, the expected effectiveness rate of fluid restriction can be estimated using the Furst formula, which calculates the ratio of the sum of urine potassium and sodium concentrations to serum sodium concentration. A ratio >1 requires the need for strict water restriction (<500mL/d), and at the same time, predicts treatment failure of fluid and water restriction alone, leading to worsening hyponatremia (39,40,41).

Fluid restriction alone is not efficient in many cases of SIADH where the underlying cause persists.

Sodium supplementation using intravenous sodium chloride is another therapeutic option. Fluids of varying tonicity (isotonic saline, 3% physiological solution) can be used in the treatment of different types of hyponatremia. Which fluid would be selected depends on the etiology, severity of hyponatremia, and the presence of symptoms. In general, isotonic solution is used in treatment of hypovolemic hyponatremia. In some cases of severe hyponatremia (serum sodium <120 mEq/l), hypertonic saline is needed. Patients with acute severe hyponatremia are treated with a rapid increase in serum sodium level of 4-6 mmol/l within 4 hours, which results in reducing intracranial pressure and managing herniation in approximately 50% per hour. In practice, this can be achieved by administering a 100 ml bolus of 3% physiological solution over 15 minutes, which may be repeated up to three times. In patients with mild or moderate symptoms,

infusion of 3% physiological solution at a rate of 0.5–2 ml/kg/h is the initial approach, with frequent measurements of serum sodium levels (42).

Two pharmacological treatment options for hyponatremia, vaptans and urea osmotic agent, deserve a more detailed discussion. Conivaptan is a non-selective inhibitor of vasopressin V1 and V2 receptors, whereas tolvaptan selectively inhibits V2. The results of placebo-controlled randomized clinical trials showed that conivaptan increased Na+ level by approximately 8 mEq/L within several days, and tolvaptan by approximately 5 mEq/L within four days after administration of an initial dose of 15 mg and titrated up to 60 mg daily. The initial expectation was that, given their ability to antagonize the effect of excess vasopressin, they would be more effective and consequently, widely used. However, as expected, not a single agent can be used in the long-term. Conivaptan is a potent CYP3A4 inhibitor with many drug-drug interactions, and is approved by the U.S. Food and Drug Administration only for short-term intravenous use. Long-term use of tolvaptan is restricted due to concerns related to hepatic damage. In Europe, only oral tolvaptan is approved for treatment of SIADH.

Urea is a long-established and cost-effective alternative to vaptans for the treatment of SIADH. It is excreted in urine, increases urinary soluble substances and enhances electrolyte-free water clearance. Retrospective studies suggest that administration of 7.5 to 90 g/d urea is associated with Na+ level of ~6 mEq/L over 4 to 5 days. Urea therapy is generally not associated with serious side effects such as overly rapid correction of Na+.

It is important to emphasize that vaptans or urea should be taken into consideration only in patients with euvolemic or hypervolemic hyponatremia with mild to moderate symptoms, and not in cases where [Na+] should be rapidly increased. In addition, vaptans should not be used in combination with hypertonic saline, according to reported cases associated with ODS (43).

Demeclocycline, an antibiotic drug (600-1200 mg/day), and lithium carbonate, an antidepressant (600-900 mg/day) can cause nephrogenic diabetes insipidus, and this effect has historically been used in the treatment of hyponatremia in SIADH. Also, loop diuretics may be used for treatment of SIADH to increase water excretion (44).

A personalized treatment approach to SIADH based on the severity of hyponatremia, symptoms and individual patient risk factors are of crucial significance to ensure safe and efficient treatment.

Cerebral Salt Wasting Syndrome CSWS

Cerebral salt wasting syndrome (CSWS) is characterized by hyponatremia caused by renal sodium wasting, with decreased extracellular fluid volume as the key distinguishing feature from similar conditions. CSWS was first described by Peters et al. in 1950. Together with the syndrome of inappropriate antidiuretic hormone (SIADH), CSWS represents one of the most common causes of hyponatremia in neurologic patients. Some authors define CSWS as a subtype of SIADH. To ensure appropriate treatment, it is of crucial importance to make accurate differentiation between these two disorders. Evaluating volemia is an important clinical characteristic that helps in distinguishing between the two syndromes. CSWS is a hypovolemic hyponatremia, induced by increased natriuresis and diuresis (45) (Table 1) (46).

Table 1. Differences in clinical manifestation between SIADH and CSWS

Clinical Feature	SIADH	CSWS
Central venous pressure	Normal or increased	Decreased
Orthostatic hypotension	Absent	Present
Body weight	Increased	Decreased
Fluid balance	Positive	Negative
Plasma volume	Increased	Decreased

Any form of cerebral aggression has the potential to lead to a hypernatremia syndrome. In most cases, CSWS is associated with subarachnoid hemorrhages (SAH); however, it has also been observed in neurological and meningeal tuberculous infections, as well as postoperative complications following tumor resection (47). CSW syndrome has been reported in patients with severe traumatic brain injury, most frequently resulting from road traffic accidents, but also injuries caused by firearms. Several theories have been proposed to explain the causality of sodium wasting in CSWS. One of the current theories suggests reduced sympathetic stimulation of juxtaglomerular apparatus, which leads to decreased reabsorption of sodium, urates and water. In addition, it is associated with reduced secretion of renin and aldosterone (47,48). Another theory proposes elevated levels of brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) in patients with SAH, resulting in renal sodium and water loss (47).

The diagnosis is based on clinical manifestations (Table 1) and biochemical analyses.

Biochemical criteria for CSWS are: low or normal serum sodium levels, elevated or normal serum osmolality, increased or normal urine osmolality, elevated hematocrit, urea, bicarbonate and albumin levels as a consequence of hypovolemia.

However, these criteria are often inconclusive. In CSWS, the total daily urinary sodium excretion exceeds sodium intake.

Additional parameters contributing to establishing the diagnosis of CSWS, and differentiating it from SIADH include monitoring the fractional excretion of uric acid and fractional excretion of phosphates. Fractional excretion of uric acid (FEUA) exceeds 10% in both syndromes. After hyponatremia correction in patients with SIADH, it decreases, but in patients with CSWS it remains high. Fractional excretion of phosphate (FEP) is normal (<10%) in patients with SIADH and increased (>20%) in patients with CSWS, making it a useful criterion for differentiation between these pathological conditions (45).

Treatment of CSWS consists of correcting hypovolemia and hyponatremia. First-line therapy includes hydration with saline solutions, either isotonic or hypertonic, depending on the severity of the symptoms. Sodium supplementation should be gradual, avoiding an increase in sodium of more than 10 mmol/L within the first 24 hours (47). Other drugs studied in cases of neurocritical hyponatremia are fludrocortisone at doses of 0.1 to 0.4 mg, which has a direct effect on the proximal renal tubules, enhancing sodium reabsorption (47,49,50). If hypothalamic-pituitary region is affected, refractory polyuria may occur, and treatment with 1-deamino-8-D-arginine vasopressin (DDAVP) can be useful. However, its use remains controversial, as it may reduce urine volume, while simultaneously increasing production of natriuretic peptide,

thereby worsening hyponatremia (51,52).

Regarding other electrolyte disturbances, it has to be stressed that hyperkalemia has been reported in 17.77% of patients with traumatic brain injury, with a prevalence of 29% within the first 12 hours after admission. It is considered to be the result of catecholamine release, blood product transfusions, and pharmacologic agents such as succinylcholine, acidosis and tissue ischemia. In contrast, hypokalemia typically occurs immediately after injury and reaches its peak during the first few days, primarily due to potassium shifts induced by catecholamines, renal potassium loss, fluid deficit, and hyponatremia. Disturbances in calcium and chloride levels are also important in patients with traumatic brain injury. Hypercalcemia frequently occurs as a consequence of prolonged immobility or hyperparathyroidism. Hypocalcemia may develop during massive transfusions and is associated with severe coagulopathy and higher mortality. Hyperchloremia may develop acutely during the first days following TBI, which coincides with the phase of hyperemia characterized by increased cerebral blood flow and reduced arterio-jugular venous oxygen differences. Hypochloremia, as well as the other electrolyte abnormalities, has also been observed in patients with severe TBI and is associated with increased mortality (53).

Conclusion

Electrolyte disturbances are common in patients with traumatic brain injury. They are important but correctable causes of neurologic deterioration. Imbalance in sodium levels show the highest incidence, and electrolyte abnormalities usually occur in the first days after the injury. Their early identification and appropriate management, as well as timely treatment, not only improve patient neurological status, but also reduce morbidity, mortality and socioeconomic losses in the country.

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REVIEW ARTICLE *UDK: 616.712-089.87-009.7-085.212*

MULTIMODAL APPROACH TO POST-THORACOTOMY PAIN MANAGEMENT

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Abstract

Thoracotomy is associated with severe postoperative pain and a high incidence of chronic post-thoracotomy pain syndrome (CPTPS). Inadequate pain control adversely affects respiratory function, delays mobilization, increases postoperative complications, and contributes to long-term morbidity. Contemporary analgesic strategies emphasize a multimodal approach that integrates regional analgesic techniques, systemic pharmacotherapy, and adjuvant agents to optimize pain control while minimizing opioid consumption. This review provides a comprehensive overview of the pathophysiology of post-thoracotomy pain and critically analyzes current evidence supporting multimodal analgesic strategies in thoracic surgery.

Keywords: *multimodal; pain management; post-thoracotomy pain syndrome; thoracotomy.*

Introduction

Postoperative pain following thoracotomy remains one of the most challenging problems in perioperative medicine. Despite advances in surgical techniques, anesthetic management, and perioperative care, open thoracotomy is still associated with intense postoperative pain due to extensive tissue injury, rib retraction, intercostal nerve trauma, and pleural irritation. Poorly controlled pain results in impaired respiratory mechanics, reduced tidal volumes, ineffective coughing, and delayed mobilization, thereby increasing the incidence of pulmonary complications such as atelectasis, pneumonia, and respiratory failure (1-4). Beyond its immediate impact, severe acute pain is a well-recognized risk factor for the development of chronic post-thoracotomy pain syndrome, defined as pain persisting for more than two to three months after surgery. The reported incidence of CPTPS ranges from 25% to 60%, with neuropathic features present in a substantial proportion of patients. These long-term consequences have prompted a shift away from opioid-centric analgesia toward multimodal, opioid-sparing strategies that target multiple pain pathways simultaneously. Multimodal analgesia is now considered a cornerstone of modern thoracic anesthesia and enhanced recovery after surgery (ERAS) programs (1,5-8).

Pathophysiology of Post-Thoracotomy Pain

Post-thoracotomy pain is multifactorial and results from the interaction of peripheral and central mechanisms. Nociceptive pain arises from surgical trauma to the skin, subcutaneous tissue,

muscles, ribs, and pleura, leading to activation of peripheral nociceptors and inflammatory mediator release. Visceral pain originates from manipulation of pulmonary and mediastinal structures (7). Neuropathic pain represents a critical component of post-thoracotomy pain and is frequently caused by direct injury, stretching, or compression of the intercostal nerves during rib retraction. Such nerve injury may result in ectopic discharges, altered ion channel expression, and long-lasting changes in neural signaling. Persistent nociceptive input can further induce central sensitization at spinal and supraspinal levels, characterized by amplified pain responses and reduced pain thresholds. These mechanisms explain the high incidence of chronic pain after thoracotomy and emphasize the need for early, mechanism-based analgesic interventions (8,9).

Concept of Multimodal Analgesia

Multimodal analgesia is defined as planned and simultaneous application of multiple analgesic techniques and pharmacological agents that act through different and complementary mechanisms of action. The primary objectives of this approach are to enhance overall analgesic efficacy through synergistic effects, reduce perioperative opioid consumption, minimize opioid-related adverse events, and promote early functional recovery (1,3).

In the context of thoracic surgery, multimodal analgesia represents a cornerstone of modern perioperative pain management due to the intensity and complexity of post-thoracotomy pain. Effective multimodal strategies address both nociceptive and neuropathic pain components while limiting the physiological stress response to surgery. By targeting pain pathways at multiple levels, this approach improves respiratory mechanics, earlier mobilization, and reduced postoperative pulmonary complications (4). Implementation of multimodal analgesia in thoracic surgery spans all phases of the perioperative period. Preoperative measures include thorough patient education, risk stratification, and the use of pre-emptive analgesic interventions aimed at reducing central sensitization. Intraoperatively, emphasis is placed on regional anesthetic techniques and opioid-sparing anesthetic strategies to optimize pain control while preserving respiratory function. Postoperatively, management focuses on the scheduled administration of non-opioid analgesics, continuation of regional analgesia when applicable, and the judicious use of rescue opioids for breakthrough pain (1,8). This comprehensive, phase-specific approach is fully aligned with Enhanced Recovery After Surgery (ERAS) principles and has been consistently associated with improved clinical outcomes, including superior pain control, reduced opioid-related complications, shorter hospital stays, and enhanced patient satisfaction (Figure 1.) (1).

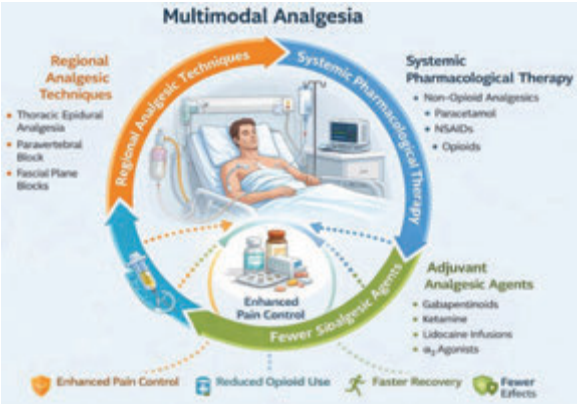

Figure 1. Multimodal analgesia

Regional Analgesic Techniques

Regional analgesic techniques play a pivotal role in multimodal pain management following thoracotomy by effectively interrupting afferent nociceptive transmission at the spinal and paraspinal levels. By directly targeting pain pathways, regional anesthesia provides superior analgesia, facilitates effective coughing and deep breathing, and supports early mobilization—key factors in optimizing postoperative recovery after thoracic surgery (3,6).

Thoracic Epidural Analgesia

Thoracic epidural analgesia has traditionally been regarded as the gold standard for postoperative pain control following open thoracotomy. By achieving a segmental blockade of thoracic spinal nerves, epidural analgesia provides excellent static and dynamic pain relief, particularly during respiratory efforts such as coughing and physiotherapy. This technique has been consistently associated with improved postoperative pulmonary function, enhanced patient comfort, and reduced incidence of pulmonary complications. Despite its well-established efficacy, the use of thoracic epidural analgesia may be limited by potential adverse effects related to sympathetic blockade, including hypotension, urinary retention, and pruritus. In addition, contraindications such as coagulopathy, systemic or local infection, and technical challenges may restrict its applicability in certain patient populations (3,6,10,11).

Paravertebral and Fascial Plane Blocks

Thoracic paravertebral block offers effective unilateral segmental analgesia by anesthetizing spinal nerves as they emerge from the intervertebral foramina. Accumulating evidence indicates that paravertebral block provides analgesic efficacy comparable to thoracic epidural analgesia while demonstrating a more favorable side-effect profile, particularly with respect to hypotension and urinary retention (Figure 2). As a result, paravertebral block is increasingly regarded as a viable alternative to epidural analgesia in thoracic surgery (4,8). In recent years, ultrasound-guided fascial plane blocks, such as the erector spinae plane block, have gained significant attention due to their technical simplicity, reproducibility, and favorable safety profile. These techniques allow for effective analgesia with minimal risk of neuraxial complications and are particularly well suited for minimally invasive thoracic procedures and for patients in whom neuraxial anesthesia is contraindicated. When integrated into a comprehensive multimodal analgesic regimen, fascial plane blocks contribute substantially to opioid-sparing analgesia and improved postoperative recovery (4,12).

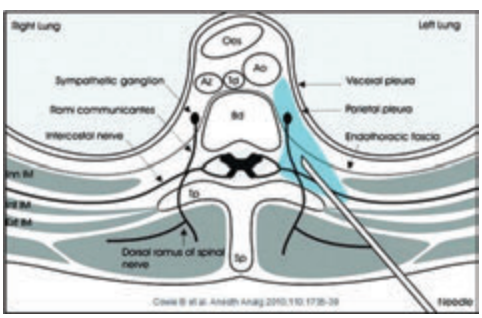

Figure 2. Paravertebral block

Systemic Pharmacological Therapy

Systemic pharmacological therapy constitutes a fundamental component of multimodal analgesia and serves as an essential adjunct to regional analgesic techniques. When used in combination, systemic agents enhance overall analgesic efficacy, address multiple pain pathways, and contribute significantly to opioid-sparing strategies in the postoperative period (13,14).

Non-opioid Analgesics

Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) represent the cornerstone of systemic analgesia within multimodal pain management protocols. Through inhibition of cyclooxygenase enzymes and subsequent reduction in prostaglandin synthesis, these agents effectively decrease inflammation and peripheral nociceptor sensitization. When administered on a scheduled, rather than on-demand basis, paracetamol and NSAIDs have consistently demonstrated a significant reduction in postoperative opioid consumption and improved analgesic outcomes. Their favorable safety profile further supports their routine use, provided that patient-specific contraindications are carefully considered (3,8).

Opioids

Opioids remain potent and effective agents for the management of moderate to severe postoperative pain, particularly in the immediate post-thoracotomy period. However, within a multimodal analgesic framework, opioids should be used judiciously and primarily reserved for the treatment of breakthrough pain. Administration at the lowest effective dose is recommended to mitigate well-recognized adverse effects, including respiratory depression, postoperative nausea and vomiting, ileus, sedation, and the development of opioid-induced hyperalgesia. Limiting opioid exposure is especially important in thoracic surgery patients, in whom adequate respiratory function is critical for optimal recovery (3,8,13).

Adjuvant Agents

Adjuvant analgesic agents play a pivotal role in targeting neuropathic pain components and modulating central sensitization. Gabapentinoids reduce neuronal excitability through modulation of voltage-gated calcium channels and have been shown to decrease postoperative pain intensity and opioid requirements. Low-dose ketamine, acting as an N-methyl-D-aspartate (NMDA) receptor antagonist, effectively attenuates central sensitization and may reduce the risk of chronic post-thoracotomy pain. Intravenous lidocaine infusions provide additional analgesic, anti-inflammatory, and anti-hyperalgesic effects, contributing to improved pain control and faster functional recovery. Furthermore, α2-adrenergic agonists offer sedative, sympatholytic, and opioid-sparing benefits, thereby enhancing analgesic quality while preserving respiratory stability (4,9,14).

Prevention of Chronic Post-Thoracotomy Pain

Preventing the transition from acute to chronic pain is a primary objective of postoperative pain management. High-intensity acute pain, intercostal nerve injury, and inadequate early analgesia

are key risk factors for CPTPS. Multimodal analgesic strategies incorporating effective regional anesthesia and early use of adjuvant agents have been shown to reduce both the incidence and severity of chronic pain.

Integration of multimodal analgesia into ERAS pathways further enhances recovery by promoting early mobilization, improved respiratory function, and reduced length of hospital stay. Emerging evidence suggests that such protocols may also improve long-term patient-reported outcomes and quality of life (1,14).

Conclusion

A multimodal approach is acknowledged as the most effective strategy for managing post-thoracotomy pain due to the intricate and multifaceted nature of pain linked to thoracic surgical procedures. Multimodal analgesia achieves superior pain control by integrating regional analgesic techniques such as: thoracic epidural analgesia, paravertebral blocks, or novel fascial plane blocks, with systemic pharmacological therapies, including non-opioid analgesics and judicious opioid use, compared to single modality strategies. This method diminishes overall opioid use and its related side effects, while enhancing respiratory mechanics, promoting earlier mobilization, and decreasing the occurrence of postoperative pulmonary complications. Moreover, efficient multimodal pain management has been linked to a diminished risk of persistent post-thoracotomy pain syndrome, thereby enhancing long-term functional results and quality of life. Due to the variety in patient features, surgical methods, and institutional resources, multimodal analgesic regimens must be customized to each patient's clinical profile. Consequently, tailored multimodal pain management procedures ought to be regarded as fundamental and standard practice in modern thoracic anesthesia.

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OPTIMIZING ORGAN PERFUSION: MANAGEMENT OF THE POTENTIAL DECEASED DONOR

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Abstract

Optimal management for a potential deceased donor is crucial to the transplantation process, as it significantly influences both the quantity and quality of organs available for transplantation. Upon determination of death by neurological criteria (DNC), the body undergoes significant physiological alterations, including hemodynamic instability, endocrine failure, poor thermoregulation, hypernatremia, metabolic acidosis, and coagulopathy. The primary objective of donor management is to restore homeostasis by ensuring sufficient blood flow and oxygen supply to the organs, thereby mitigating ischemic harm and enhancing the likelihood of transplant survival.

Hemodynamic stability remains a central determinant of organ viability in the potential deceased donor. Targeting key hemodynamic and vital parameters through goal-directed therapy is essential for maintaining adequate organ perfusion. Continuous or intermittent monitoring—using available techniques such as invasive arterial pressure, central venous pressure, or advanced cardiac output monitoring—guides individualized therapy. Fluid resuscitation should primarily rely on balanced crystalloids, among which Ringer's or Plasma-Lyte solutions are preferred over normal saline due to their favorable acid–base profile and reduced risk of hyperchloremic acidosis. The use of colloids is generally discouraged; however, in cases unresponsive to crystalloids, albumin may be considered. When adequate perfusion cannot be achieved with fluids alone, vasopressors and inotropes should be titrated based on clinical response. Norepinephrine is preferred for maintaining mean arterial pressure due to its predictable α-adrenergic effect, while dobutamine is the inotrope of choice in donors with myocardial dysfunction, enhancing contractility and cardiac output. Vasopressin may be added as an adjunct agent because of its stable vasomotor action, absence of cardiotoxicity, and catecholamine-sparing effect, particularly in donors with diabetes insipidus. Low-dose dopamine (≤3μg/kg/min) may be considered selectively in hemodynamically stable donors, as some studies suggest a potential renal-protective and immunomodulatory benefit; however, its use is controversial and not routinely recommended due to the risk of arrhythmias and metabolic instability.

Endocrine replacement therapy, including methylprednisolone (15 mg/kg), triiodothyronine (T3), and desmopressin (DDAVP), is incorporated in several donor management protocols to enhance hemodynamic stability, preserve hormonal balance, and attenuate the inflammatory cascade. Desmopressin is preferred for the treatment of diabetes insipidus due to its selective V_2-receptor activity, effective antidiuretic action, and lack of vasoconstrictive or cardiotoxic effects. While the routine use of thyroid hormone supplementation remains debated, corticos-

teroids play a crucial role in restoring vascular responsiveness, improving cardiac output, and reducing cytokine-mediated inflammation following brain death.

Protective mechanical ventilation (tidal volume 6–8 mL/kg, PEEP 8–10 cmH_2O, PaO_2/FiO_2 >300) should be maintained to prevent barotrauma and volutrauma. Early administration of corticosteroids and bronchodilators (salbutamol or terbutaline) helps improve alveolar fluid clearance and lung preservation. Prevention of hypothermia through active warming (maintaining core temperature above 35°C) reduces arrhythmias, coagulopathy, and metabolic acidosis. Nutritional support, parenteral or controlled enteral feeding, should continue up to the time of organ retrieval to maintain metabolic balance and prevent catabolism.

Continuous, multidisciplinary coordination among intensivists, anesthesiologists, and transplant coordinators is vital for donor stabilization and optimal organ perfusion. Any delay or inconsistency in donor management increases the risk of secondary ischemic injury and reduces the number of viable grafts. In modern transplant medicine, maintaining perfusion in the deceased donor is not merely the continuation of intensive care but a deliberate strategy to preserve organ function. Implementation of standardized donor management algorithms, close monitoring of oxygenation and hemodynamic parameters, and targeted hormonal stabilization have proven essential for achieving successful multi-organ procurement and improving post-transplant outcomes

Keywords: *potential deceased donor; donor by neurological criteria; organ perfusion; donor management.*

Introduction

Organ transplantation constitutes a definitive life-sustaining treatment for patients with end-stage organ failure. Nevertheless, the disparity between organ demand and supply continues to widen worldwide. Organ donation primarily occurs after the determination of death by neurological criteria (DNC) or, in an increasing number of countries, after the determination of death by circulatory criteria (DCD). While both pathways are recognized within international frameworks, their implementation varies according to national legislation, clinical infrastructure, and organizational maturity of the transplant program (1-3).

In the Republic of North Macedonia, organ donation and transplantation are currently performed through living donation and deceased donation following DNC. Donation after circulatory death has not yet been introduced into clinical practice, although it is recognized as a strategic future step for expanding the donor pool and aligning with European trends (4).

Brain death induces profound systemic disturbances, including cardiovascular instability, endocrine dysregulation, inflammatory activation, and loss of thermoregulatory control. Without targeted physiological support, these disruptions jeopardize organ viability, reducing both the number and quality of transplantable grafts. Therefore, optimal donor management is understood as a continuation of intensive therapy, shifting the clinical objective from neurological recovery to the preservation of organ perfusion, oxygen delivery, and metabolic homeostasis (5).

International guidelines, including the Council of Europe EDQM Guide to the Quality and Safety of Organs for Transplantation (9th Edition), emphasize that structured, protocol-driven donor

management measurably increases organ utilization rates and improves graft survival outcomes. These principles form the foundation of donor care within our national practice as well (1,6).

Pathophysiological Changes Following Brain Death

The transition to death determined by neurological criteria (DNC) precipitates a complex cascade of pathophysiological alterations that affect multiple organ systems simultaneously. The initial phase is characterized by a profound autonomic disinhibition, wherein abrupt and massive sympathetic discharge leads to marked hypertension, tachyarrhythmias, and increased myocardial oxygen consumption. This catecholaminergic surge may induce myocardial stunning, mediated by β-adrenergic receptor downregulation and subendocardial ischemia, leading to reduction in left ventricular systolic function (1,7).

Subsequently, as brainstem integrity deteriorates, sympathetic tone collapses, resulting in systemic vasodilation, vasoplegic shock, decreased coronary perfusion pressure, and declining cardiac output. The combination of reduced preload, impaired vascular responsiveness, and myocardial dysfunction significantly compromises global organ perfusion (1,8).

Simultaneously, disruption of the hypothalamic–pituitary axis results in marked endocrine dysfunction. The most frequent consequence is diabetes insipidus (DI), manifesting as excessive polyuria, hypovolemia, and hypernatremia, which directly threatens renal, hepatic, and cardiac graft integrity. Additionally, adrenal insufficiency leads to inadequate cortisol-mediated vascular support, further blunting the physiological stress response. Reduced circulating concentrations of triiodothyronine (T3) and thyroxine (T4) impair cellular oxygen utilization, myocardial contractility, and thermogenic capacity, thereby worsening hemodynamic instability (1).

In parallel, DNC triggers a systemic inflammatory response syndrome (SIRS). Pro-inflammatory cytokines increase endothelial permeability, contributing to interstitial edema, particularly within the lungs, where it may progress to neurogenic pulmonary edema and reduced oxygenation capacity. At the microcirculatory level, dysregulated nitric oxide and catecholamine signaling contribute to capillary maldistribution and impaired tissue oxygen delivery, further jeopardizing graft viability (1,2).

Loss of central thermoregulatory control leads to progressive hypothermia, which exacerbates coagulopathy, arrhythmogenic vulnerability, and reduced metabolic efficiency. When uncorrected, hypothermia accelerates the decline of organ function in the hours following DNC (1).Collectively, these alterations illustrate that brain death is not a hemodynamically stable state, but rather a dynamic and rapidly evolving pathophysiological syndrome. Prompt, targeted, and protocol-driven stabilization is therefore essential to preserve adequate organ perfusion, oxygenation, and metabolic homeostasis, ensuring optimal graft quality and transplantation outcomes (1).

Table 1. Incidence of Pathological alteration

Pathological alteration	Incidence (%)
Hypotension	81–97
Diabetes insipidus	46–78
Disseminated intravascular coagulation (DIC)	29–55

Pathological alteration	Incidence (%)
Cardiac arrhythmias	25–32
Pulmonary edema	13–18

Management Strategy

Hemodynamic monitoring is essential for donor stabilization; nevertheless, no single parameter offers a comprehensive depiction of circulatory sufficiency. Conventional monitoring techniques in critical care and perioperative medicine—such as non-invasive blood pressure, heart rate, and urine output measurements—are prevalent due to their accessibility. However, each variable is affected by physiological and non-physiological factors that undermine their reliability as standalone indicators of effective organ perfusion. Arterial pressure may indicate variations in systemic vascular resistance more than actual intravascular volume or cardiac output, whereas urine output is affected by neurohormonal regulation, renal concentrating capacity, and pharmacological agents rather than just renal perfusion (1,3). Crucially, sustaining a "normal" mean arterial pressure (MAP) does not inherently correspond to sufficient oxygen delivery (DO_2) to tissues. Research involving sedated patients and individuals having significant vascular surgeries reveals an inconsistent linear correlation between mean arterial pressure (MAP) and oxygen delivery (DO_2), mostly attributable to fluctuating microvascular tone and varying organ autoregulatory thresholds. In this scenario, tissue hypoperfusion may persist despite an appropriate mean arterial pressure, a phenomenon known as hidden or occult hypoperfusion. Clinically, this indicates that the assessment of perfusion adequacy should rely on dynamic or integrative signs rather than on pressure readings solely, including lactate trends, venous oxygen saturation, and peripheral perfusion indices (1,9).

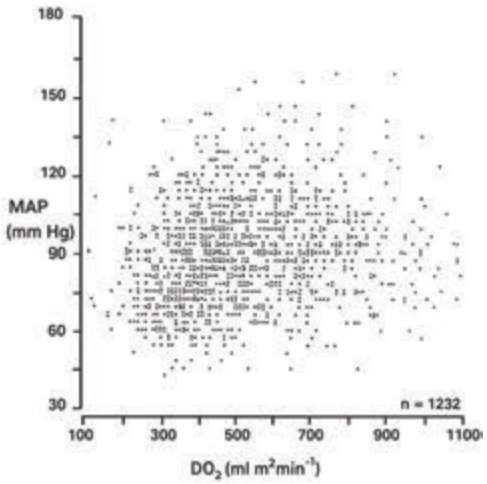

Figure 1. Correlation of O_2 delivery (DO_2) with mean arterial pressure (MAP) in the perioperative period in patients undergoing abdominal aortic surgery (9).

The aim of hemodynamic monitoring in potential deceased donors is to sustain adequate systemic blood flow and oxygen delivery to maintain cellular metabolism, rather than to normalize isolated pressure metrics. Modern monitoring techniques can be classified based on their level of invasiveness and the nature of the information they yield. Invasive techniques, such the pulmonary artery catheter and transpulmonary thermodilution systems, provide direct evaluation

of cardiac output and volumetric preload indicators. Minimally invasive systems, such as pulse-wave contour analysis or lithium dilution, provide continuous cardiac output monitoring with reduced procedural complexity. Non-invasive techniques, like targeted cardiac ultrasonography and thoracic bioimpedance, provide significant real-time information on ventricular filling and contractility without the need for vascular hardware (1).

The selection of monitoring modality is contingent upon institutional resources, physician proficiency, and donor stability. Irrespective of the technique employed, therapy must adhere to a goal-oriented methodology, focusing on perfusion optimization rather than attainment of arbitrary numerical benchmarks.

Table 2. Target Parameters for Optimizing Organ Perfusion

Parameter	Clinical Objective	Interpretation Note
MAP 65–75 mmHg	Supports coronary and renal perfusion	MAP alone does not reflect DO_2; always evaluate trends and context
CVP 6–10 mmHg	Helps guide volume status	Extreme values are more informative than single measurements
Lactate (trend)	Marker of global perfusion	A downward trend is more meaningful than a single value
Urine output 0.5–3 mL/kg/h	Surrogate of renal perfusion if DI is excluded	Interpret together with sodium and serum osmolality

Fluid Therapy

Fluid therapy in a possible deceased donor should focus on restoring and maintaining sufficient intravascular volume to support cardiac output and organ perfusion, while preventing fluid excess and metabolic disturbances. Balanced crystalloids, including Ringer's Lactate or Plasma-Lyte, are preferred as primary solutions due to their more physiological electrolyte composition and reduced risk of inducing hyperchloremic metabolic acidosis, a complication frequently linked to the extensive infusion of 0.9% sodium chloride. This acidity may hinder renal blood flow and microcirculatory function, making it undesirable in the donor context (1,9).

When crystalloids alone fail to attain hemodynamic stability, albumin solutions may be judiciously administered to enhance intravascular oncotic pressure and facilitate volume expansion. Albumin 4% is used for intravascular volume replenishment in cases of suspected relative hypovolemia or fluid redistribution into the interstitial compartment. Conversely, albumin 20% may be indicated in cases of pronounced hypoalbuminemia or systemic edema, with the therapeutic objective of redistributing interstitial fluid into the vascular compartment and alleviating tissue congestion, particularly in the pulmonary system. The administration must be meticulously titrated to prevent a rapid increase in intravascular volume that may aggravate cardiac dysfunction (9). Synthetic colloids, such as hydroxyethyl starch solutions, are typically eschewed because of their recognized correlation with renal impairment, tissue accumulation, coagulopathy, and inferior post-transplant graft outcomes. Their application offers no benefit compared to crystalloid treatment in this clinical situation and may be detrimental to transplantable organs (1). The entire strategy advocates for a methodical, objective-oriented therapy - utilizing balanced crystalloids as the cornerstone of volume resuscitation, thereafter employing albumin selectively when crystalloids fail to ensure stable perfusion and sufficient organ oxygenation (9).

Vasoactive Support

When optimization of intravascular volume fails to maintain adequate perfusion and organ oxygenation, vasoactive drugs are administered in a systematic, objective-driven approach. The choice of agent is contingent upon the primary hemodynamic disturbance, including vasoplegia, diminished cardiac contractility, or catecholamine resistance (1). Norepinephrine is typically advised as the primary vasopressor for donors experiencing vasodilatory hypotension. It commences at 0.02–0.2 μg/kg/min and is adjusted based on the desired mean arterial pressure and overall perfusion condition. Its primarily α-adrenergic impact elevates systemic vascular resistance and enhances coronary perfusion without notable chronotropic stimulation (1,10).

Dobutamine is the preferred inotropic drug for cardiac dysfunction, particularly after myocardial shock linked to the initial catecholamine spike in brain death. It is often administered at a dosage of 2–10 μg/kg/min, to enhance stroke volume and cardiac output. Meticulous titration is essential to prevent tachyarrhythmia and elevated myocardial oxygen demand.

Vasopressin is crucial for donors exhibiting catecholamine-resistant vasoplegia or concurrent DI. In these cases, vasopressin enhances vascular tone via V1 receptor-mediated vasoconstriction while concurrently diminishing polyuria through V2 receptor activation in the kidney. It is typically supplied at a rate of 0.01–0.04 units per minute via continuous infusion. Crucially, at these dosages, vasopressin does not induce direct cardiotoxicity nor elevate myocardial oxygen demand, rendering it particularly advantageous for donors with cardiac susceptibility (1,11).'

Low-dose dopamine, once utilized to enhance renal perfusion, is now typically eschewed due to its arrhythmogenic risks, unknown endocrine consequences, and little evidence for improving transplant outcomes. Consequently, its routine application in donor management is not advised. The primary objective is to attain hemodynamic stability while reducing myocardial stress and maintaining microcirculatory flow, with vasoactive therapy meticulously included with fluid and endocrine management techniques (1,11).

Endocrine Stabilization

Endocrine disorders frequently occur after DNC, primarily because of hypothalamic-pituitary dysfunction. DI is treated with desmopressin (DDAVP 1–4 μg IV) and meticulous free water replenishment to prevent hypernatremia and hypovolemia. If hypotension continues despite sufficient fluids and vasopressors, adrenal insufficiency must be evaluated, and methylprednisolone 15 mg/kg IV should be given to enhance vascular reactivity. While diminished T3/T4 levels are common, routine thyroid hormone replacement is not advised and should be reserved solely for refractory cardiac failure. Corticosteroid medication also provides anti-inflammatory benefits that contribute to the maintenance of lung function for transplantation (11).

Temperature Management

Hypothermia (core temperature < 35°C) commonly results from impairment of central thermoregulation following DNC. The fall in body temperature correlates with diminished metabolic activity and oxygen utilization, while leading to reduced cardiac output, heightened risk of

arrhythmias, and systemic hypoperfusion. The stiffness of erythrocyte membranes increases at lower temperatures, obstructing microcirculatory flow and reducing effective oxygen delivery at the tissue level. Moreover, hypothermia induces coagulopathy by impeding enzymatic processes in the coagulation cascade.

Consequently, the preservation of normothermia (≥ 36°C) is advised in standard donor management, generally accomplished through active warming techniques including heated airway circuits, fluid warmers, and external warming blankets. Evidence indicates that modest therapeutic hypothermia may provide distinct advantages in certain donors, particularly by mitigating ischemia-induced renal damage and enhancing early graft function in kidney transplantation. Continuous clinical assessment is enhancing the equilibrium between normothermic stabilization and regulated mild hypothermia in organ-specific preservation techniques (1,12).

Lung-Protective Ventilation

Mechanical ventilation in the potential deceased donor should follow a lung-protective strategy in order to preserve alveolar integrity and optimize oxygenation while preventing ventilator-induced lung injury. Tidal volumes are generally maintained between 6 and 8 mL/kg of predicted body weight, with the application of moderate positive end-expiratory pressure (PEEP 8–10 cmH_2O) to support alveolar recruitment and prevent atelectasis. Peak airway pressures are kept below 35 mmHg to limit barotrauma. A closed suctioning system is preferred to reduce derecruitment, and recruitment maneuvers may be used intermittently when oxygenation declines. Inspired oxygen concentration is titrated to the lowest FiO_2 capable of maintaining adequate oxygenation, aiming for PaO_2 of 80–100 mmHg and a PaO_2/FiO_2 ratio greater than 300 mmHg, while maintaining $PaCO_2$ between 35 and 45 mmHg and arterial pH of 7.3–7.35 (1,13,14).

Supportive measures further contribute to improved lung preservation. These include adequate humidification of inspired gases, the use of mucolytics when secretions are viscous, and bronchoscopy for airway clearance when needed. Nursing strategies such as elevating the head of the bed to 30°, periodic repositioning every two hours, diligent oral care, and repeated imaging to monitor pulmonary status help to reduce ventilator-associated complications and maintain lung suitability for transplantation (1,13).

Nutritional and Metabolic Support

Globally, there is no standardized policy regarding donor feeding or fasting, with practices differing according to institutional standards and donor clinical stability. Enteral nutrition should be sustained whenever possible, to ensure metabolic substrate availability and support cellular homeostasis. Preventing prolonged hunger is crucial, as heightened catabolism may jeopardize graft healing and post-transplant functionality (15,16).

Hemostasis and Coagulation Management

Disruption of the cerebral tissue during the progression to death by neurological criteria can trigger systemic coagulation abnormalities, ranging from disseminated intravascular coagulation (DIC) to hyperfibrinolysis. These alterations are further intensified by hypoperfusion, ac-

idosis, and inflammatory activation. Early recognition and correction are essential to preserve organ perfusion and reduce the risk of intraoperative bleeding during retrieval.

Key laboratory targets generally include: Platelet count > 50 × 10^9/L; Fibrinogen > 1 g/L; INR < 1.5. Hemoglobin and hematocrit thresholds should be individualized based on donor age, comorbidity profile, and evidence of impaired oxygen delivery (e.g., reduced SvO_2, rising lactate). When transfusion is required, leukocyte-depleted blood products are recommended to reduce the risk of cytomegalovirus transmission and inflammatory graft injury (1,14).

Thromboprophylaxis

Thromboembolic risk remains clinically relevant, particularly in donors maintained in intensive care for prolonged periods. Thromboprophylaxis should include: mechanical measures (e.g., intermittent pneumatic compression) in all donors and/or pharmacological prophylaxis (low molecular weight heparin or unfractionated heparin) unless contraindicated because of active bleeding risk or uncontrolled coagulopathy. This balanced approach aims to maintain effective microcirculatory flow while minimizing hemorrhagic complications during organ procurement (1).

Antimicrobial Treatment

Microbiological monitoring and prompt anti-infective intervention are essential elements of standard donor management. Upon identifying a suitable donor, blood, urine, tracheal aspirate, and, where appropriate cerebrospinal fluid, cultures should be collected, with additional sampling directed by clinical progression. Upon confirmation or high suspicion of infection, antimicrobial therapy should be promptly commenced and tailored based on microbiological results, prioritizing drugs that ensure sufficient tissue penetration.

In donors lacking clinical, laboratory, or imaging indicators of infection and who are not undergoing antimicrobial therapy, routine antibiotic prophylaxis is not advised, as it has not shown efficacy in enhancing graft outcomes and may foster antimicrobial resistance (1,17,18).

Organ Procurement

The concluding stage of donor management involves the organization and implementation of organ procurement. The donor's physiological state during retrieval directly influences graft survivability and post-transplant functionality. The key goal during this time is to maintain sufficient organ perfusion, oxygen transport, and metabolic equilibrium.

In hemodynamically stable donors, multiple studies suggest that a controlled delay in organ procurement (exceeding 20 hours post-confirmation of stabilization) may facilitate partial recovery of organ function by enhancing microcirculatory regulation and mitigating the inflammatory response. Such a technique should only be contemplated when donor stability is maintained and logistical conditions permit synchronized retrieval without the risk of secondary deterioration.

Upon finalization of consent and planning of the retrieval procedure, delays must be minimized to prevent growing hemodynamic instability. It is crucial to sustain normovolemia, adequate

oxygenation, and sufficient cardiac output throughout the procurement process until aortic cross-clamping occurs. Sudden hemodynamic alterations, hypoxia, or hypovolemia during the immediate pre-retrieval phase can jeopardize transplant quality (1).

Conclusion

Donor management following DNC is a proactive, protocol-driven extension of intensive care, focused on maintaining organ perfusion and cellular equilibrium. Structured hemodynamic optimization, endocrine stabilization, lung-protective ventilation, temperature regulation, metabolic support, and coordinated interdisciplinary care are crucial for maximizing organ utilization and enhancing post-transplant outcomes.

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END OF LIFE AND PALLIATIVE CARE IN THE INTENSIVE CARE UNIT

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Problems Anesthesiologists Face in the ICU with Patients at the End of Life

In the Intensive Care Unit (ICU), critically ill patients receive life-sustaining therapies to restore and maintain organ function. Palliative care in the ICU is a widely discussed topic and is increasingly applied in clinics. The aim of intensive care is the maintenance of vital functions to reduce mortality and prevent morbidity in patients with severe critical illness. Despite the development of new technologies and the improvement of care, the mortality rate in the intensive care unit (ICU) remains high, ranging from 20 to 35%, with variations across geographical regions. In recent years, ICU admissions in the last month of life have increased up to 30%. Around 13% of patients admitted to critical care in Europe die in the Intensive Care Unit (ICU). The European Society of Intensive Care Medicine (ESICM) has developed evidence-based recommendations and expert opinions about end-of-life (EoL) and palliative care for critically ill adults. The aim of these guidelines is to optimize patient-centered care, improve outcomes of relatives, and support intensive care unit (ICU) staff in delivering compassionate and effective EoL and palliative care.

EoL legislation and the importance of respecting the autonomy and preferences of patients were paid close attention. Differences in EoL care depending on country income and healthcare provision were considered. Structured EoL decision-making strategies are recommended to improve outcomes of patients and relatives, as well as staff satisfaction and mental health. Early integration of palliative care and the use of standardized tools for symptom assessment are recommended for patients at high risk of death. Communication training for ICU staff and printed communication aids for families are advocated to improve outcomes and satisfaction.

Definition of Death: An individual who has sustained either:

- Irreversible cessation of circulatory and respiratory functions, or
- Irreversible cessation of all functions of the entire brain, including the brain stem.

Type of death in ICU:

- After an initial successful resuscitation
- End-stage chronic disease
- New diagnosis of life-limiting conditions
- Sudden
- Traumatic
- Brain stem death

When the organ dysfunction of critical illness does not respond to treatment, and the goals of care cannot be achieved anymore, or when life support becomes disproportional to expected prognosis, ICU physicians should provide an acceptable death. When life-sustaining therapies are unable to meet the patient's goals or, paradoxically, become more burdensome than beneficial, withdrawal and withholding of therapies is a common practice among ICU physicians. In the ICU, deciding to move from curative to EoL care is particularly challenging, because it involves withdrawing or withholding life-supporting treatments (LSTs). EoL care practices are shaped by ethical principles, legal frameworks, cultural norms, and available resources and therefore vary substantially across countries and healthcare systems. Clinical teams share LST limitation decisions with patients and families, whereas in others these decisions are made solely by clinicians. No single approach is optimal for all patients, and clinical judgment is therefore needed to tailor EoL care decisions.

End of life care: some definitions

- Life-threatening illness
- Permanent alteration of functional status
- Life-limiting illness

Life-threatening illness: Potentially, but not necessarily fatal illness. For example: serious car accident resulting in major trauma, severe infection, or early-stage breast cancer. Patients with life-threatening illnesses may come to the brink of death and be saved by medical care, and return to a normal quality of life.

Permanent alteration of functional status: An illness or injury that has led to a permanent, severe change in functional status. For example: anoxic encephalopathy, massive intracranial hemorrhage, or other conditions leading to persistent vegetative state or minimally conscious state. Life could be maintained, however, the quality of life of the patient is such that it is not clear whether they would want it prolonged.

Life-limiting illness: An incurable, progressive illness which will eventually result in the patient's death, although it may take many years. Advanced cancer (most widely metastatic solid tumors), end-stage congestive heart failure or pulmonary disease, Alzheimer's dementia. Most of the leading causes of death in adults are these life-limiting illnesses. Medical care can prolong life and improve quality of life but cannot cure these illnesses. Patients with life-limiting illnesses will eventually die of this illness. As their disease progresses, they have an illness trajectory from having a life-limiting illness, to being terminally ill, to actively dying.

Terminal illness: As life limiting illnesses progress, patients become terminally ill. Deteriorating functional status and failure to respond to treatments of underlying condition are hallmarks of this phase of a life-limiting illness. There are limited options, if any, to prolong life, however, death is likely to occur within months.

Actively dying: People with life-limiting illnesses who are at the very end of life are in the process of actively dying. They are minimally responsive or unresponsive, no longer eat or drink, are bedbound, and have altered breathing patterns. Usually, they have hours to days to live.

Use of life-supporting technology: In life-threatening illness - CPR, mechanical ventilation and artificial feeding are techniques originally developed for patients with acute, life-threat-

ening illnesses. In this setting, they are applied to support the patient's life, while the patient is undergoing treatment aimed at reversing the underlying cause of cardiac or pulmonary failure. Use of life-supporting technology: permanent alteration of functional status. Most of the famous bioethics cases involve this situation. Patients can live for a long period of time in a vegetative state if artificial feeding and treatment of complications and infections continue. Patients and their families have the right to choose if they would want this type of life prolongation. Use of life-prolonging technology: life-limiting illness. All patients with life-limiting illnesses eventually develop cardiac and respiratory failure at the end of life as part of the normal illness trajectory. Life-supporting technology is less effective (often much less effective) in these conditions because the underlying condition causing cardiopulmonary failure cannot be reversed. Life-limiting illness: The number of patients with these illnesses is increasing as our population ages. A large share of health care spending is devoted to these conditions. Physicians, patients and family members struggle with how best to care for the patients suffering from these illnesses. Prognosis and functional status: One of the measures that has been shown to best predict prognosis for a variety of patients with life-limiting illnesses is determining the functional status. Functional status is the ability of an individual to function physically and mentally, and to stay well nourished.

Illness trajectory: Natural history of a chronic progressive (life-limiting) disease. Dementia, metastatic lung cancer (stage 4), end-stage chronic obstructive pulmonary disease or congestive heart failure.

Goals of care: Treating aspiration pneumonia in patients with Alzheimer's dementia will not cure dementia or even prevent further decline. Such aspiration events will likely recur in the future. If the treatment of the pneumonia is successful, it may prolong life and reverse acute symptoms. If the patient develops respiratory failure, should we use mechanical ventilation or CPR? There are ethical aspects to these questions, but medically speaking we also need to know: how well do those interventions work? Do these interventions prolong life or improve the quality of life for people with advanced dementia? Patients, if possible, their families and the medical team caring for the patient need to determine what types of treatment are warranted in light of the stage of illness, and the patient's quality of life and values. To make these decisions, they need to consider what will happen to the patient if they get the medical treatment, now and in the future.

- Metastatic lung cancer: treatment decisions - Do you recommend undergoing first-line chemotherapy? Second-line chemotherapy? Third or fourth line? What about CPR, or mechanical ventilation?

- Cardiac disease and end of life care: Treatments that prolong life often improve functional status and quality of life as well! It is harder to predict mortality than cancer or other illnesses. Several interventions (implantable defibrillators, pacemakers) prevent sudden death caused by arrhythmias and prolong life. These devices do not cure CHF, and cannot prevent eventual functional deterioration. If the patient's functional status has deteriorated to the point where they would no longer want it prolonged, what do we do with these devices?

Other choices: Patients with a permanent alteration in the functional status have a different illness trajectory. These patients have an injury or illness that places them in a functional state that is severely reduced, without having progressive symptoms. Traumatic brain injuries or strokes that lead to permanently altered mental status or even vegetative states are one example of such illnesses. These are illnesses in which life could be maintained for a prolonged period of

time, but the quality of life is such that many would not want their lives prolonged.

In such situations, anesthesiologists should be aware that in any case, the expected survival time is not necessarily an absolute factor for decision-making, as the deterioration of the patients' condition in the postoperative period, suffering from complications and hospitalization, in other words, quality of life, should also be considered. This should not be confused with slow euthanasia, where clinicians sedate patients nearing the end of life with the primary goal of facilitating their death. Most centers use midazolam because of the drug's short half-life, ease of administration, and good efficacy. Opioids should not be used for the primary purpose of sedation, but should be reserved for analgesic purposes or analgo-sedation in patients with a favorable prognosis.

In conclusion: Integrating palliative care experts into the work of intensive care units can benefit patients, families, and ICU physicians. The palliative care team dramatically changed the way dying patients in ICU are treated, compared to patients who died without consulting the team in question. Therefore, it is necessary to develop standards for decision-making that will facilitate the treatment of these patients.

Decision-Making Standards. In the United States and many other countries, limiting life support is ethically and legally justified under the principle of autonomy. U.S. law grants patients with decision-making capacity the right to refuse any and all therapies, including those that sustain life. This standard is problematic in the ICU, however, where as many as 95% of patients may not be able to make decisions at the end of life, and information should be delivered in ways that are sensitive to the patient's cultural, religious, and language needs. Physicians should take their responsibility to make recommendations and guide families seriously, ensuring that their guidance aligns with their decision-making preferences. Practical advice on withdrawing life-sustaining treatments draws on theoretical considerations, empirical data, and clinical experience. Although the phrase "withdrawal of care" is often heard, it is important to distinguish between the withdrawal of life-sustaining interventions and the withdrawal of care. While the former is common, the latter should never occur. Language is important, particularly to patients and their families.

Conclusion:

End-of-life care is emerging as a comprehensive area of expertise in the ICU and demands the same high level of knowledge and competence as all other areas of ICU practice.

Key points:

- ICU clinicians should be competent in all aspects of end-of-life care.
- Integration of palliative care experts into surgeries in the ICUs may be of benefit to patients, families, and critical care clinicians.
- Communication issues with the relatives are essential, as an appropriate relationship improves patient care and family outcomes in the last days of life, allowing us to share the same objectives and expectations.

As a final reflection:

As the great moral philosophers of our time say:

You can't always get what you want, but if you try sometimes, you get what you need.

REVIEW ARTICLE *UDK: 711-009.7-092*

BASIVERTEBRAL NERVE ABLATION FOR VERTEBROGENIC CHRONIC LOW BACK PAIN: CURRENT EVIDENCE AND CLINICAL IMPLICATIONS

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Abstract

Chronic low back pain (CLBP) is one of the leading causes of disability worldwide and represents a major clinical challenge in anesthesiology and pain medicine. While discogenic and facetogenic mechanisms have traditionally dominated diagnostic paradigms, increasing evidence supports vertebrogenic pain as a distinct entity mediated by the basivertebral nerve (BVN), particularly in patients with vertebral endplate degeneration and Modic type I or II changes on magnetic resonance imaging.

The aim of this review is to summarize current knowledge on vertebrogenic pain pathophysiology, the anatomical and biological role of the BVN, and the clinical evidence supporting basivertebral nerve radiofrequency ablation (BVN RFA) as a treatment option for chronic low back pain.

A narrative review of randomized controlled trials, prospective cohort studies, and systematic reviews was performed, focusing on clinical efficacy, durability of outcomes, safety profile, and patient selection criteria. Available evidence demonstrates clinically meaningful and sustained reductions in pain intensity and disability following BVN ablation in appropriately selected patients, with benefits persisting for several years and a low incidence of serious adverse events.

Basivertebral nerve ablation represents a promising minimally invasive intervention for vertebrogenic CLBP and may expand therapeutic options available to anesthesiologists and pain specialists. Further independent studies are needed to refine patient selection and confirm long-term outcomes.

Key words: *basivertebral nerve; chronic low back pain; Modic changes; radiofrequency ablation; vertebrogenic pain.*

Introduction Epidemiology of Low Back Pain

Low back pain (LBP) is a major global health problem affecting all age groups, with lifetime prevalence estimates exceeding 60% in many populations (1,2). It is the leading global cause of years lived with disability and it imposes substantial socioeconomic burden due to healthcare utilization, work absenteeism, and functional impairment (1,3). CLBP — usually defined as pain persisting beyond 12 weeks — contributes disproportionately to chronic disability (1,3). The

heterogeneous etiology of CLBP has historically challenged clinicians. In many cases, definitive pain generators could not be established, leading to a diagnosis of non-specific low back pain in up to 85% of patients (4). Disc degeneration has long been considered a principal cause ("discogenic pain"), with nociceptors within the degenerated annulus fibrosus implicated in symptom generation (5-7). However, accumulating evidence suggests that nociceptive input from vertebral endplates mediated by the BVN also plays a significant role in a subset of patients (4,8,9).

Shift from Discogenic to Vertebrogenic Pain Paradigm

For decades, the dominant model for CLBP centered on disc degenerative changes and associated annular nociception ("discogenic pain") (5). However, advances in spinal imaging and histologic studies have revealed a robust population of nociceptive fibers within vertebral endplates and along the BVN (10). Endplate damage and associated inflammatory processes correlate with specific MRI findings termed Modic changes (type I and II), which are strongly associated with persistent CLBP and poorer response to conventional conservative treatments (11-13). Anatomically, the BVN originates within the vertebral body, entering through the basivertebral foramen and innervating adjacent endplates. Damaged or degenerated endplates show increased density of nociceptive fibers expressing substance P and related neuropeptides, supporting a distinct vertebrogenic pain mechanism transmitted via the BVN (10,14-16). In recognition of this mechanistic subset, vertebrogenic pain has been conceptualized as a phenotype distinct from discogenic, facetogenic, or neuropathic pain (14).

Other Pain Generators in Low Back Pain

CLBP is multifactorial, with several well-recognized pain generators:

- Discogenic pain: Nociceptor activation in annular fissures of degenerated intervertebral discs (5,6).
- Facetogenic pain: Facet joint arthropathy with nociception from medial branch nerves (17).
- Sacroiliac joint pain: Inflammation or dysfunction of the sacroiliac joints (18).
- Radiculopathy: Nerve root compression or irritation producing radiating symptoms (19).
- Musculoligamentous pain: Soft-tissue strain or dysfunction contributing to pain without a clear structural lesion (20).

Emerging evidence recognizes vertebrogenic pain — where endplate pathology and BVN-mediated nociception drive axial low back pain — as an important and potentially treatable component of CLBP (4,10).

Basivertebral Nerve Ablation: Mechanism and Technique

BVN ablation aims to disrupt nociceptive signal transmission from sensitized vertebral endplates to the central nervous system (21). Radiofrequency energy is delivered intraosseously to thermally ablate the BVN via a transpedicular approach under fluoroscopic guidance (21,22).

Patient selection typically includes axial LBP of at least 6 months' duration, failure of conservative therapies, and the presence of Modic type I or II changes on MRI, which serve as imaging biomarkers for vertebrogenic pain (11,23-25).

Clinical Evidence for BVN Ablation

Multiple clinical studies, including randomized controlled trials (RCTs), cohort studies, and meta-analyses, support the efficacy of BVN ablation in appropriately selected patients. An early sham-controlled multi-center RCT demonstrated significantly greater improvements in Oswestry Disability Index (ODI) scores and responder rates in the BVN ablation arm at 3 months compared with sham controls (26). Other prospective trials have shown sustained improvements in pain and function at 12- and 24-month follow-up (9,27).

A systematic review with single-arm meta-analysis reported that approximately 65% of patients achieved ≥50% pain relief at 6 and 12 months post-BVN RFA, with similar proportions showing clinically meaningful functional gains (28). Likewise, comparative analyses indicate significant improvements in visual analog scale (VAS) and ODI scores at various follow-up intervals versus baseline (7,29). Importantly, real-world pooled analyses confirm these findings across multiple study designs (24,30).

Safety profiles are favorable, with low rates of serious adverse events reported when appropriate patient selection and technique are applied (27,29). Nevertheless, the literature underscores the need for more high-quality, non-industry-funded studies to validate these outcomes across broader patient populations (28.29).

Meta-Analysis and Comparative Effectiveness

While early meta-analyses historically included a limited number of studies, recent systematic reviews strengthen the evidence base. A single-arm meta-analysis of six unique BVN RFA study populations (414 treated patients) demonstrated that approximately 65% of patients achieved ≥50% pain reduction at both 6 and 12 months, and ~75% experienced ≥15-point ODI improvement at these time points (1).

Another meta-analysis combining randomized and prospective non-randomized studies (total n = 429 participants) reported a significant pooled mean ODI difference of –28.08 points and VAS difference of –3.16 cm favoring BVN RFA versus control groups, underscoring consistent and clinically relevant improvements in pain and disability across heterogeneous study designs (2).

A broader systematic review and meta-analysis comparing BVN ablation with other minimally invasive interventions found that BVN ablation produced statistically significant improvements in pain and function at 6-, 12-, and 24-month follow-ups relative to other modalities such as annular disc RFA, facet joint procedures, or injections. BVN ablation, biological therapy, and multifidus stimulation were among the only interventions showing durable benefits beyond short-term relief, with no significant differences in serious adverse events (SAEs) across treatment modalities (13).

Discussion

The growing body of evidence investigating BVN ablation highlights its promise as a targeted, minimally invasive intervention for vertebrogenic CLBP, particularly in patients with Modic changes on MRI that reflect endplate degeneration and vertebral body inflammation. This shift in conceptualizing pain — from predominantly discogenic or nonspecific mechanisms to a vertebrogenic phenotype — has been substantiated by both experimental and clinical trial data demonstrating that nociceptive fibers within the endplates and BVN carry significant pain signals, making them viable therapeutic targets (10,14,15).

Clinical Trial Evidence

The first large randomized, double-blind, sham-controlled multicenter trial provided rigorous evidence supporting the efficacy of BVN ablation. In this study (n = 225), patients randomized to BVN radiofrequency ablation (RFA) had significantly greater improvements in Oswestry Disability Index (ODI) and Visual Analog Scale (VAS) pain scores at 3 months compared with sham controls. In the per-protocol analysis, mean ODI reduction was greater by ~20 points in the treatment arm ($p < 0.001$), and responder rates (≥10-point ODI improvement) were higher (75.6% vs 55.3%) (12).

Significantly, these benefits were sustained at 12 months with continued large effect sizes — average ODI decreases ~25.7 points and VAS reductions ~3.8 cm from baseline, with ~64% achieving ≥50% pain relief and ~29% reporting being pain-free. [7] Longer term follow-up further strengthens the durability of BVN ablation outcomes. In the same cohort, the five-year treatment arm data showed sustained improvement in both pain and function (ODI and VAS) and reduced reliance on injection or opioid therapies compared with the baseline, corroborating that the clinical benefit is not merely short-lived (15).

Real-world prospective cohort data align with these RCT results. In a 60-participant real-world study, over half of the participants achieved clinically meaningful improvements (≥30% ODI improvement and ≥50% NRS/VAS reduction) at 12 months, and more than half judged themselves "much improved" on global impression measures (3). Similarly, community practice cohorts have reported statistically and clinically significant reductions in ODI and VAS at multiple early and late follow-ups, demonstrating that outcomes observed in controlled research are generalizable to routine clinical settings (8).

Clinical Interpretation and Patient Selection

The consistency of the positive results — across RCTs, meta-analyses, and real-world cohorts — supports the notion that BVN ablation as a true biological effect rather than a transient placebo response. The magnitude of ODI and VAS changes frequently exceeds established minimal clinically important differences (MCIDs), suggesting real functional and quality-of-life improvements for patients (1,3,7,8).

Accurate phenotyping appears critical to achieving optimal results. Most trials required either Modic type I or II changes or evidence of vertebrogenic pain syndrome — a subset distinct from

patients with primarily discogenic, facetogenic, or sacroiliac joint–related pain (4,7,12).

Limitations and Future Directions

Despite compelling data, the literature contains certain limitations that must be acknowledged:

- Many studies are industry-sponsored and may have inherent biases (1,8,24).
- The number of high-quality, large-scale independent trials remains limited, and more non-industry–funded research is needed (1,8).
- Longer-term comparative data with standard surgical or multimodal strategies are still evolving.

Future research would benefit from direct head-to-head comparisons with alternative interventions, detailed cost-effectiveness analyses, and further biomarker refinement (e.g., quantifying Modic changes) to enhance patient stratification (14).

Conclusion

The advent of BVN ablation reflects a significant evolution in understanding CLBP pathophysiology and offers a promising therapeutic option for vertebrogenic pain. Current evidence demonstrates meaningful pain and disability reduction in selected patients, with acceptable safety. Continued research, particularly large-scale pragmatic trials, is needed to refine selection criteria, long-term outcomes, and comparative effectiveness relative to other established interventions.

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REVIEW ARTICLE *UDK: 616-089.5-031.3*

THE IMPACT OF REGIONAL ANESTHESIA ON INFLAMMATORY AND STRESS RESPONSE TO SURGERY

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Abstract

The operative trauma triggers an inflammatory response that leads to a series of cascade changes known as the stress response to surgery. During extensive surgical procedures, the development of excessive stress response can result in transient suppression of the immune system. Natural killer cells (NK cells) and Cytotoxic T lymphocytes (CTLs) are the basis of the innate immunity, which is considered the primary defense against the dissemination of malignant cells and infection. One very significant discovery in anesthesiology was that anesthetic treatment can limit the excessive stress response after surgery. It is confirmed that both intravenous lidocaine as a part of a combined anesthesia protocol and regional anesthesia (RA), have positive effects in the reduction of proliferation and migration of malignant cells, as well as in the prevention of excessive and potentially harmful inflammatory reaction and preservation of the innate immunity. Regional anesthesia techniques have already surpassed their primary role in performing operative analgesia. Rather, they are a valuable addition to anesthetic strategy in the prevention of excessive and potentially harmful inflammatory reaction and preservation of the innate immunity.

Aim: we conducted a literature search to identify the most recent available data on the inflammatory and stress responses associated with the use of regional anesthetic techniques. In addition, we also provide our practical experience with these two techniques.

Key words: *inflammation; malignancy; regional anesthesia; stress response; surgery.*

Introduction

Aim: The aim of this educational review is to discuss the most recent literature data, and to take into consideration our experiences regarding the role and the potential benefit of both intravenous lidocaine and regional anesthesia in reducing the stress response and the preservation of innate immunity during surgery in patients with malignant disease.Methods: A search using PubMed, Google Scholar, EMBASE, and Scopus databases with the terms "regional anesthesia", "stress response", "inflammation", "malignancy" and "surgery" was performed. The most recent articles were reviewed and this review was written relying on the most current information.

Stress Response to Surgery

The level and magnitude of the stress response and inflammatory reaction are considered proportional to the severity of tissue destruction caused by surgical trauma. The main aim of the

secretion of inflammatory mediators (cytokines, chemokines and catecholamines) is the activation of cell-based immunity in order to repair and heal the damaged tissues and organs. However, during extensive and prolonged surgical procedures, we can expect the development of stronger and even excessive stress responses, which can paradoxically produce transient immunosuppression and inhibition of cellular immune elements. Surgical excision of the malignancy inevitably causes significant stress and potential damage to the surrounding tissues that additionally triggers prolonged inflammation in the postoperative period.

The knowledge of the influence of the stress response and inflammation on immune competence derives from research conducted over the past 10 years. One of the pioneers in this field is Horowitz, who introduced the term "inflammatory response syndrome" for the first time in 2015, in order to emphasize the negative impact of the immune suppression on dissemination of malignant cells and infection during surgery. (1) This is particularly important in oncology patients where the rapid division rate of the malignant cells and the hypoxic microenvironment are main stimuli of the inflammatory reaction and secretion of pro-inflammatory cytokines (IL6, IL10, HIFα and VEGF). Changes in the immune function are most profound in the early postoperative period when strong inflammatory response can cause decreased number and lower activity of T lymphocytes. Current data show that impaired innate immunity in any phase of the treatment of malignancy has strong negative prognostic value, in terms of tumor recurrences, metastatic spread as well as overall survival. (2,3)

Innate Immunity

Although there isn't a rigid distinction, immune processes are generally divided into innate and adaptive immunity, which regularly intertwine in different clinical scenarios. The primary defense against the dissemination of malignant cells and/or infection is the activity of innate immune cells. These subtypes of T lymphocytes have a natural ability to eliminate malignant, infected, or damaged cells without prior training, memory, or activation. This inherited cytotoxicity is basically the foundation of modern immune-based therapies that are replacing classic cytotoxic therapy. Following initial contact with malignant cells, these groups of T lymphocytes undergo a complex and still not well-understood activation process during which their cytotoxicity increases several times. The main carriers of this T lymphocytes subgroup also called "Innate lymphoid cells - ILCs", are Natural killer cells – NK cells and Cytotoxic T lymphocytes – CTLs.

NK Cells

NK cells are primarily cytotoxic T lymphocytes that exert a dual mechanism of action against malignant and infected cells. Innate cytotoxicity is mediated through direct lysis of damaged cells via exocytosis of lytic granules containing perforin and granzyme B, as well as through activation of death receptors and induction of genetically programmed cell apoptosis. Additionally, these T lymphocytes are considered the primary source of secretion for the anti-inflammatory cytokines group (IL2, IL12, IL18 and IFNγ) that oppose pro-inflammatory cytokines and excessive inflammatory reactions. According to the available data, the secretory phase and excretion of cytokines occur after the primary receptor activation period on the surface of NK cells. In the period that follows, NK cells exert direct cytotoxic activation by degranulation of lytic granules and elimination of malignant cells. (4) During the activation phase of the immune cells, a series

of morphological and phenotypic changes on NK cells can be detected. Increased cell metabolism is necessary for the rapid increase in cytokines secretion and rise in the anti-inflammatory cytokines concentration, both locally and in circulation. Once activated, NK cells have higher rate of exocytosis of lytic granules and a several-fold increase in cytotoxicity. (5,6)

Cytotoxic T Lymphocytes – CTLs

CTLs are the 2nd active element of the innate immune response that also have a direct cytotoxic activation mechanism. A part from the exocytosis of lytic granules and secretion of perforin and granzyme B, CTLs create direct synapse-like connections with the membranes of malignant and infected cells. Damaged cells can also be eliminated by activating death receptors and initiating genetically programmed apoptosis. The average circulating half-life of NK cells and CTLs is 17 days, however, recent studies have confirmed the existence of long-living NK cells that can be isolated from circulation several months after the initial invasion of the organism. After restimulation, these so-called "memory NK cells and CTLs" have a significantly stronger direct immune response compared to non-stimulated "naive" T lymphocytes. Additionally, research data indicate that memory NK cells and CTLs exhibit cross-reactivity and retain strong cytotoxic potential against malignant cells, even after non-malignant stimulation. These findings are the foundation of modern immunotherapeutic approaches to malignancies that are resistant to standard cytotoxic therapy. (4,7)

During malignant cell elimination, a part from the absolute number of NK cells and CTLs, their activation process that results in increased cytotoxic and secretory function is particularly important. According to the results of experimental and clinical studies, oncology patients who had a lower average number of NK cells and CTLs in the early postoperative period also had a worse prognosis in the final treatment outcome. These patient populations in the 3- and 5-year follow-up period had significantly higher incidence of metastatic spread and recurrence of the malignancy compared to patients with normal or above the average concentration of NK cells and CTLs. (5) The continuous follow-up of the concentration and the activity of T lymphocytes plays an important role in the creation of a prognostic profile during the treatment of patients with different forms of malignancy.

The Role of Anesthetic Management and Regional Anesthetic Techniques in Innate Immunity

One of the more significant recent discoveries in anesthesiology is the fact that certain anesthetics and anesthesiology techniques can modulate the severity and duration of the inflammatory response and preserve the immune function. (8-11) Anesthesiology techniques that can limit excessive stress response after surgery include: regional anesthetic techniques, combined anesthesiology treatment, and non-opioid anesthesia. However, there is only a small number of high-quality randomized clinical studies and the majority of scientific data comes from experimental and in-vitro research that are inconsistent and difficult to translate into clinical recommendations. (12)

Lidocaine is the only amide local anesthetic that is safe for intravenous use in patients. Indications for intravenous use of lidocaine are expanding in recent years as a result of recent findings

from clinical and experimental studies. In addition to its primary antiarrhythmic indication, lidocaine is beneficial in controlling and reducing the inflammation and operative stress response. Modern approaches include intravenous lidocaine (i.v. bolus and continuous infusion) in creating an anesthesia protocol based on combined anesthetic strategies. In-vitro and clinical trials have confirmed that lidocaine has a positive effect in reducing proliferation and the invasive potential of malignant cells. Moreover, lidocaine stimulates the cytotoxicity of NK cells in the early postoperative period. (13) Patients treated with continuous intravenous infusion of lidocaine have lower postoperative concentration of pro-inflammatory cytokines (IL1, IL4, IL6, IL10 and VEGF). (14) The impact of lidocaine on the immune system remains a subject of ongoing debates, as 4 activation mechanisms have been identified thus far: 1) apart from the sodium channels, lidocaine also has an inhibitory effect on M1 muscarine receptors. 2) the anti-inflammatory potential of lidocaine opposes the pro-inflammatory cytokines by inhibiting the Src signal protein that plays a vital role in the destruction of cell membranes and proliferation of malignant population. (15) 3) lidocaine engages in direct interaction with the membranes of NK cells and CTLs and stimulates their cytotoxicity. 4) the analgesic properties of intravenous lidocaine are particularly important, as it create an opioid-saving effect during combined administration of general anesthesia (GA).

There is still no clear consensus on the recommended intravenous dose of lidocaine. For different clinical settings, most authors recommend intravenous bolus dose of lidocaine 1-1.5mg/kg followed by continuous infusion of 1.5-2mg/kg until the end of surgery. The safe therapeutic range for plasma lidocaine concentrations is 1.5-5.0μg/ml, as concentrations >5μg/ml are considered toxic and cause most complications. (16)

Bupivacaine is a local anesthetic used exclusively for epidural, spinal and regional anesthesia (RA). Regional anesthetic techniques are used both as independent techniques and as part of combined general anesthesia. The principal action of RA is the blockade of the sensory neural transmission, thereby providing sufficient analgesia in the affected dermatomes. The additional effect of neuraxial anesthesia and regional techniques is the blockade of the sympathetic transmission that effectively reduces the stress response to the surgical trauma. The damage caused by the surgery triggers neuro-endocrine, metabolic, and inflammatory response, which leads to a series of cascade changes known as the stress response to surgery. In the postoperative period, the end result of these defense mechanisms is suppression of innate immunity and prolonged immunodeficiency, which can be detrimental in oncology patients.

Regional anesthesia techniques (RA) have a great potential in reducing the level of stress response, primarily by blocking the afferent neurotransmission of nociceptive impulses to the CNS. As RA is performed before surgery and before the occurrence of tissue damage, many authors emphasize this preemptive modality. (17) With the introduction of new and more advanced ultrasound aids, new approaches and safer regional techniques for different operative procedures are emerging. It should be noted that most of the available data regarding the positive effects of RA on inflammatory and stress response come from experimental studies; and implementing these findings into clinical practice remains challenging. In recent years the results of randomized clinical studies comparing the impact of GA and combined anesthesia modalities including RA in different clinical settings were published. Most authors report that the clinical benefits of RA as an analgesia providing tool during surgery or other painful procedures exceeds its primary role. (18-20)

Conclusion

The activity of the innate immunity is a natural defense mechanism against the dissemination of malignant cells and the spread of infectious disease. This is especially important during surgeries and in the postoperative period when multiple factors that promote malignancy progression occur. Excessive inflammation and stress response have a detrimental impact on the immune response expressed as a decrease in both concentration and activity of NK cells and CTLs. Regional anesthesia techniques have already significantly extended their role in providing operative analgesia within the corresponding dermatomes. The use of regional anesthetics, both intravenously (lidocaine) or as a nerve plexus block (bupivacaine), is a valuable addition to the anesthesia plan, in terms of preventing the excessive and potentially harmful inflammatory reaction. It is clear that the individualized approach is the future of anesthetic strategy when it comes to applying the most beneficial technique and anesthetic agent for different clinical scenarios. The significance and role of RA in clinical practice remain to be fully established, as additional high-quality, randomized clinical trials across various surgical procedures are needed; however, the immense potential of these techniques is already recognized.

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REVIEW ARTICLE *UDK: 615.387:611.018.52*

PLATELET TRANSFUSION STRATEGIES IN SURGERY AND ANESTHESIA

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Abstract

Importance: Platelet transfusions are lifesaving in specific clinical contexts, particularly for patients with thrombocytopenia (low platelet counts) or platelet dysfunction. However, the procedure is not without risks. Platelets are biologically active and prone to cause immune and non-immune adverse events more frequently than red blood cell transfusions.

Objective: To provide recommendations in adult and pediatric populations in whom platelet transfusions are commonly performed.

Evidence Review: *The new platelet transfusions guidelines established* by the Association for the Advancement of Blood and Biotherapies (AABB) and the International Collaboration for Transfusion Medicine Guidelines (ICTMG), including Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology were based on data of 21 randomized controlled trials and 13 observational studies all of which examined transfusion strategies using restrictive or liberal amounts of platelets. The authors noted that overall evidence demonstrated that restrictive transfusion strategies were not associated with increased risk of mortality, or increased bleeding, in most patient populations.

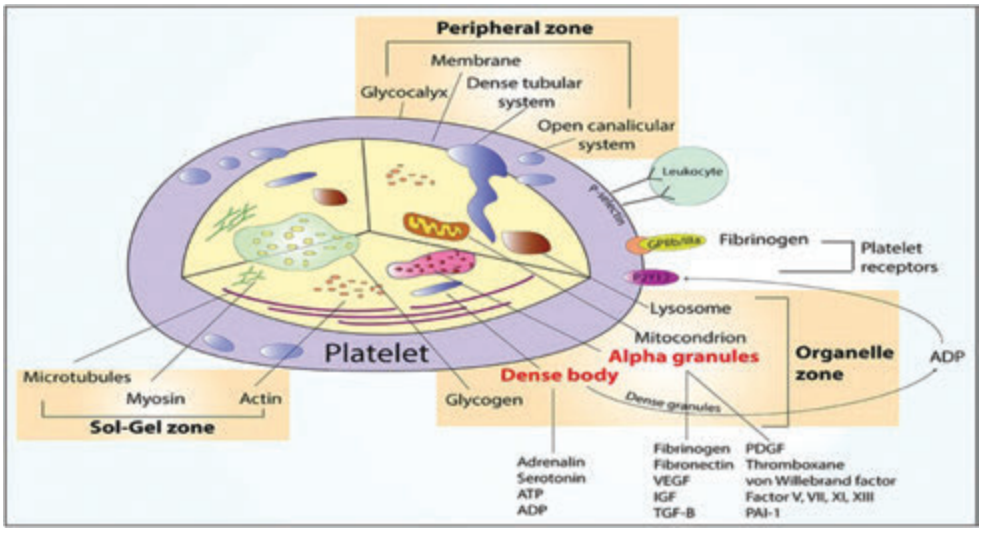
Keywords: *anesthesia; platelets; surgery; platelets transfusion.*

Introduction

Circulating thrombocytes or platelets are anuclear discoid cells derived from bone marrow from megakaryocytes during fragmentation. Thrombopoietin is the main growth factor controlling megakaryocyte production. The circulating life span of native platelets is approximately 10 days, and that of transfused platelets is approximately 3 days in a stable recipient. Platelets have receptors on their surface and granules inside, allowing them to participate in adhesion, aggregation, and clot formation on the surface of injured endothelium, forming a haemostatic plug.

The number of circulating platelets for in adults ranges between 150×10^9/L and 450×10^9/L. Decreased number of platelets (thrombocytopenia) refers to any situation where the patient's platelet concentration is below 150×10^9/L, in an adult. Both thrombocytopenia and platelet dysfunction without thrombocytopenia can cause bleeding. Actively bleeding patients might require support from platelet transfusions. Platelets are also used for prophylactic transfusions

to prevent bleeding in patients with platelet production undergoing chemotherapy, and/or haematopoietic stem cell transplantation (HSCT). In addition, platelets are transfused to patients who have an increase in platelet destruction/consumption.



Causes of thrombocytopenia

Patients undergoing chemotherapy, HSCT, and those with chronic infections can have **decreased platelet production**. Another common cause of thrombocytopenia is an **increase in platelet destruction/consumption** that can have an immune (20%) or non-immune aetiology (80%) . Immune-mediated thrombocytopenia (ITP) is caused by different types of antibodies (autoimmune or alloimmune) that are produced to different platelet antigens and lead to elimination of the platelets in the spleen. Non-immune mechanisms cause platelet consumption and/or sequestration due to bleeding, enlarged spleen (sequestration) or vascular thrombi formation. It is not uncommon to have a combination of both immune and non-immune causes.

Decreased platelet production

- Chemotherapy;
- Preparation for and recovery from HSCT (including conditioning treatment with chemotherapy and sometimes radiation therapy);
- Radiation therapy;
- Aplastic anaemia and other bone marrow failure syndromes;
- Bone marrow suppression or infiltration due to chronic infections (e.g., tuberculosis, malaria, visceral leishmaniasis [kala-azar]).

Increased platelet destruction/consumption

Immune

- ITP;
- Drug-induced ITP (e.g., heparin-induced thrombocytopenia);

- Neonatal alloimmune thrombocytopenia;
- Post-transfusion purpura.

Non-immune

- Febrile state;
- Thrombotic microangiopathies (e.g., thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome);
- DIC;
- Active bleeding;
- Splenic sequestration;
- Cavernous hemangioma.

Doses of prophylactic platelates

An adequate dose for prophylactic platelet transfusions is 1 apheresis unit (without Le, and from one donor) or a dose of 4–5 pooled whole-blood-derived platelet units (from several donors) for an average-size adult (70 kg). Whena smaller-than-expected increase in the platelet count increment occurs after transfusion of an adequate platelet dose, platelet refractoriness should be considered. One unit of random donor platelets derived from a unit of whole blood can increase the platelet count in an average-sized adult by 5,000–10,000/μL. Therefore, a dose of one random donor platelet per 10 kg of body weight is generally recommended. Pooled platelets prepared by pooling 4–6 units of whole blood-derived platelets can give a post-transfusion increment of 20,000 to 40,000/μL in an average-sized adult. The same increment would be expected from a dose of apheresis platelets.

New recommendations on platelet transfusions

The Association for the Advancement of Blood and Biotherapies **(AABB)** in partnership with the International Collaboration for Transfusion Medicine Guidelines **(ICTMG)**, developed New Platelet Transfusions Guidelines published on 29 May, 2025 in JAMA.

The new guidelines offer recommendations for transfusion based on specific patient criteria, and these vary depending on individual patients' needs. In general, the guidelines support the implementation of restrictive platelet transfusion strategies.

The authors of the new guidelines, led by Ryan Metcalf, MD, from the Department of Pathology at the University of Utah, noted that restrictive strategies reduce the risk of adverse reactions, mitigate platelet shortages, and reduce costs. "It is good practice to consider overall clinical context and alternative therapies in the decision to perform platelet transfusion," they wrote.

The guidelines were based on data from 21 randomized controlled trials and 13 observational studies, all of which examined transfusion strategies using either restrictive or liberal platelet transfusion strategies. The authors noted that overall evidence demonstrated that restrictive

transfusion strategies were not associated with increased risk of mortality or increased bleeding in most patient populations.

Recommendations

The authors categorized their recommendations based on the degree of evidence. They developed the following recommendations, considered to be **"strong recommendations with high/moderate-certainty evidence":**

- To address hyperproliferative thrombocytopenia in nonbleeding patients receiving chemotherapy or undergoing allogeneic stem cell transplant, platelet transfusion is recommended when the platelet count is less than $10x10^3/\mu L$.
- For consumptive thrombocytopenia in neonates without major bleeding, platelet transfusion is recommended when the platelet count is less than $25x10^3/\mu L$.
- In patients undergoing lumbar puncture, platelet transfusion is recommended when the platelet count is less than $20x10^3/\mu L$.
- In patients with consumptive thrombocytopenia due to dengue without major bleeding, platelet transfusion is not recommended.

The authors also developed guidelines for additional patient populations but noted that these are **"conditional recommendations with low/very low-certainty evidence."**

These recommendations include:

- For hypoproliferative thrombocytopenia in nonbleeding adults undergoing autologous stem cell transplant or with aplastic anemia, prophylactic platelet transfusion is not recommended.
- In adults with consumptive thrombocytopenia without major bleeding, platelet transfusion is recommended when the platelet count is less than $10\ x10^3/\mu L$.
- In adults undergoing central venous catheter placement in compressible anatomic sites, platelet transfusion is recommended when the platelet count is less than $10\ x10^3/\mu L$.
- In adults undergoing interventional radiology, platelet transfusion is recommended when the platelet count is less than $20\ x10^3/\mu L$ for low-risk procedures and less than $50\ x10^3/\mu L$ for high-risk procedures.
- For adults undergoing major nonneuraxial surgery, platelet transfusion is recommended when platelet count is less than $50\ x10^3/\mu L$.
- For nonthrombocytopenic patients undergoing cardiovascular surgery in the absence of major hemorrhage, including those receiving cardiopulmonary bypass, platelet transfusion is not recommended.
- For nonoperative intracranial hemorrhage in adults with platelet count more than $100\ x10^3/\mu L$, including those receiving antiplatelet agents, platelet transfusion is not recommended.

Comments

Claudia Cohn, MD, PhD, AABB's chief medical officer and one of the authors of the guidelines, said these new guidelines were an important advancement for optimal transfusion strategies. "These new evidence-based guidelines move the field forward for many different patient populations," Cohn said. "Overall, the guidelines prioritize patient safety and help conserve the limited platelet inventory." In a related commentary published in ***Transfusion (June 2025)***, the authors underscored two major findings that informed the development of the new guidelines. First, they found that there is no consistent evidence that liberal platelet transfusion strategies improve mortality or reduce bleeding; and second, while current data support restrictive practices, the review found that the quality of the evidence varies substantially across patient populations.

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REVIEW ARTICLE *UDK: 616-089.844-089.5-056.257*

TUMESENT LOCAL ANESTESIA WITH ANALGOSEDATION (REMIFENTANIL, DEXMEDETOMIDINE) IN LIPOSUCTION AND LIPOSCULPTURING

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Abstract

Tumescent local anesthesia has revolutionized the field of liposuction and body contouring by enabling large-volume fat removal with minimal blood loss and enhanced patient safety. This technique involves the subcutaneous infiltration of a dilute solution of local anesthetic (commonly lidocaine) and epinephrine, producing profound regional anesthesia, vasoconstriction, and tumescence of the targeted tissue. When combined with analgosedation, particularly with short-acting agents such as remifentanil and dexmedetomidine, it offers a balanced approach between patient comfort and procedural control.

Remifentanil, an ultra–short-acting opioid, provides potent analgesia with rapid onset and offset, allowing precise titration to surgical needs and a smooth recovery profile. Dexmedetomidine, a selective α2-adrenergic agonist, provides anxiolysis, sedation, and analgesic-sparing effects while maintaining respiratory stability-a key advantage in procedures performed under local anesthesia. The synergistic combination of these agents minimizes intraoperative discomfort, reduces the need for higher doses of lidocaine, and improves overall patient tolerance. This review summarizes current evidence and clinical experience supporting the use of tumescent local anesthesia with remifentanil–dexmedetomidine sedation in liposuction and liposculpture. The approach enhances patient satisfaction, optimizes perioperative hemodynamics, and ensures faster recovery with a low incidence of complications, making it an increasingly preferred modality in modern aesthetic surgery.

Keywords: *analgosedation, dexmedetomidine, remifentanil, liposuction ,tumescent local anesthesia.*

Introduction

The number of body contouring procedures has increased globally and liposuction has become the second most common cosmetic procedure. This aesthetic surgical procedure removes excess fat from a specific region of the body, most commonly from the abdomen, hips, thighs, upper arms and additional body areas (1). The combination of removing fat from one body region and reusing it in terms of lipofilling or fat grafting in others is called liposculpture. Liposculpture aims to model and define the contours of the body to achieve a more aesthetic, natural, and harmonious appearance (2).

With the rising demand for body contouring procedures, many hospitals are transitioning these procedures to one-day (ambulatory) surgical settings, aiming to reduce healthcare costs and

decrease the incidence of postoperative complications for patients (1). It is prudent for the anesthesiologist to be familiar with the techniques used to facilitate liposuction, the options for anesthesia, and the recognition and management of complications in order to provide safe care to patients (3,4).

Modern era of liposuction began in the 1970s./80s with the work of Giorgio Fischer, who introduced the "dry technique" using a cannula, a method with considerable postoperative morbidity and blood loss of up to 25 % of the aspirated volume. A pivotal peer advancement occurred in France, where Yves-Gerard Illouz and Pierre Fournier refined the so-called "wet technique", incorporating vacuum cannulas and wetting tissue solutions, an approach that significantly improved effectiveness of fat removal procedures and moreover, the safety of the patients (5,6). In 1987, Jeffrey A. Klein introduced the concept of tumescent local anesthesia (TLA), a development that fundamentally transformed the practice of liposuction. The tumescent technique, which involves infiltration of large volumes of dilute local anesthetic and vasoconstrictor solution, greatly enhanced patient comfort, minimized bleeding, and became the gold standard of care in contemporary liposuction practice that can even be performed ambulatory (7-10). Modern advancements in technology and technique have further expanded the scope and precision of body contour. And lately, high-definition liposculpture (HD liposculpture) has been developed to accentuate and define muscular contours, particularly in areas such as the abdomen, flanks, and torso (11).

Contemporary methods incorporate energy-assisted modalities, such as ultrasonic-assisted liposuction, which selectively targets fat cells while preserving connective tissue, as well as PAL (Power Assisted Liposuction), which enhances fat removal efficiency and surgeon control (12,13).

Tumescent Local Anesthesia (TLA) Technique

The tumescent technique is the most commonly used method of local anesthesia in liposuction. It involves subcutaneous infiltration of large volumes of fluids containing highly diluted local anesthetic (usually lidocaine) combined with epinephrine, resulting in tissue oedema and firmness that facilitates both anesthesia and hemostasis. Originally developed for liposuction, its use has expanded to other surgical procedures, including plastic surgery, breast, ENT, and vascular surgery (14,15). TLA provides effective local anesthesia, often eliminating the need for general anesthesia in massive liposuction, significantly reduces blood loss and bruising through epinephrine-induced vasoconstriction and hydrostatic compression, decreases postoperative pain and extends analgesia due to slow systemic absorption of lidocaine, and furthermore, it facilitates quicker recovery with lower complication rates compared with procedures under general anesthesia (16-18). Liposuction can be classified by aspirate volume into small-volume (<4 L) and large-volume (>4 L) procedures. Larger volumes of tumescent solution are required for high-volume liposuction, underscoring the importance of careful fluid management and monitoring to mitigate fluid-related complications (19.20).

Tumescent / Wetting Solutions

The classic formulation described by Klein includes lidocaine diluted in 0.9% isotonic saline (approximately 0.05–0.10% lidocaine concentration), epinephrine at 1: 1,000,000 concentration,

and sodium bicarbonate to buffer the acidity and facilitate analgesia (21,22). While isotonic saline as a diluent is associated with a burning sensation upon infiltration, lactated Ringer's solution is not, and it reduces the sodium load (23). Therefore, there are modifications of the original solution, like the one according to Hunstadt (19). [Table 1].

Table 1. Types of wetting solution

Klein's solution	Hunstadt's solution
1000 ml Normal saline	1000 ml Ringer's lactate
50 ml, 1% lignocaine	50 ml, 1% lignocaine
1 ml, 1:1,000 epinephrine	1 ml, 1:1,000 epinephrine
12.5 ml, 8.4% sodium bicarbonate	

Local Anesthetics

Lidocaine is the most commonly used local anesthetic in tumescent liposuction solutions. In standard local infiltration with epinephrine, the maximum recommended dose is 7 mg/kg; however, the pharmacokinetic properties of tumescent anesthesia allow much higher total doses because of delayed systemic absorption and reduced peak plasma levels. For liposuction, the recommended maximum lidocaine doses are generally 35–45 mg/kg, with accepted safe limits up to 55 mg/kg in most patients when epinephrine is included in the solution. Peak plasma lidocaine levels typically occur several hours after infiltration and remain below toxic thresholds due to slow absorption and removal of some anesthetic during fat aspiration. Factors that further reduce systemic uptake and toxicity risk include low blood flow in subcutaneous fat, vasoconstriction from epinephrine, and sequestration of lidocaine in adipose tissue. Lidocaine is predominantly metabolized in the liver by CYP3A4 and CYP1A2; therefore, doses should be reduced in patients who take drugs that inhibit these enzymes or in patients with impaired hepatic function, as this may increase the risk of systemic toxicity (24-26).\

Vasoconstrictors, Sodium Bicarbonate, and Steroids

Vasoconstrictors decrease tissue blood flow and delay the systemic absorption of local anesthetics, enhancing the safety of tumescent anesthesia. Epinephrine is the most widely used vasoconstrictor in tumescent solutions, with recommended concentrations of 0.25–1 mg/L, adjusted according to tissue vascularity (higher in more vascular areas and lower in less vascular regions). The total epinephrine dose should not exceed 50 μg/kg, and if this limit is likely to be exceeded, the procedure may be staged to reduce the risk. In an alternative approach, Lalinde et al. used l-ornithine 8-vasopressin at 0.01 IU/mL in chilled saline, reporting reduced blood loss compared with conventional epinephrine-containing solutions (27-30).

Sodium bicarbonate is added to tumescent anesthetic solutions to raise the pH and reduce acidity, which significantly reduces the pain and the burning sensation associated with injection of acidic lidocaine-epinephrine mixtures. This buffering increases the proportion of non-ionized lidocaine, facilitating faster diffusion into nerve fibers and improving patient comfort. (29-33). Steroids, especially triamcinolone acetat, as anti-inflammatory additive have been shown to ex-

ert anti-inflammatory and circulatory stabilizing effects when added to tumescent solutions, potentially reducing tissue inflammation and postoperative swelling (34).

Preoperative Assessment

Comprehensive preoperative evaluation and optimization of comorbid conditions are essential. Severe cardiovascular disease, active coagulation disorders, and pregnancy are contraindications for liposuction. A detailed history, including all medications, herbal products, and supplements, should be obtained while anticoagulants or drugs that may interfere with lidocaine metabolism (e.g., CYP3A4 inhibitors) should be discontinued. Preoperative investigations typically include complete blood count with platelet assessment, coagulation profile (prothrombin time (PT), activated partial thromboplastin time (aPTT)), liver function tests, and pregnancy testing in women of childbearing age. Perioperative pharmacological and mechanical thromboprophylaxis (e.g., low-molecular-weight heparin and sequential compression devices) should be considered in high-risk patients to reduce the risk of venous thromboembolism. Additional tests—such as ECG, renal function, or specialized cardiac evaluation—may be indicated based on patient age, clinical history, or ASA classification. Preoperative anxiolysis may be provided to reduce procedural anxiety and attenuate related hemodynamic responses (e.g., tachycardia, hypertension, arrhythmias). Oral alprazolam (0.25–0.5 mg) the night before and on the morning of surgery is commonly prescribed for this purpose (31,33,35,36).

Anesthesia Technique

Liposuction can be performed under local, regional (neuraxial), or general anesthesia, alone or in combination. No single technique has been definitively shown to be superior; the choice of anesthesia depends on the patient's clinical profile, areas treated, and planned volume of aspirate, as well as considerations for day-case versus inpatient surgery (35-37).

Local techniques such as tumescent local anesthesia (TLA) or monitored anesthesia care with sedation are commonly used for small volume or localized liposuction, allowing ambulatory procedures with faster recovery and reduced anesthetic risk. In contrast, general anesthesia is typically preferred for large volume liposuction or when more extensive surgical areas are treated, as it provides complete analgesia, immobility, and facilitated airway control (37). Large volume procedures are associated with risks of late-onset local anesthetic systemic toxicity (LAST) and significant hemodynamic shifts, often necessitating inpatient monitoring (28).

The combination of TLA with analgosedation offers the benefits of limited bleeding and intrinsic analgesia, allowing consideration of ambulatory procedures with earlier recovery and lower costs. Paradigm shift is successfully used in larger liposuctions with/without fat grafting, especially when the patient's cooperation is needed (patient's position has to be changed) (28,29). It substitutes general anesthesia, thus shortening the operating time when patient mobility is acquired. However, intensive intraoperative monitoring by the anesthesiologist and accurate titration of sedation are required continuously. Commonly used sedative agents for TLA include midazolam, propofol, ketamine, clonidine, or dexmedetomidine, with supplemental opioids such as fentanyl or remifentanil as required; however, the primary analgesia facilitating the procedure is provided by the TLA itself (25-27).

Sedation and analgesia for liposuction can be effectively achieved with dexmedetomidine combined with adjuncts such as remifentanil. (Fig 1). This combination provides reliable sedation and analgesia while maintaining hemodynamic stability and satisfactory operative conditions. A common challenge with dexmedetomidine–remifentanil sedation is balancing adequate depth of sedation with preservation of spontaneous respiration. Dexmedetomidine produces sedative and hypnotic effects via α_2-adrenergic receptors in the locus coeruleus, offering sedation with relatively minimal respiratory depression, whereas remifentanil—being a ultra-short-acting opioid—carries a higher risk of respiratory depression (29,30). Esketamine, the S-enantiomer of ketamine, may counteract opioid-induced respiratory depression and enhance analgesia when used as an adjunct. Perioperative low-dose esketamine has been associated with improved postoperative comfort, reduced anxiety, better sleep quality, and enhanced patient and surgical team satisfaction when combined with dexmedetomidine and remifentanil in liposuction anesthesia. These effects are likely attributed to its N-methyl-D-aspartate receptor (NMDAR) antagonism and sympathomimetic properties that support hemodynamic stability (31-34).

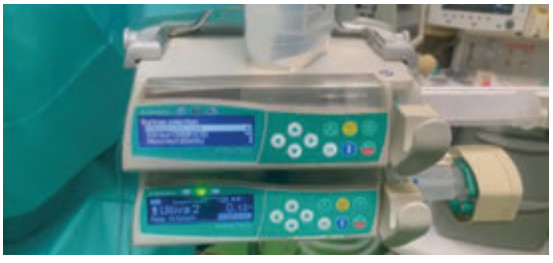

Figure 1. Perfusor with dexmedetomidine and remifentanil

Monitoring

Standard anesthesia monitoring is mandatory for all patients undergoing liposuction, regardless of the anesthetic technique used. This should include continuous assessment of pulse oximetry (SpO_2), non-invasive blood pressure (NIBP), electrocardiogram (ECG), end-tidal carbon dioxide monitoring (capnography) when sedation is administered, and temperature, to enable early detection of physiological changes and maintenance of homeostasis (35).

For patients under sedation, continuous capnography is essential to assess ventilation and detect hypoventilation or airway obstruction early, in line with recognized anesthesia monitoring standards. Routine non-invasive monitoring may suffice for small-volume procedures. High-risk patients or those undergoing large-volume liposuction often require enhanced monitoring, such as invasive arterial blood pressure measurement and central venous pressure monitoring, due to the potential for significant fluid shifts and hemodynamic alterations (36). In lengthy procedures, insertion of a urinary catheter is useful for monitoring hourly urine output as a surrogate for intravascular volume status and overall fluid balance. Regular urine output assessment helps guide fluid therapy and detect early signs of hypovolemia or fluid overload (34-36).

Patient Positioning

Patient positioning during liposuction is determined by the anatomical area being treated; while the supine position is most common, areas such as the buttocks and posterior thighs

may require prone positioning to allow optimal surgical access. Careful attention must be paid to padding pressure points to prevent nerve and soft-tissue injuries—this includes cushioning the face, breasts, iliac crests, knees in the prone position, and the elbows and heels in the supine position. Protection of the eyes, for example with lubrication and padding, is essential when patients are prone to avoid corneal injury. (Figure 2) For large-volume liposuction and prolonged procedures, the use of intermittent pneumatic compression devices on the lower limbs is recommended intraoperatively to reduce the risk of deep vein thrombosis (DVT) and support thromboembolism prophylaxis (37).

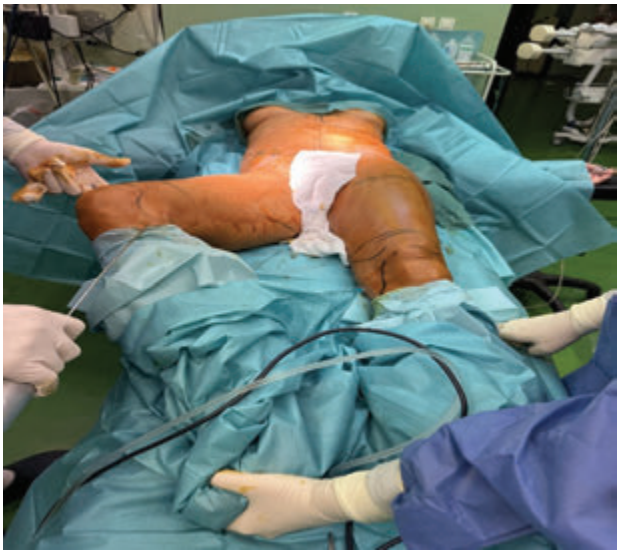

Figure 2. Infiltration of TLA

Hemodynamics

While small-volume liposuction is generally well tolerated with minimal hemodynamic disturbance, large-volume liposuction (defined as > 4 L of aspirate) is associated with significant cardiovascular changes during the perioperative period (25). Studies of large-volume liposuction demonstrate increases in cardiac index, heart rate, mean pulmonary arterial pressure, stroke volume index, and right ventricular work index, often accompanied by decreases in mean arterial pressure and systemic vascular resistance. These changes reflect a state of relative hyperdynamic circulation and fluid redistribution during the procedure (26,27). The routine use of large doses of epinephrine to achieve vasoconstriction and a relatively bloodless field can contribute to tachycardia and elevated cardiac output, as higher circulating catecholamine levels augment cardiac performance. In contrast, the observed reduction in systemic vascular resistance and mean arterial pressure is likely multifactorial, involving the effects of general anesthetic agents and opioids, as well as β_2-mediated vasodilation in skeletal muscle (25-30).

Thermoregulation

Patients undergoing large-volume liposuction are at an increased risk of intraoperative and early postoperative hypothermia. This risk arises from several procedural and environmental factors, including exposure of large body surface areas, infusion of large volumes of relatively cold

wetting solutions, prolonged operative times, general anesthesia, heat loss during mechanical ventilation, low ambient operating room temperature, and administration of intravenous fluids (38-40).

Hypothermia can have serious physiological consequences, such as cardiac dysrhythmias, coagulopathies, oliguria, and electrolyte imbalances. These complications may be exacerbated by even mild reductions in core body temperature, and both hemodynamic and thermoregulatory disturbances can persist for more than 24 hours after the start of surgery (25).

Postoperative Care

In the postoperative care, it is important to monitor the patients, especially those undergoing large-volume liposuction. Postoperative monitoring should continue beyond the immediate recovery period to observe f delayed hemodynamic changes, fluid shifts, and complications, such as pulmonary edema or fat embolism. The analgesia provided by the tumescent local anesthetic often results in minimal postoperative pain requirements. Adding epinephrine to lidocaine prolongs analgesia for several hours. When appropriate, non-steroidal anti-inflammatory drugs (NSAIDs) can be prescribed postoperatively for additional pain control. Early movement after surgery should be encouraged as soon as possible. Lower extremity muscle-contracting exercises, early mobilization, adequate hydration, and low-molecular-weight heparin reduce the risk of venous stasis and deep vein thrombosis (DVT) (38-40).

Complications

Although liposuction is frequently performed as a day-case procedure, it carries potentially serious complications, particularly with large volumes of aspirate. The overall complication rate for liposuction is approximately 5%, with most being minor; however, major systemic complications and deaths have been reported (40-42). Serious postoperative complications include: deep vein thrombosis (DVT), pulmonary embolism (PE), pulmonary edema and fluid overload, local anesthetic toxicity, infection and sepsis, including rare cases of necrotizing fasciitis or visceral perforation. The incidence of mortality associated with liposuction varies across studies but is estimated to be rare yet significant, especially when large volumes are aspirated, procedures are prolonged, or surgery is combined with other major operations. (41)

The most frequent late complications are unfavorable aesthetic outcomes following liposuction or fat grafting, often requiring subsequent surgical management (42).

Discussion

Tumescent local anesthesia (TLA) with adjunctive remifentanil and dexmedetomidine offers advantages over general anesthesia and sedation alone for many liposuction procedures: it provides prolonged local analgesia and reduced blood loss (epinephrine vasoconstriction), lowers postoperative pain scores, and often allows for ambulatory treatment with faster recovery and lower costs. The remifentanil–dexmedetomidine combination yields rapid, easily titratable analgesia and cooperative sedation that preserves patient responsiveness—facilitating intraop-

erative communication and safe repositioning—while reducing total opioid requirements and postoperative nausea (12,14,17). Compared with regional or MAC alone, this regimen gives superior control during painful moments (infiltration/aspiration) and greater hemodynamic stability than high-dose opioids, but both agents carry risks: remifentanil can cause respiratory depression and chest-wall rigidity (especially with large boluses) and dexmedetomidine produces dose-dependent bradycardia and hypotension; these effects may be additive when used in combination. The main persistent safety concern with high-volume TLA remains LAST; therefore, strict lidocaine dose calculation, tailored concentrations, slow infiltration, continuous capnography and hemodynamic monitoring, and readiness with airway equipment, lipid emulsion, reversal agents, and vasopressors are mandatory. Evidence favors TLA with or without analgosedation for many cutaneous/subcutaneous procedures; however, heterogeneity in dosing and limited RCT data mean that the choice should be individualized based on patient comorbidities, procedural extent, and available facility resources (19,25,27,29).

Lidocaine systemic toxicity remains a critical risk when large tumescent volumes are used; therefore, precise calculation of total lidocaine dose is mandatory (commonly cited upper limits ~35 mg/kg, though local protocols vary). The existing literature is limited by heterogeneity in dosing regimens, small sample sizes, retrospective designs, and few RCTs specifically evaluating the remifentanil and dexmedetomidine combination in tumescent liposuction (20,21).

The use of lidocaine concentrations and volumes has to be tailored to the patient's weight and comorbidities. Remifentanil should be administered in small boluses or as a low-rate infusion (avoid large rapid boluses). The same applies to the use of dexmedetomidine It is mandatory to have reversal agents and resuscitation equipment immediately available (naloxone, airway devices, vasopressors, atropine)(13,19,29).

Conclusion

Liposuction is a widely performed procedure for the removal of excess adipose tissue and is associated with significant hemodynamic and physiological perturbations, particularly in large-volume cases. Anesthetic management for liposuction demands a comprehensive understanding of these physiological changes and a proactive approach to anticipate and mitigate potential complications. Meticulous intraoperative monitoring and strict adherence to established fluid therapy and anesthesia guidelines are essential to optimize patient safety and surgical outcomes.

The combination of dexmedetomidine and remifentanil is an effective and safe regimen for sedation and analgesia in liposuction anesthesia. Evidence indicates that this combination provides stable hemodynamics, facilitates adequate analgesia and sedation, and maintains respiratory function with minimal compromise. Compared with alternative sedative-analgesic strategies, adjunctive use of dexmedetomidine with remifentanil has been shown to enhance patient and surgical team satisfaction, reduce intraoperative opioid requirements, and contribute to improved postoperative outcomes, including better sleep and reduced anxiety levels. Furthermore, this combination may be associated with fewer episodes of respiratory depression, sinus bradycardia, and patient movement during the procedure, contributing to a smoother intraoperative course and overall perioperative experience.

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PERIOPERASTIVE NEUROLOGICAL COMPLICATIONS AND COGNITIVE DYSFUNCTION

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Abstract

Perioperative neurological complications and cognitive dysfunctions are common in elderly patients. Neurological complications are often seen in the perioperative period and these complications are damaging to patients' well-being. Neurophysiological dysfunction in the perioperative period is the result of hypotension, hypoperfusion and brain hypoxia. Cytokine inflammatory response to operative trauma can damage neurological function at subcellular level.

Neurological complications can be acute, or de novo events such as stroke, nerve injury and delirium. Also, neurological complications can occur as decompensation of chronic neurological disease. In acute and chronic neurological impairment, patients can suffer from health problems that are affecting their social and medicolegal wellbeing. Most common neurological complications are delirium, stroke, postoperative cognitive disorder, neuroleptic malignant-like syndrome. Delirium is a devastating life-threatening disorder that has a great impact on the brain cell metabolism. Stroke is a rare complication, however it is 20 times more frequent among patients who had a stroke before surgery. In the perioperative period we can witness aggravation of a significant number of diseases, including Parkinson's disease, myasthenia gravis, epilepsy. We also have to mention the perioperative peripheral neuro injuries. Local anesthetics that are used as painkillers, such as lidocaine, can cause central nervous system toxicity. The interaction of the medications, such as beta blocker antiarrhythmics, should be considered a factor for enhancing the neurotoxicity of the local anesthetics. Cognitive postoperative disorder includes a wide spectrum of symptoms during the perioperative period. They can manifest preoperatively as acute preoperative delirium, postoperative delirium – an event that can manifest hours to days after surgery, delayed cognitive dysfunction- an event that can occur within 30 days after surgery and postoperative neurocognitive dysfunction, which can occur between 30 days to 1 year after surgery.

Key words: *delirium; neurocognitive; perioperative.*

Introduction

Neurological complications and cognitive dysfunction are common in the perioperative period. They are the result of hypoperfusion of the brain, hypotension and hypoxia. These factors can cause changes in the brain tissue perfusion. The usage of neuroactive substances during the operative period can impair the neurological functions on subcellular level. Neuroinflammation is a key factor for developing neurological disorders. Operative trauma and the assosicated inflammatory response of the brain can initiate neuroinflammation, which is characterized

by the presences of microglial astrocytes cells and inflammatory cells. Biochemically, the two biomarkers that are connected to the brain damage are β-amyloid protein and intraneuronal neurofibrillary tangles (tau). Changes in their levels is a prediction for developing cognitive disorders. Neurocognitive disorders can last for a short period of time -days or long period of time - months or even years. They affect the quality of everyday living, affect the patient's sense of self-care and impact the socioeconomic stability, which sometimes can result in lethal outcome. As populations age, and the proportion of individuals undergoing surgery after 60 increases, neurocognitive disorders are becoming an important part of every society. The incidence of perioperative neurological complications is about 44 % in noncardiac operations. The percentage is higher in cardiac operations, especially in bypass operations. The term "Neurocognitive Disorders" (NCD) is used to describe the overall situation identified during the pre- and postoperative periods. Neurological complications can be classified as acute, de nuovo, or they can be a result of the decompensation of chronic neurological disease. Complications such as delirium, can occur 7 days after surgery, while the cognitive decline can last 30 days after and cause delayed neurocognitive recovery. Neurocognitive decline that exists 12 months after surgery is postoperative neurocognitive disorder.

Delirium is most common neurocognitive disorder with incidents of 25% in the perioperative period. Initially, it is manifested with confusion, loss of memory, problems with maintaining attention, and problems with understanding common sentences. Delirium can be presented in a hypoactive or a hyperactive form, or combined. Delirium has fluctuations during the day.

Risk factors related to neurocognitive disorders include age, previous NCDs, functional impairments, hearing impairments, comorbidity, high ASA score in perioperative disorders such as inadequately treated pain, fluid and food fasting, medications opioids, anticholinergic drugs, intraoperative depth of anesthesia management, blood loss, cerebral desaturation, hypotension, hypothermia. They also include the type and the duration of surgery, postoperative factors such as pain infections, prolonged ICU stay and ventilation, extended periods of opioid use, and anticholinergic drugs. Anticholinergic drugs can be categorized as anticholinergic drug with weak effect - score 1:Atenolol Codeine, Diazepam, Digoxin, Furosemide, Morphine, Prednisolone; drugs with medium effect - score 2 : Amantadine , Carbamazepine, Loperamide, Nefopam, Theophylline, Tramadol Amitriptyline, and drugs with strong effect - score 3 :Atropine, Chlorphenamine, Oxybutynin, Quetiapine, Solifenacin , Tolterodine. If the sum of the drug scores patients receive is higher than 3, it is likely that they can develop confusion in the perioperative period. The recommendation is patients to stop consumming alcohol two weeks prior the operation, detoxification. The use of the second generation of antipsychotic drugs such as dexmedetomidine, melatonin and gabapentin have a positive effect for treatment of delirium. Delirium prevention consists of preoperatively routine in therapy, exercise, cognitive stimulations, solid sleep routine, hydration and adequate nutrition. Intraoperative prevention consists of anesthetic technics for delirium prevention, such as the usage of the bi spectral index-BIS, entropy, NIRS, cerebral oxygen saturation monitoring, regional anesthesia, and reduced use of opioids. Ketamine and dexmedetomidine are recommended drugs for delirium prevention. In the postoperative period, delirium prevention consists of enhanced sleep and therapy routines, early mobility vision and hearing optimization, exercise, analgesia prevention of infections, and short stay at the ICU. For delirium monitoring, it is recommended to use the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) or Intensive Care Delirium Screening Checklist (ICDSC).

Postoperative cognitive dysfunction is cognitive dysfunction that last for more than 30 days. It is common among elderly patients but it can also occur in patients who have not underwent surgery. The main question is: is it a different clinical entity as it is very similar to delirium.

Neurological disorders

Stroke is not a very common neurological disorder, but it can have catastrophic consequences when it occurs. Therapy consists of thrombolysis, but it is a compromising technique in the postoperative period. One of the main risk factors is suffering from a recent stroke as the risk is 20 times higher to cause a perioperative stroke. It is recommended to stop oral anticoagulation therapy 48 to 72 hours before surgery, ad to stop administering clopidrogel 7 days before surgery. There is no need to stop the use of aspirin before surgery. If the stroke occurs postoperatively, then it is recommended to apply mechanical thrombectomy.

Patients with Parkinson's disease are in a higher risk of developing postoperative neurocognitive disorder. It is recommended that these patients take their therapy regularly. With signs of decompensation, such as difficulty in swallowing or rigid musculature, the symptoms can increase and the risk of aspirations during the intubation can also increase, while during the postoperative period, the muscle rigidity can affect the respiratory function. Patients with Parkinson's disease should be in optimal condition before the elective surgery. In nonelective surgery we should be aware of the risks of developing neuroleptic malignant syndrome during operation, hyperthermia with signs of muscle rigidity, difficulty in swallowing, malfunctioning of the autonomic nervous system , which can create increase in kinase that indicative of the possibility for a cardiac arrest, stroke, etc. These patients often exhibit signs of altered state of consciousness. Patient should receive therapy through a nasogastric tube or transdermal levodopa. A high possibility for the occurrence of neurocognitive disorder during the perioperative period is found among patients with myasthenia gravis. These patients should be in optimal condition and a perioperative examination is necessary if there are signs of bulbar syndrome, such as difficulty in swallowing, impairment of the speech, weakness of facial muscle. There is also a high risk of aspiration dyspnea and pneumonia. During the perioperative period, myasthenia gravis crises can occur, as well as bulbar syndrome. The level of acetylcholine receptors antibodies is higher than 100nmol/l. Medications that can worsen the situation are muscle relaxants, therefore, they should be applied with great conscience. We should be careful with aminoglycosides, macrolides, fluoroquinolones, glucocorticoids,β-adrenoceptor blocker and calcium channel blockers.

Conclusion

Neurocognitive disorders are common in elderly patients who have underwent surgery. Early diagnosis, preventing risk factors, implementing the strategies that can prevent, cure and optimize the patients' condition as soon as possible are imperative.

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REVIEW ARTICLE *UDK: 616-009.7-053.3*

MANEGMENT OF PAIN IN NEONATES, INFANTS AND SMALL CHILDREN

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Abstract

Effective pain management in neonates, infants, and young children is a critical clinical and ethical imperative. The immature yet functional nociceptive system in this population, characterized by underdeveloped inhibitory pathways and a tendency for wind-up hyperexcitability, means they experience pain intensely and are vulnerable to its detrimental short-term physiological effects and potential long-term neurodevelopmental sequelae. This review underscores the role of frequent, objective pain assessment using validated, age-appropriate tools to guide therapy. It advocates for a proactive, multimodal approach that integrates non-pharmacological interventions—such as sucrose, breastfeeding, skin-to-skin contact, and distraction—as first-line strategies. For more significant pain, a tailored pharmacological strategy is essential. This involves a stepped approach utilizing non-opioid analgesics (e.g., paracetamol, NSAIDs, metamizole), judicious opioid administration, and adjuncts like ketamine and dexmedetomidine. The paper highlights the importance of locoregional anesthetic techniques (e.g., caudal, epidural, and peripheral nerve blocks) in providing superior intraoperative and postoperative analgesia while minimizing systemic drug exposure. Dosing must account for profound age-related pharmacokinetic and pharmacodynamic differences. Ultimately, successful pediatric pain management requires a paradigm shift towards preemptive and multimodal analgesia, meticulous assessment, and interdisciplinary collaboration to ensure patient safety, alleviate suffering, and improve outcomes.

Key words: *multimodal analgesia, pediatric, postoperative analgesia,*

Introduction

Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." (1). For children who cannot verbally articulate this experience, this definition underscores the subjective nature of pain and the clinician's responsibility to infer its presence. Untreated pain in the pediatric population, particularly neonates, is not merely a matter of transient discomfort. It triggers a cascade of detrimental physiological stress responses, including cardiorespiratory effects such as hypertension, tachycardia, increased intracranial pressure, and desaturation; metabolic effects, such as catabolism, hyperglycemia, and lactic acidosis; suppression of immune function; and behavioral changes, such as sleep disturbances, feeding difficulties, and irritability. Furthermore, repeated painful experiences in early life can lead to altered pain perception, making children more sensitive to pain later in life, and can potentially contribute to long-term neurodevelopmental

impairments. (2) Therefore, proactive and effective pain management is a moral and clinical imperative to mitigate both short-term harm and long-term sequelae.

Neurophysiology of Pain in Children

Understanding pain processing in young children and youth is crucial for effective intervention. The nervous system of a neonate is immature but fully capable of transmitting nociceptive signals. (3)

- Nociception is intact: By the 24th gestational week the anatomical structures for pain transmission (peripheral receptors, spinal cord tracts, thalamus) are developed. However, the descending inhibitory pathways, which modulate and dampen pain signals, are underdeveloped until later in infancy. This results in a relative imbalance in which excitatory signals dominate, meaning that neonates may experience pain more diffusely and intensely than older individuals for a given stimulus.
- Wind-Up Phenomenon: Repeated painful stimuli can lead to "wind-up," a state of spinal cord hyperexcitability where the response to subsequent stimuli is amplified. This underscores the importance of pre-emptive analgesia.
- Pharmacokinetic and Pharmacodynamic Differences: Key differences profoundly impact drug dosing:
- Body Composition: Higher total body water and lower fat and muscle mass affect the volume of distribution for water-soluble (e.g., morphine) and lipid-soluble drugs.
- Hepatic Metabolism: Immature enzyme systems (e.g., cytochrome P450, glucuronidation) prolong the half-life of many drugs (e.g., morphine, midazolam).
- Renal Excretion: Lower glomerular filtration rate (GFR) delays the clearance of drugs and their active metabolites (e.g., morphine-6-glucuronide).
- Blood-Brain Barrier: More permeable in neonates, allowing greater drug penetration to the CNS and increasing the risk of toxicity.

Pain Assessment

Accurate assessment is the cornerstone of effective pain management. (4) Since self-report, the gold standard, is impossible in pre-verbal children, clinicians must rely on behavioral and physiological cues. Assessment must be done frequently, at least three times per day, documented, and used to guide therapy. Pain is considered a vital sign and is measured accordingly.

Pain Assessment Tools for Neonates and Infants

These tools combine behavioral and physiological indicators.

- Premature Infant Pain Profile (PIPP/PIPP-R): A well-validated tool for both preterm and term neonates. It scores seven indicators: gestational age, behavioral state, heart rate, oxygen saturation, brow bulge, eye squeeze, and nasolabial furrow. The total score characterizes pain as none, minimal, moderate, or severe.

- Neonatal Infant Pain Scale (NIPS): A simple, fast tool useful in clinical settings. It assesses facial expression, crying, breathing patterns, arm movements, and leg movements. Scores range from 0 (no pain) to 7 (maximum pain).
- FLACC Scale: The most widely used tool in children approximately 2 months to 7 years old. It scores five categories: Face, Legs, Activity, Crying, and Consolability. Each category is scored 0-10, for a total of 0 (no pain) to 10 (severe pain). A revised version (r-FLACC) allows parents to provide input on behaviors specific to their child (e.g., "my child grabs his ears when in pain").

Pain Assessment for Verbal Children

- Wong-Baker FACES Pain Rating Scale: For children as young as 3 years old. The child points to one of six faces that best represents their pain, from a smiling "no hurt" face to a crying "worst hurt" face.
- Visual Analog Scale (VAS) & Numeric Rating Scale (NRS): For older children (e.g., >8 years). The VAS is a 10 cm line where the left end is "no pain," and the right is "worst pain imaginable." The NRS asks the child to rate their pain from 0 (no pain) to 10 (worst pain).

Non-Pharmacological Management of Pain

Non-pharmacological interventions are effective, safe, and should be used as first-line for minor procedures and as adjuncts to medications for more significant pain. They provide comfort, reduce anxiety, and block pain transmission through competing sensory input.

Interventions for Neonates and Young Infants

- Sucrose/Breastfeeding: The most evidence-based intervention. Sweet-tasting solutions (24% sucrose or glucose) administered orally via pacifier or syringe 2 minutes before a procedure provide potent analgesia. The mechanism is believed to be the release of endogenous opioids. Breastfeeding is equally, if not more, effective, combining sucrose, skin-to-skin contact, sucking, and smell.
- Non-Nutritive Sucking (NNS): Providing a pacifier for sucking can have a calming and analgesic effect.
- Facilitated Tucking/Swaddling: Holding the infant contained in a flexed position (facilitated tucking) or swaddling provides comfort and promotes physiological stability.
- Kangaroo Care (Skin-to-Skin Contact): Placing the diaper-clad infant skin-to-skin on the parent's chest regulates heart rate, oxygen saturation, and reduces behavioral pain responses.

Interventions for Infants and Young Children

- Distraction is a powerful tool. It can include blowing bubbles, watching videos, listening to music, interactive toys, or using interactive apps.
- Parental Presence and Involvement: A parent's voice, touch, and presence are profoundly calming. Coaching parents to be actively involved (e.g., holding, singing, assisting with distraction) reduces the child's and the parent's anxiety.

- Other Techniques: For older children, guided imagery, deep breathing exercises ("blow out the birthday candles"), and hypnosis can be highly effective.

Pharmacological Therapy

When pain is anticipated to be more severe, pharmacological agents are necessary. The key principle is to use a multimodal approach and combine drugs from different classes (e.g., opioids, NSAIDs, local anesthetics) to target pain pathways synergistically (5,6). This allows the use of lower doses of each drug, minimizing side effects. Analgesics should be administered by the clock, on a scheduled basis, to maintain therapeutic levels and prevent "breakthrough" pain, rather than "as needed". We should also use preemptive analgesia, which means administering analgesia before a painful procedure (e.g., pre-operative analgesia) to prevent wind-up and reduce total analgesic requirement.

What is the anesthesiologist's responsibility? Is it just to cover the intraoperative needs for analgesia, or the whole perioperative period? The answer to these questions is to be provided by every institution itself, depending on many factors. However, close communication between the anesthesiologist, surgeon and pediatrician is necessary.

Let us divide the perioperative period for practical reasons of explaining analgesia.

1. *Preoperative.* This is usually administered as preemptive analgesia by itself or with premedication. Paracetamol 10-15 mg/kg per os or Ibuprofen 10mg/kg per os.
2. *Intraoperative.* After induction of anesthesia, the rectal route can be used to give paracetamol 40-60mg/kg or i.v 10-15 mg/kg, or metamizole i.v 10-15 mg/kg. Of course, the opioids are the mainstay in general anesthesia, and usually fentanyl is used 1-3mcg/kg, depending on the surgery, its length, the extubation plan, the child's condition, the surgeon's expertise, etc. Furthermore, morfium, sufentanyl and remifentanil can also be used. As an adjunct to the opioids, a dose of 0,5mg/kg i.v of ketamine is used.

Locoregional Anesthesia

The primary use of regional techniques in pediatric anesthesia has been to supplement and reduce the requirement for general anesthetics and to provide better postoperative pain management. Blocks range in complexity from relatively simple peripheral nerve blocks (e.g., penile block, ilioinguinal block); to brachial plexus block, sciatic nerve block, femoral nerve block, and TAP (transversus abdominis plane) block; to central blocks (e.g., spinal or epidural techniques). Regional blocks in children (as in adults) are often facilitated by ultrasound guidance, and less commonly by nerve stimulation.

Spinal anesthesia is a safe and valuable technique in infants and children, particularly ex-premature babies, undergoing short lower abdominal or urological surgeries. Its key benefit is reducing life-threatening respiratory complications associated with general anesthesia. Dosing is primarily based on **milligrams per kilogram (mg/kg)** of body weight, not on a fixed volume. Infants and children usually experience minimal hypotension from sympathectomy.

Table 1. Dosage of local anesthetic in spinal anesthesia

Age Group	Typical Weight Range	Recommended Dose (mg/kg) of Isobaric Bupivacaine 0.5%
Preterm & Term Neonates	2 - 5 kg	1,0 mg/kg (0,2ml/kg)
Infants	5 - 15 kg	0,4 mg/kg (0,08ml/kg)
Children (>6 months - 5 years)	>15 kg	0.3 mg/kg, max 5-6mg (0,06ml/kg)

According to Update in Anesthesia. Paediatric spinal anaesthesia. Rachel Troncin and Christophe Dadure

Caudal blocks are reportedly useful after a variety of operations, including circumcision, inguinal herniorrhaphy, hypospadias repair, anal surgery, clubfoot repair, and other subumbilical procedures. Contraindications include infection around the sacral hiatus, coagulopathy, or anatomical abnormalities. The patient is usually lightly anesthetized or sedated and placed in the lateral position. For pediatric caudal anesthesia, 22-gauge needles are used. If the loss-of-resistance technique is applied, the syringe should be filled with saline rather than air, because of the latter's possible association with air embolism. After the characteristic "pop" that signals penetration of the sacrococcygeal membrane, the angle of the needle is reduced, and the needle is inserted only a few millimeters further to avoid entering the dural space or the anterior body of the sacrum. Aspiration is used to detect blood or cerebrospinal fluid. The local anesthetic can then be injected slowly. Failure of a 2-mL test dose of local anesthetic with epinephrine (1:200,000) to produce tachycardia helps to rule out intravascular placement. The most commonly used anesthetics are 0.125% to 0.25% bupivacaine or 0.2% ropivacaine. Morphine sulfate (25 mcg/kg) can be added to the local anesthetic solution to prolong the period of postoperative analgesia in inpatients, but this will increase the risk of delayed postoperative respiratory depression. The required volume of local anesthetic depends on the desired block level, ranging from 0.5 mL/kg for a sacral block to 1.25 mL/kg for a midthoracic block. Single injections usually last 4 to 12 hours. Placement of 20G caudal catheters with continuous infusion of a local anesthetic (e.g., 0.125% bupivacaine or 0.1% ropivacaine at 0.2–0.4 mg/kg/h) or opioid (e.g., fentanyl, 2 mcg/mL at 0.6 mcg/kg/h) allows for prolonged anesthesia and postoperative analgesia. Complications are rare but include local anesthetic toxicity from elevated blood concentrations (e.g., convulsions, hypotension, arrhythmias), spinal block, and respiratory depression. Urinary incontinence is not a problem after a single dose of caudal anesthesia. Lumbar and thoracic epidural catheters can be placed in anesthetized children using a standard midline loss-of-resistance technique or paramedial access. In young children, caudal epidural catheters can be brought into the thoracic position with the tip localized radiographically. Unilateral TAP blocks are most commonly used to provide analgesia after hernia repair. Bilateral TAP blocks can be used to provide effective postoperative analgesia after abdominal surgery where a lower midline incision was made.

3. Postoperative analgesia

Due to practical reasons, we are going to divide postoperative pain management in the PACU room and on the ward. In the PACU room, adequate monitoring allows the use of stronger analgesics and, on the ward, we should be very careful in administering them.

In the PACU room.

We usually give intravenous analgesics, such as: metamizole 10-15mg/kg, fentanyl 0,5-1mcg/kg, morfium 0,025-0,1 mg/kg, tramadol 1-1,5mg/kg and ketamine 0,5mg/kg.

On the ward Paracetamol, metamizole and NSAIDs (nonsteroidal anti-inflammatory drugs) (Table 1) are the first choice drugs for the treatment of postoperative pain (7,8) On the day of surgery, they are usually administered intravenously, and then when the child begins to take fluids and food, the drug is switched to enteral form. For more severe postoperative pain, opioid analgesics are used in the form of boluses or continuous intravenous infusion, but they are not recommended without adequate monitoring of their side effects.

Table 2. Example of a guideline for prescribing analgesia in children

	Dosage Suggestions
Oral NSAIDs	
Ibuprofen	10 mg kg−1 every 8 h
Diclofenac	1 mg kg−1 every 8 h
Rectal paracetamol	
Paracetamol	20–40 mg kg−1 (15 mg kg−1 if< 10 kg) Single loading dose in association with anesthesia; the higher dose is due to poor bioavailability from rectal route of administration
Oral paracetamol	
Paracetamol	10 to 15 mg kg−1 every 6 h (max daily dose: 60 mg/kg)
Intravenous paracetamol	
Paracetamol	loading dose: 15–20 mg kg−1 (Intravenous preparation: 10 mg ml−1) 10–15 mg kg−1 every 6–8 hours
Intraoperative Opioids depending on age of the patient and the type of procedure	
Fentanyl	1–2 micrograms kg−1
Morphine	25 to 100 micrograms kg−1 depending on age, titrated to effect
Sufentanil	0.5–1 micrograms kg−1 bolus, continuous infusion of 0.5–1 micrograms kg−1 h−1
Remifentanil	0.05 to 0.3 micrograms kg−1 min−1
Intraoperative use of Ketamine/S-Ketamine	
Ketamine	0.5 mg kg−1 may be used as adjunct to intraoperative opioids, consider reduced dose (0.25–0,5 mg kg−1) when using S-ketamine, followed by continuous infusion of 0.1 – 0.2 mg kg−1 h−1 (max: 0.4 mg kg−1 h−1) is optional

	Dosage Suggestions
Intraoperative use of Co-analgesic Drugs	
Lidocaine	intravenous bolus: 1.5 mg kg−1, continuous infusion 1.5 mg/ kg−1 h−1 until the end of the procedure
Methylprednisolone	1 mg kg−1
Dexamethasone	0.15−0.25 mg kg−1 (max: 0.5 mg kg−1)
Clonidine	intravenous bolus: 1−3 micrograms kg−1
Dexmedetomidine	intravenous bolus: 0.5−1 micrograms kg−1, continuous infusion 0.2−0.7 micrograms kg−1 h−1 until the end of the procedure
Intraoperative/postoperative intravenous Metamizole	
Metamizole	10 to 15 mg kg−1every 8 h 2.5 mg kg−1 h−1 (continuous infusion following an intraoperative loading dose) (Due to the risk of agranulocytosis after long-term use metamizole is recommended for short term postoperative use in a hospital setting only)
Intravenous analgesics for breakthrough pain in PACU depending on age and procedure	
Fentanyl	0.5 to 1.0 micrograms kg−1, titrated to effect
Morphine	25 to 100 micrograms kg−1 depending on age, titrated to effect
Tramadol	1 to 1.5 mg kg−1, titrated to effect
Ketamine/S-Ketamine	0.5 mg kg−1, titrated to effect consider reduced dose (0.25−0.5 mg kg−1) when using S-ketamine,
Intravenous analgesics for breakthrough pain in the ward, including adequate monitoring	
Tramadol	1 to 1.5 mg kg−1, every 4−6 hours
Morphine	< 3 months 25−50 micrograms kg−1, every 4−6 hours 3−12 months 50−100 micrograms kg−1, every 4−6 hours 1−5 years 100−150 micrograms kg−1, every 4−6 hours 5−18 years 150−200 micrograms kg−1, every 4−6 hours single dose adjusted according to response
Metamizole	10 to 15 mg kg−1 every 8 h
Oral analgesics for breakthrough pain in the ward	
Tramadol	1−1.5 mg kg−1, every 4−6 hours
Metamizole	10 mg kg−1every 8 h
Morphine	When changing from intravenous to oral administration, the daily dose should be increased by 2−3 times due to lower bioavailability. <3 months 50−100 micrograms kg−1, every 4−6 hours 3−12 months 100−150 micrograms kg−1, every 4−6 hours 1−5 years 150−200 micrograms kg−1, every 4−6 hours 5−18 years 200−300 micrograms kg−1, (max10 mg) every 4−6 hours single dose adjusted according to response

	Dosage Suggestions antiemetic drugs	
Dexamethasone	0.15 mg kg−1 every 12 h	
Ondansetron	0.15 mg kg−1 every 8 h	not to be combined with tramadol
Metoclopramide	0.1 mg kg−1 every 8 h	not to be combined with tramadol; not if <1y old

Taken and modified from Vittinghoff M, Lönnqvist PA Postoperative Pain Management in children: guidance from the Pain Committee of the European Society for Paediatric Anaesthesiology (ESPA Pain Management Ladder Initiative) Part II. Anaesth Crit Care Pain Med. 2024

Conclusion

The management of pain in neonates, infants, and children is a complex but achievable goal. It requires a paradigm shift from reactive to proactive care. Clinicians must **understand** the unique neurophysiology of pain in development, **utilize** validated, age-appropriate pain assessment tools, **use a multimodal strategy** that combines non-pharmacological comfort measures with a stepped pharmacological approach, and **tailoring** every plan to the individual child, their specific context, and the type of pain anticipated.

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REVIEW ARTICLE *UDK: 616.893-089.168*

POSTOPERATIVE DELIRIUM: WHAT HAPPENS AND HOW CAN THE ANESTHESIOLOGISTS PREVENT IT?

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Abstract

Perioperative neurological complications pose a significant challenge in modern anesthesiology, as they represent a major source of morbidity, affecting quality of life, threatening patients' long-term survival, and increasing healthcare resource utilization. A perioperative neurological complication is any new injury or damage to the nervous system that occurs during anesthesia or surgery, including symptoms such as stroke, confusion, or nerve damage. Perioperative cognitive disorders like delirium and postoperative cognitive dysfunction (POCD) are important; however, toften go unnoticed. Routine monitoring during the perioperative period is not standard practice in general, except for specific procedures. Prevention, early detection, and multidisciplinary management are crucial for effectively reducing the incidence of these complications and improving patient outcomes.

Key Words: *confusion, delirium, perioperative neurological complications.*

Introduction

Delirium is one of the most significant neurological complications that occur after surgery and anesthesia, because it is common and affects up to 70% of patients over 60 who undergo major hospital surgeries. Delirium is associated with adverse outcomes such as an increased risk of death, ongoing cognitive decline, longer stays in intensive care unit, extended hospitalizations, and a higher likelihood of institutionalization. Postoperative delirium (POD) can occur in patients of any age, from children to the elderly. Older patients are considered at greater risk due to factors such as pre- existing cognitive impairment, additional health conditions, multiple medications, sensory deficits, malnutrition, reduced functional status, and frailty, which tend to accumulate and overlap with aging (1-6). Postoperative delirium is an acute neurocognitive disorder that usually occurs within the first few days after surgery and anesthesia. It is characterized by impaired attention, disorganized thinking, and altered consciousness with a fluctuating course (7,8). POD typically develops 24 to 72 hours after surgery in the hospital ward; it can occur immediately after anesthesia in the recovery room, or may be present upon admission to the intensive care unit. Agitation refers to delirium that occurs immediately following anesthesia. Clinically, delirium can manifest as hyperactive (agitated, aggressive, and combative), hypoactive (decreased alertness and motor activity, with anhedonia), or mixed (showing both hyperactive and hypoactive symptoms). Among these subtypes, hypoactive delirium may be associated with a worse prognosis (9). The 2024 update of the European Society of Anaesthesiology and

Intensive Care (ESAIC) guidelines includes significant advances in understanding, preventing, and managing POD (10). The essential skills for physicians involved in perioperative patient care include identifying high-risk patients, promptly diagnosing postoperative delirium (POD), and effectively managing patients with POD. Delirium as an indicator of healthcare quality for geriatric patients has been incorporated into the patient safety agenda (11,12,13).

Risk Factors and Pathophysiology

The multifactorial model of delirium explains how patients with an underlying susceptibility or vulnerability are exposed to one or more precipitating factors, including perioperative injuries that can lead to delirium. Risk factors are varied and include patients aged 60 years and older (since older patients are at higher risk as predisposing factors accumulate and overlap with aging), the presence of multiple comorbidities (such as anemia, low ejection fraction, carotid artery stenosis, or high serum creatinine levels), functional disability, and pre-existing cognitive impairment. During the perioperative period, the precipitating factors include the surgical procedure itself (considering duration, complexity, and invasiveness) and anesthesia; however, it is unclear whether the choice of anesthetic significantly impacts the development of delirium. Other perioperative precipitating factors include exposure to sedatives, especially benzodiazepines, poorly managed postoperative pain, prolonged stays in the intensive care unit, and postoperative complications (14,15).

The pathogenesis of POD is not fully understood; however, numerous studies offer evidence on the underlying processes of this complex clinical syndrome. Potential mechanisms can be categorized into two groups: neuroinflammation and oxidative stress, which likely interact by promoting neurotransmitter imbalance and neuronal network dysfunction. Several harmful stimuli, such as surgical stress and/or infection, activate the inflammatory cascade, leading to the rapid release of inflammatory mediators into the bloodstream. Inflammation and other factors can weaken the blood-brain barrier, allowing inflammatory mediators and other harmful substances to enter the brain, thereby inducing the activation of brain parenchymal cells (microglia and astrocytes) and the production of proinflammatory cytokines and mediators. These neuroinflammatory changes cause neuronal and synaptic dysfunction, leading to the emergence of neurobehavioral and cognitive symptoms (16,17,18). The oxidative stress hypothesis suggests that during surgery and anesthesia, especially during periods of impaired perfusion and reperfusion, reactive oxygen species (ROS) are rapidly generated. These molecules cause excitotoxicity, apoptosis, and local inflammation. Acetylcholine deficiency is widely recognized as a mechanism, as its synthesis is sensitive to low oxygen levels resulting from systemic inflammation and microcirculatory dysfunction. Dopamine and other neurotransmitter systems are also impacted by the inflammatory process (16,19,20).

Genetic Predisposition

Individual genetic factors may also influence susceptibility to postoperative delirium. Polymorphisms in genes encoding for cytokines, neurotransmitter receptors, and other molecules involved in the inflammatory response and neuronal function may predispose certain individuals to develop delirium. The association between postoperative delirium and polymorphisms in apolipoprotein genes has been an area of research in recent years. Apolipoprotein E (ApoE) is a

protein that supports recovery in the central nervous system (CNS) after injury. It is essential for maintaining normal neuronal function by facilitating cholesterol transport and promoting cell repair. Three ApoE isoforms—E2, E3, and E4—result from different variants of the apolipoprotein E gene. Among them, ApoE4 is more prone to degradation, which limits the mobilization of lipids needed for tissue repair (21,22). The ε4 allele of the apolipoprotein E gene has been hypothesized as a genetic risk factor for delirium (23,24). The results of our study "Does the apolipoprotein E genotype increase the risk of postoperative delirium in adult patients?" indicate an association between the apolipoprotein E gene polymorphism containing the minor allele e4 and postoperative delirium in this group of adult patients. To reach more valid conclusions a larger patient group is necessary (25).

Screening and Diagnosis

For the preoperative assessment of cognitive function, tools such as the Mini-Mental State Examination (MMSE), the MoCA, and the Mini-Cog are commonly used (26). The Mini-Cog is comprised of two parts: remembering three words (e.g., apple, table, money) and drawing a clock. The patient is asked to draw a clock showing a specific time (e.g., 11:10), then repeat the three words. If they correctly recall the words and draw the clock accurately, the cognitive function is considered normal. If they have difficulties, then mild cognitive impairment or dementia may be present (additional tests are needed). The test takes 3–5 minutes and is commonly administered to older adults. Unfortunately, daily POD screening is not yet routinely performed for all surgical patients, likely due to misconceptions that it is difficult and time-consuming (27).

The diagnosis of delirium relies on history, physical examination, laboratory tests, and imaging studies. Use validated tools such as CAM and Nu-DESC daily for first three postoperative days, beginning in the recovery room. The most commonly used tool for non-psychiatric staff to identify delirium is the Confusion Assessment Method (CAM), which was developed based on criteria adapted from DSM-V. The CAM has higher specificity (89%) and sensitivity (94%) than assessments by geriatric psychiatrists (28,29). It includes 10 items: fluctuating course, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, psychomotor agitation, psychomotor retardation, and sleep-wake disturbances, each scored as 0 (absent), 1 (present or mild), or 2 (severe).

Prevention and Treatment

There is not enough evidence to recommend a specific anesthetic, including whether to use general anesthesia, conscious sedation, or regional anesthesia. It is also unclear whether neuraxial anesthesia reduces the risk of delirium compared to general anesthesia. The BIS monitor helps guide the adjustment of anesthetic drugs. A target value between 40 and 60 for general anesthesia is considered ideal, helping to prevent excessively deep anesthesia. Benzodiazepines have been associated with the development of delirium, with midazolam exposure identified as a risk factor for delirium in surgical and ICU patients. Routine use of benzodiazepine premedication should be discouraged, except in cases of prior severe anxiety or withdrawal from benzodiazepines or alcohol. Prophylactically administered subanesthetic doses of ketamine and dexmedetomidine have shown benefits in reducing delirium. Appropriate multimodal pain management should be implemented, and prolonged fasting and dehydration should be avoided (10).

Non-pharmacological strategies to reduce postoperative delirium include providing orientation (e.g., with a clock or communication), using visual and auditory aids, minimizing noise and promoting sleep, avoiding unnecessary catheterization, encouraging early mobilization, and supporting early feeding. In addition to staff care, family members or close friends can play a vital role in managing a patient's symptoms.

Pharmacological treatment should only be initiated to improve patient safety if non-pharmacological measures fail. The use of low-dose haloperidol or low-dose atypical neuroleptics is recommended for treating POD. Low-dose haloperidol usually starts at 0.25 mg and is gradually increased to a maximum of 3.5 mg. Doses exceeding 6 mg per day should be avoided. Careful patient monitoring is essential, not only to assess effectiveness, but also to detect side effects. Haloperidol is linked to an increased risk of Q-T interval prolongation, so ECG monitoring is advised. Regarding the use of antipsychotics for treating delirium, current guidelines recommend using the "lowest effective dose" for the shortest necessary duration and only after non-pharmacological interventions have failed (10,30).

Conclusion

Postoperative delirium can only be prevented through proactive, patient-specific, multidisciplinary interventions. Clinicians must prioritize early screening, create personalized care plans, and establish effective team communication to reduce the incidence of POD and improve surgical outcomes. The anesthesiologist plays a crucial role. Our responsibility does not end with a successful surgery. A positive outcome depends on compassionate care, effective communication with the family, early detection of risk, and active prevention and treatment of delirium. The way we care for our most vulnerable patients demonstrates the true value of our profession and health system maturity.

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REVIEW ARTICLE *UDK: 616-089.168/.17*

OPTIMIZING POSTOPERATIVE ANALGESIA IN ENCHANCED RECOVERY AFTER SURGERY THE ERAS PROTOCOL

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Abstract

Due to its capacity to reduce morbidity, shorten the length of hospital stay and lower costs, enhanced recovery after surgery has become the standard of care in various surgical procedures, while having no negative impact on readmission rates or mortality.

The main objectives of enhanced recovery after surgery are: reducing complications, length of hospital stay and new readmissions, reducing variability of care and costs. This kind of care is patient-focused, outcome-driven, standardized, evidence-based and interdisciplinary. The main recommendations provided by the Enhanced Recovery after Surgery Society are based on quality of evidence and are categorized in the following way: high, moderate, low and very low; whereas its guidelines are divided into 3 groups: preoperative, intraoperative and postoperative.

The pathways of enhanced recovery after surgery offer safe and cost-effective approaches to perioperative care, which improve patient outcomes without increasing rates of complications.

Keywords: *Enhanced recovery after surgery, complications, evidence-based.*

Introduction

Enhanced recovery after surgery (ERAS) has become the standard of care across various surgical procedures due to its ability to reduce morbidity, shorten the length of stay (LOS), and lower costs, while having no negative impact on readmission rates or mortality (1). But even in modern-day surgery, there are still dogmas in everyday practice. We ask ourselves what is dogma? The term /ˈdɒgmə/ *noun* refers to 'a principle or set of principles laid down by an authority as incontrovertibly true,' applies to certain strong beliefs whose adherents are not willing to rationally discuss them. Therefore, how can we identify dogmas in general surgery? The answer: in preoperative prolonged fasting, mechanical bowl preparation (MBP), nasogastric tube insertion (NGT), drains and prolonged bed rest. The solution? The evidence always trumps dogma. The ERAS protocols were first introduced in the 1990's, by Dr. Henrik Kehlet, a Danish surgical gastroenterologist (2). His patient-centered, evidence-based, outcome-driven, multidisciplinary team developed pathways for surgical specialties and facility environment to maintain preoperative organ function and reduce the profound stress response following surgery, as well as to optimize their physiologic function, and facilitate recovery. The goal was fast-track surgery. These recommendations form an integrated continuum, as the patient moves from home through the prehospital/preadmission stage, following the preoperative, intraoperative, and postoperative

phases of surgery and home again (2).

The main objectives of ERAS are: reducing complications and LOS and new readmissions, reducing variability, reducing costs, improving quality of care, and increasing value = quality/cost (3). What is the main difference between traditional care vs ERAS care? The traditional care is provider-focused, has high variability, and physician-driven. On the other hand, the ERAS care is patient-focused, outcome-driven, standardized, evidence-based and interdisciplinary. The main ERAS recommendations are based on the quality of evidence and can be categorized as: high, moderate, low and very low. The guidelines in the ERAS protocol are divided in 3 groups: preoperative, intraoperative, and postoperative. The preoperative guidelines include: patient information, optimization of preexisting medical conditions, adequate nutrition and fasting time, carbohydrate intake prior to surgery, pre-anesthetic medication and anti-thrombotic prophylaxis. The intraoperative guidelines include: antimicrobial prophylaxis, multimodal anesthesia, adequate approach for preventing postoperative nausea and vomitus (PONV), optimal fluid therapy and prevention of hypothermia; whereas the postoperative guidelines include: fluid management, postoperative glycemic control, adequate postoperative nutrition, early mobilization, rapid hydration and nourishment, appropriate intravenous therapy, early catheter removal, regular oral anesthesia, and avoiding opiates (4).

In terms of the patient information, the preadmission understanding of the surgery and treatment-related implications, as well as counselling to reduce the patient's fear and anxiety and to improve the postoperative wound healing, perioperative nourishment, mobilization and pain control are of utmost importance. Thoug evidence may be week, the ERAS protocols pay great attention to these recommendations.

In terms of medical optimization, the most important preexisting conditions that must be taken into consideration are smoking habits, and alcohol and drugs consumption. Do they make any difference? And when should the patient quit these habits prior to the surgery? Yes, they definitively do. Alcohol and smoking consumption should be halted 4 weeks prior surgery (5,6).

Patients' nutrition is significantly important as it is a common ground that impaired physiological performance in malnutrition can alter the body fluid dislocation, muscle strength, healing of the wound itself, and immune deficiency. Poor wound healing, increased volume for drug distribution, possible respiratory infections, suture dehiscence and ineffective complications lead to an increased intra-hospital mortality rate. Therefore, the question is who should receive preoperative nutrition support? It should always be the moderately and severely malnourished patients. In terms of elective surgical procedures, the nutrition support should be administered 7 to 10 days prior surgery; while the enteral route is preferred when possible, combined with postoperative nutrition and immune-enhanced formulas. The fasting time prior to surgery in standard practice is from midnight on the day before. The goal is to reduce the volume and acidity of the stomach content and decrease the risk of pulmonary aspiration. However, the Cochrane review of 22 RCTs, fasting from midnight showed no reduction in gastric content and no rise in pH of gastric fluid (7). On the contrary, it demonstrated that this kind of fasting challenges the normal physiology, and offers no guarantee of an empty stomach. Prolonged fasting carries a risk of dehydratation, hypotension when administering anesthesia, which increased the need for more fluids, while the end result is fluid overload. The ERAS guidelines are clear: light preoperative food intake 6 hours and clear fluids 2 hours prior surgery that lead to less intravenous fluid demand and improved outcomes.

In regard to surgical stress, it is well known that it increases with insulin resistance. That's why undergoing a carbohydrate treatment prior to surgery is important: 20% glucose IV or a 12.5% carbohydrate drink (400 ml) 2h before anesthesia + 800 ml in the evening before. The effects of preoperative carbon hydration are: reducing the metabolic stress of surgery, reducing insulin resistance, improving pre-/postoperative wellbeing and postoperative muscle function, reducing lean body mass losses, and faster recovery (3,4).

The preanesthetic medication and antimicrobial prophylaxis are imperative in reducing the risk of surgical infections. The optimal time is 30-60 minutes before the incision, while repeated doses should be administered during prolonged procedures (≥3h)/Massive blood loss/fluid loading through intravenous route, with a spectrum covering the suspected pathogens (aerobic ± anaerobic bacteria)(3,4).

In addition to the preoperative guidelines of the ERAS protocol, the anti-thrombotic prophylaxis is very important because of the risk od deep vein thrombosis in 30% and pulonary embolisam in 1% of the patients undergoing major surgery. This prophylaxis could be mechanical (compression stocking with intermitent pneumatic compression) or pharmacological (low molecule weight of heparin LMWH administrated 2 hours before surgery) (8).

The intraoperative guidelines of the anesthesia protocal should focus as much as possible on regional anesthesia, considering the reduced postoperarive use of opiates, quicker awakening and early enteral intake and mobilization. The use of multimodal and regional analgesia is superior to opioids (epidural analgesia, i/v analgesia, wound catheters/infiltration and peripheral blocks) (9).

Another intraoperative component that should be prevented when possible is PONV. The risk factors include: female patients, non smokers, motion sickness desease, volatile anesthetics, intravenous opioids and nitrous oxide. The prevention incorporates multimodal approach consisting of pharmacological and non-pharmacological techniques: total intravenous anesthesia TIVA, minimal fasting, carbonchydrate loading, adequate hydratation, regional anesthesia and non steroid inflamatory drugs NSAID (10).

Intraoperative fluid management is an art of medicine. Based on personal judgments, it is vital in terms of the postoperative outcome. In different patients, the fluid requirements vary; therefore, the fluid shifts should be minimized. This is the reason why fluid administration should be goal-directed. The type of preferred fluid is balanced isotonic crystalloid solutions, and they should be discontinued as soon as possible. Vasopressors are indicated in hypotensive normovolemic patients (11).

When we discuss hypothermia prophylaxis, we should define the term hypothermia-central temperature < 36 C. Risk factors include: wound infections, prolonged cicatrisation, cardiac events, shivering that increases O2 consumption, bleeding, coagulation disorders, trombocites dysfunction, postoperative ileus, increased pain, prolonged emergence time, etc.

Preventive methods for hypothermia: warming devices (forced air warming blankets), warmed intravenous fluids, warm gases in laparoscopic surgery (12).

According to the ERAS protocols, postoperative analgesia is the principal and significantly most important part of the puzzle. The goal is to achieve effective pain relief with optimal analgesia. This is important in the reduction of cardiovascular, cognitive, endocrino-metabolic complications in all patients, decreasing the risk of chronic pain, allowing early mobilisation and early

return of gut function and feeding. The preferred analgesia techniques are: multimodal analgesia with avoidance of intravenous pioids, regional anesthesia techniques, thoracic epidural analgesia (TEA), spinal analgesia, local anesthetic techniques, transversus abdominis plane (TAP) block, etc. The analgesic regimen is specific to the type of surgery/incision. The effect of opioid sparing is: reduction in PONV, POI, sedation, and respiratory depression. Drugs of choice are: paracetamol and NSAIDS, lidocaine, and dexmedetomidine infusion (13).

Postoperative fluid management, the same as in the intraoperative setting, should also be goal-oriented (11).

In the postoperative phase of the treatment, the control of insulin resistance is key for successful pain management. Despite the traditional belief that hyperglycemia in the acutely stressed patient is "not dangerous", all glucose levels > 11mmol/L should be treated (14).

Despite the low to moderate risk of womiting, early enteral nutrition postoperatively is highly recommended because it can lower the rate of dehiscence, as well as the rate of infections, pneumonia, and intra-abdominal abscess (15).

Early mobilization is a crucial component of the enhanced recovery after surgery (ERAS) pathways. It can counteract the adverse physiological consequences of surgical stress and immobilization. It reduces the risk of postoperative complications, accelerates the recovery of functional walking capacity, positively impacts patient-reported outcomes and reduces hospital stay, thereby reducing care costs (16).

Enhanced recovery as a main concept in 'fast-track' surgical recovery may be seen as a resistance to the traditional patient-centered approach, which is fundamental to modern healthcare. The perception that ERAS protocols are rushing patient care is certainly not the case, as ERAS has been proven to reduce mortality and complication rates, and lower the overall costs of care. In Dai et al.'s study about the Whipple procedure, the ERAS group demonstrated: lower morbidity rate than the conventional group (50% vs. 90.8%; P¼0.00), fewer issues of delayed gastric emptying compared to conventional care patients (0 vs. 11.2%; P¼0.011), reduced incidence of pancreatic fistula – grade B, C – than conventional care (14.7 vs. 30.6%; P¼0.018) (17). Kobayashi et al. also demonstrated the value of ERAS in reducing complications after surgery, this time related to liver resection, with different complexity grades: grade I, low; grade II, intermediate; and grade III, high complexity. The study included 437 patients and it found that not applying the ERAS protocol was a significant predictor of postoperative complications for every complexity grade (18). Between 2019 and 2020, Shen et al. studied benign hysterectomy in 475 women. Their results showed that compliance with ERAS resulted in significant reductions in postoperative complications, with rates of 20.4% vs. 41.2% vs. 38.1% for groups I, II and III, respectively. Early removal of the urinary drainage and early mobilization and oral nutrition can be significantly associated with fewer complications after surgery (19). Zhou et al's laparoscopic bariatric surgery of patients with applied ERAS protocols and those with conventional care once again demonstrated the wisdom of ERAS implementation across the surgical spectrum. Overall, 435 patients were included, 198 of whom were included in the conventional group and 237 patients in the ERAS cohort, resulting in a significant reduction of complications in the ERAS group (2.1% vs. 8.6%; P<0.01) (20).

ERAS pathways offer safe and cost-effective approaches to perioperative care, which improve patient outcomes without increasing the rates of complication. Since the inception of ERAS in

1997, so-called 'fast-track' surgical pathways have become widely used in multiple specialties, and the standard of perioperative care has improved substantially, in no small share, due to the work of the ERAS Society. Key advancements have been made, including preoperative carbohydrate loading, patient education and early enteral nutrition.

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REVIEW ARTICLE *UDK: 616.833.34-089.5-053.2*

ULTRASOUND-GUIDED REGIONAL ANESTHESIA IN PEDIATRIC POPULATION WITH FOCUS ON UPPER EXTREMITY NERVE BLOCKS

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Abstract

Postoperative pain management in children is quite challenging. There are numerous benefits from regional anesthesia as a part of multimodal anesthesia protocols, while failure to achieve postoperative pain control in children can cause delay in physical healing and psychological effects in the long term, such as sleep disorders, anxiety, and chronic pain. Anatomical, physiological, and pharmacological differences between adults and the pediatric population should be understood before performing regional anesthesia in children.

In the past two decades, relying on ultrasound guidance, the regional anesthesia in pediatric patients of any age has seen significant development and evolved to the point of setting a new standard. This review is based on studies, guidelines, and peer-reviewed articles focusing on pediatric regional anesthesia in current literature. This review includes descriptions and illustrations of the relevant sonoanatomy of brachial plexus on different levels, ultrasound probe positioning, surgical indications, and associated potential complications. The aim of this review hopefully, is to serve as a foundation for a better understanding of the block techniques of the upper extremity, with their clinical indications, as well as to facilitate improved perioperative pain management in children.

Key words: *pediatric regional anesthesia, brachial plexus blocks, ultrasound–guided.*

Introduction

Postoperative pain management in pediatric patients continues to be a significant challenge (1). Insufficient pain control may be explained by "the fear" of opioid use or inadequate analgesic use (2). The use of regional anesthesia in perioperative pain management for pediatric patients can become standardized in terms of analgesic use (3). The benefits from regional anesthesia include: lower rate of opioid complications such as respiratory depression (4,5) and decreased gastrointestinal mobility (6) or immune depression; reduced postoperative pain score; lower rate of postoperative nausea and vomiting; protective effect in reducing surgical stress and early discharge after surgery (7). Failure to achieve postoperative pain control in children can also cause delay in physical healing and psychological effects in the long term, such as sleep disorders, anxiety, and chronic pain (8). Regional anesthesia in infants improves hemodynamic stability, decreases catecholamine production, the metabolic stress response to surgery, the inci-

dence of postoperative respiratory complications and indorses a fast return of gut function and feeding (9).

In the early 1980s, Dalens had established the first pediatric regional anesthesia teaching program in France; nevertheless its role in the pediatric anesthetic practice was boosted with the use of ultrasound (10). In 1994, Kapral and colleagues, published the first report of the use of ultrasound in regional anesthesia in adults (11). A few years later, its first application in regional anesthesia in pediatric population was reported (12). In the past two decades, relying on ultrasound guidance on the regional anesthesia in pediatric patients of any age has seen significant development and evolved to the point of setting a new standard (13,14).

This review is based on studies, guidelines and peer-reviewed articles focusing on pediatric regional anesthesia in current literature. The literature search included terms such as "pediatric regional anesthesia," "ultrasound-guided peripheral nerve blocks," "postoperative pain," with an emphasis on "upper extremity peripheral nerve blocks". To create a comprehensive narrative review of ultrasound-guided regional anesthesia used in upper extremity pediatric surgeries, a targeted literature search was conducted using PubMed, Google Scholar and Embase, focused on English-language studies addressing the safety, efficacy, and technical aspects of these techniques in pediatric patients. This review includes descriptions and illustrations of the relevant sonoanatomy of the brachial plexus at different levels. The illustrations are created by the author of this review. The sonoanatomy images were obtained using a portable ultrasound unit (Simens, Acuson P500) with linear probe, frequently used in the author's institution for pediatric ultrasound-guided regional anesthesia. The aim of this review hopefully, is to serve as a foundation for better understanding upper extremity block techniques and clinical indications, and to facilitate improved perioperative pain management in children.

Differences Between Children and Adults

Neonates and infants have anatomical, physiological, and pharmacokinetic differences from older children and adults. The key anatomical differences include: smaller superficial nerves, vessels and tendons that lie closer together in young children. Their nerves have shorter diameter with incomplete myelination whose completion may take several years. Also, the endothelium has less connective tissue. These are the reasons why the onset of blockade is faster and the duration of regional anesthesia is usually shorter in younger children than in adults. In physiological and pharmacological aspects, infants have increased systemic absorption and accumulation of local anesthetics due to their increased cardiac output and immature hepatic function with larger distribution volumes, longer half-lives, and reduced protein binding of local anesthetics than in adults. Hepatic metabolism of local anesthetics fully matures by 9 months of age. A relatively high proportion of cardiac sodium-gated channels are in an open state, with a high affinity to local anesthetics. The main proteins to which local anesthetics bind are α1-acid glycoprotein and albumin, and their concentration is reduced by the first year of age. Therefore, the main reason for local anesthetic systemic toxicity (LAST) is the high dose of the free and hence pharmacologically active fraction of any local anesthetic (15). The risk of drug accumulation rises when a continuous infusion or multiple injections are used (16). Hence, the maximum dose for every child should be calculated individually (17).

Awake Vs Asleep

It's a fact that children and infants are afraid of needles and can develop severe anxiety of injections, so it's almost impossible to perform a safe block in a child who is moving. Therefore, pediatric anesthesiologists prefer to perform regional anesthesia under deep anesthesia or general anesthesia. With deep anesthesia or under general anesthesia, the child becomes "cooperative" and immobile, while complete control of the vital signs is ensured. However, when the child is under general anesthesia or deep sedation, early warning signs of complications from regional anesthesia, such as the first neurological signs of LAST or technical mistakes, would not be detectible; the test dose is not reliable, and the patient can't report paresthesia or pain during injection. In 2014, Taenzer et al. published a report from The Pediatric Regional Anesthesia Network that included 50,000 patients and demonstrated that performing blocks while awake or under light sedation was associated with a higher incidence of postoperative neurologic symptoms compared with performing blocks under general anesthesia (rate of 6.82/1000 vs 0.93/1000, respectively) (18).

There are two main registries for complications from regional anesthesia in the pediatric population, the French-Language Society of Pediatric Anesthesiologists and Reanimateurs (Association des Anesthésistes et Reanimateurs Pédiatriques des d'Expression Francophone [ADARPEF]) and the Pediatric Regional Anesthesia Network (PRAN). In 1996 and 2010, ADARPEF reported similar complication rates of 0.09% and 0.12% respectively (95% confidence interval [CI]: 0.09-0.17) (19,20). Data from the PRAN registry, comprising more than 100,000 nerve blocks, confirmed similar findings (21). Transient neurological deficit was recorded in only 25 cases (2.4 in 10,000 [95% CI: 1.6-3.6 in 10,000]), but none led to permanent sequelae. The most common adverse events were catheter malfunctions (displacement, occlusion) that occurred in 4% of cases.

In 2017, the European Society of Regional Anesthesia and Pain Therapy (ESRA) and the American Society of Regional Anesthesia and Pain Medicine (ASRA) joint committee published evidence-based recommendation in which they advise performing pediatric regional anesthesia under general anesthesia or deep sedation (category B2) (22). Injection of local anesthetic should be very slow and fractionated, with frequent aspiration tests and careful ECG monitoring, particularly the T wave. When test dose of epinephrine (1mcg/kg) is used, following any ECG changes, it is recommended that in the next 90 seconds an accidental intravenous injection of local anesthetic is detected.

Ultrasound Advantages Compared to Landmark-based Technique and Neurostimulator

Previously, high volumes of local anesthetics were used to compensate for inaccurate needle placement during landmark-based regional blocks, potentially exposing children to the risk of LAST. Ultrasonography provides additional information, including direct visualization of the neural structures to be blocked, the spread of local anesthetic around the nerve and within the appropriate fascial plane, and visualization of anatomical variations and vital structures surrounding the nerves. Sometimes, the responses to a peripheral nerve stimulator (PNS) can be unreliable and the muscle contractions elicited by these stimuli can be harmful in children with skeletal or connective tissue disorders, such as epidermolysis bullosa and syndactyly. In such cases, ultrasound guidance in preforming neural blocks prevents the need to use a PNS and reduces the risk for tissue damage (12). Studies in children and adults have shown that ultra-

sound-guided regional nerve blocks enable faster block performance, increase accuracy and success rates, hasten block onset, and reduce the volume of injected local anesthetics (23).

Upper Extremity Peripheral Nerve Blocks

Some of the most frequent operations in pediatric populations are fractures of the upper and lower extremities. The reported incidence of fractures is 20.2 in 1000 children per year (24). Various levels of pain have been reported in children with extremity fractures, experiencing moderate-severe pain. The most severe postfracture pain is experienced in the first 48 hours (25).

The motor and sensory innervation of the upper extremity is provided by the brachial plexus, except for the part of the shoulder, which is innervated by the cervical plexus. The medial aspect of the upper arm has sensory innervation from the intercostobrachial nerve, a branch of the 2nd intercostal nerve. The brachial plexus is formed by the anterior branches of the spinal nerve roots of C5, C6, C7, C8, and T1 and may often contain fibers from the fourth cervical and second thoracic spinal roots. Depending on the location and the type of surgery, the brachial plexus can be blocked on different levels, such as interscalene, supraclavicular, infraclavicular, and axillary blocks. The type of blocks should not be determined only by the type of surgery; it also depends on the patient characteristics and experience of the anesthesiologist who is performing the block.

Interscalene brachial plexus block (IBPB)

Indications. An interscalene block is performed for shoulder surgery or surgery of the proximal part of the humerus. Shoulder surgery is very rare in children, thus this approach to the brachial plexus is infrequently performed.

Position of the patient. The patient is placed in a supine position with the head turned contralateral to the side where the block needs to be performed (Fig. 1).

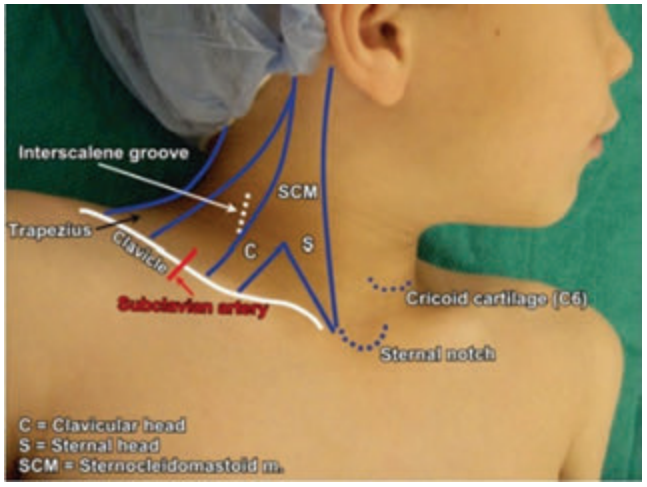

Figure 1. Position of the patient for performing the interscalene block

Anatomy and ultrasound characteristics. As previously mentioned, the brachial plexus is formed by the anterior branches of the spinal nerve roots of C5 - C8 and T1. The branches of

these spinal nerves leave the corresponding intervertebral foramina and emerge in the interscalene groove which is formed by the anterior and middle scalene muscles. At this level, trunks are formed (the upper trunk is formed by C5 and C6, the middle trunk is a continuation of C7, and the lower trunk originates from C8 and T1). The lineal ultrasound probe is placed transversely over the neck, into the interscalene groove (proximally to the clavicula and over the external jugular vein if visible) (Fig. 2a). In small children and infants, the ultrasound probe is wide enough to capture the internal jugular vein and carotid artery together with the brachial plexus. Lateral to the great vessels lies the anterior scalene muscle and more posterolaterally lies the middle scalene muscle. Between these muscles lies the hyperechogenic interscalene sheath containing the brachial plexus (Fig 2b). The brachial plexus trunks in this section are usually visualized as more than three round or oval-shaped hypoechoic structures. In literature, this is described as sign of a "snowman" or "traffic light".

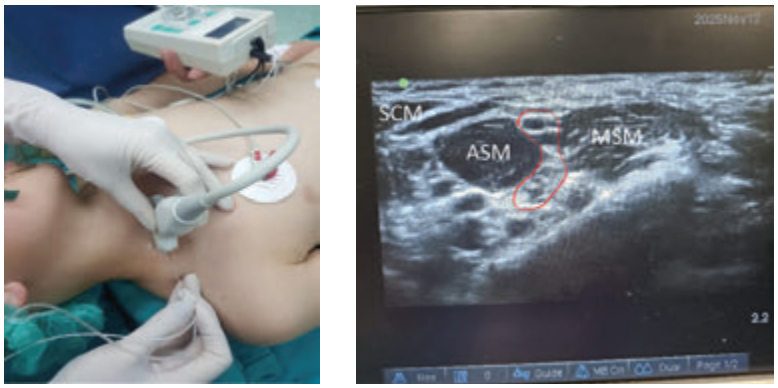

Figure 2. a – position of the ultrasound probe and additional use of neurostimulator; b- ultrasound findings of interscalene brachial plexus block: case of a 3-year-old child: SCM – sternocleidomastoids muscle, ASM – anterior scalene muscle, MSM – middle scalene muscle, brachial plexus is outlined with a red line

Local anesthetic and dose. 0.2% ropivacaine up to 0.5ml/kg or 0.25% bupivacaine 0.2-0.3 ml/kg (max 2mg/kg). Continuous infusion: 0.1– 0.15ml/kg/h (max 10ml/h) (26).

Complications. Possible complications in this region are intrathecal or intravascular injections of local anesthetic, phrenic nerve palsy and Horner's syndrome.

Clinical tips.

- In infants, use hockey stick ultrasound probe.
- In-plain approach from posterior to anterior is safer then out-plane approach
- Place the needle in the interscalene sheath (between the middle and lower trunk) and follow the spreading of local anesthetic upwards, followed by frequent aspirations.
- Use color Doppler to avoid accidental vascular puncture

Supraclavicular brachial plexus block (SCBP)

Indications. The suprascapular block is performed for all upper arm surgical procedures on the upper arm and distal to the shoulder, including extensive hand, forearm, and elbow surgery. This block is often refered to as spinal anesthesia of the upper extremity. For shoulder surgery,

interscalene block is considered more appropriate than the SCPB because the interscalene block also blocks the suprascapular nerve. Supraclavicular plexus block also eliminates pain caused by the tourniquet.

Position of the patient. The patient is placed in a supine position with the head turned contra-laterally to the side where the block needs to be performed. A pillow/roller under the shoulders should be used to achieve inline positioning of the head with the upper body (since small children have bigger heads compared to the body). The arm that needs to be blocked should be adducted to the body.

Anatomy and ultrasound characteristics. The three trunks emerging from the interscalene groove and pass downward and laterally to the subclavian artery. On this level, each trunk divides into anterior and posterior divisions. The linear probe needs to be placed coronal-oblique in the supraclavicular fossa (Fig. 3). The subclavian artery, the first rib and pleura should be visualized with the brachial plexus, which at this level appears as a hypoechogenic "cluster of grapes" posterolaterally to the subclavian artery (Fig. 4). In-plane technique is used, and the needle should be visible to avoid accidental puncture of vessels, nerves, and pleura. Always insert the needle from lateral to medial.

Figure. 3. Position of the linear probe in performing supraclavicular brachial plexus block

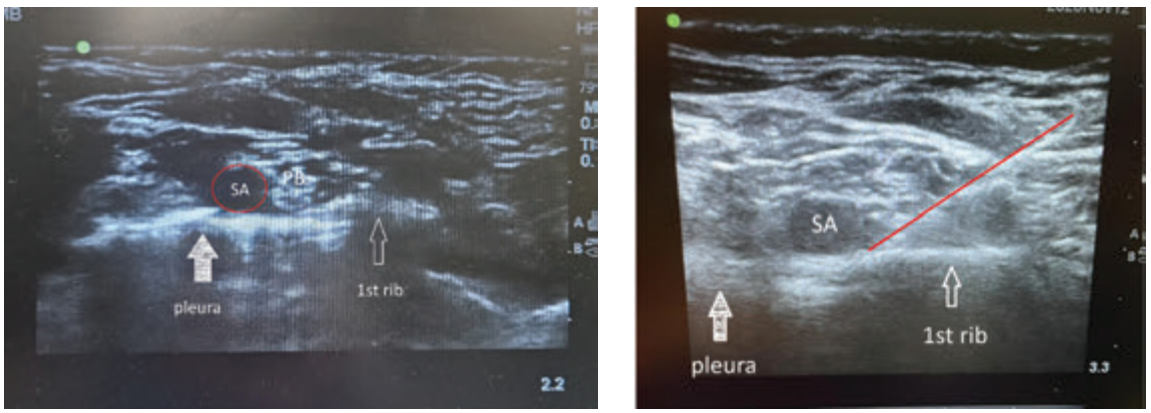

Figure 4. Ultrasound findings of supraclavicular brachial plexus block: pleura, first rib, SA- subclavian artery, and PB - brachial plexus posterolateral to the artery. The first image shows a US scan on a 2-year-old patient and the second an 11year old patient. The red line is directed on the "corner pocket"

Local anesthetic and dose. 0.15– 0.5 ml/kg bupivacaine 0.25% (max 2.5mg/kg) or 0.2% ropivacaine or 1% lidocaine (max 5mg/kg). In infants under 6 months of age, the dose should be halved (26).

Complications. Possible complications in this region are arterial and pleural puncture (pneumothorax), phrenic nerve palsy, and Horner's syndrome. The latter two are more common complications in the interscalene block.

Clinical tips.

- When the patient is correctly positioned, the components of the brachial plexus become more superficial and the block's administration in most children is easy
- Deposition of local anesthetic in "corner pocket" improves successful supraclavicular block. This region borders inferiorly by the first rib and medially by the subclavian artery (Fig. 4b) and on this level, the nerve fibers for the ulnar nerve emerge, which innervate the medial side of the arm.
- Use color Doppler to avoid accidental vascular puncture (possible presence of dorsal scapular and transverse cervical arteries that branch from the subclavian artery and pass through the brachial plexus)

Infraclavicular brachial plexus block

Indications. The infraclavicular block is performed for surgical procedures on distal humerus, elbow, forearm and hand. The infraclavicular block indications are similar to those for supraclavicular brachial plexus block.

Position of the patient. The patient is placed in a supine position with the head turned contralaterally to the side of the block needs to be performed and the arm that needs to be blocked should be positioned in adduction; the elbow should be flexed by 90° degrees and the forearm should be placed on the patient's abdomen. A pillow/roller should be used to line the head with the upper body.

Anatomy and ultrasound characteristics. On this level, anterior and posterior divisions form lateral, medial and posterior cords, named according to their position to the axillary artery. A linear probe is placed in parasagittal plane below the clavicula and medially to the coracoid process (Fig. 5a). Beneath the pectoral muscles lies the axillary artery, which is surrounded by three cords of the brachial plexus; and the axillary vein is poisitioned medial and caudal to the artery (Fig. 5b). The cords of the plexus are visualized as hyperechoic oval structures, but sometimes the medial and posterior cords can be difficult to identify because of their anatomical variations. The in-plane technique is safer, and the needle is advanced from cranial to caudal with target point at 7-8 of the clock level under the axillary artery. At this point, deposition of the local anesthetics encircles the axillary artery in a "U-shape" and provides blocking of all three cords.

Local anesthetic and dose. 0.2– 0.3 ml/kg bupivacaine 0.25% (max 2.5mg/kg) or 1% lidocaine (max 5mg/kg). Continuous infusion – 0.4ml/kg/h (max: 8-10ml/h) (26).

Complications. Complications in this block are extremely rare, however, they may include vascular puncture, nerve injury and pneumothorax.

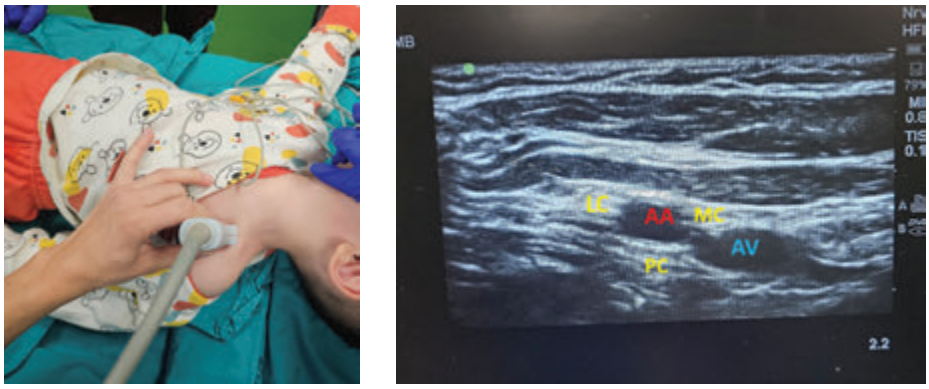

Figure. 5. a – position of the linear probe for performing infraclavicular brachial plexus block; b – ultrasound findings of infraclavicular block in a 3-year-old child: AA – axillary artery, AV – axillary vein, LC – lateral cord, MC – medial cord and PC – posterior cord of the brachial plexus

Clinical tips.

- Place the linear probe medial to the coracoid process and inferior to the clavicle in parasagittal plane
- After identifying the axillary artery, advance the needle toward the posterior cord
- Sometimes, for improved visualization of the cords, abduct the arm to 90°, which brings the cords more superficially and laterally to the axillary artery.

Axillary brachial plexus block

Indications. Axillary block is performed for surgical procedures distal to the elbow.

Position of the patient. The patient is placed in a supine position with the arm that needs to be blocked abducted to 90°; the shoulder should be externally rotated; the elbow should be flexed to 90° degree and the hand should be placed upwards (Fig 6).

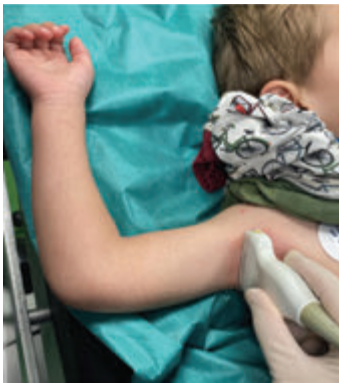

Figure 6. Position of the patient and the linear probe for performing axillary block.

Anatomy and ultrasound characteristics. At the level of the axillary block, the median, ulnar and radial nerves are blocked. The target nerves are located in variable positions around the axillary artery, due to frequent anatomical variations (Fig. 7). The linear probe is placed in the

axilla, and the target nerves are located around the anechoic axillary artery (Fig. 6 and 7). The median nerve usually lies superficially above the artery; the ulnar nerve is commonly located superficial and medial to the artery; whereas the radial nerve lies under and medial to the artery. The musculocutaneous nerve appears as a hyperechogenic oval structure between the coracobrachialis and biceps muscles. It needs to be blocked when tourniquet is applied.

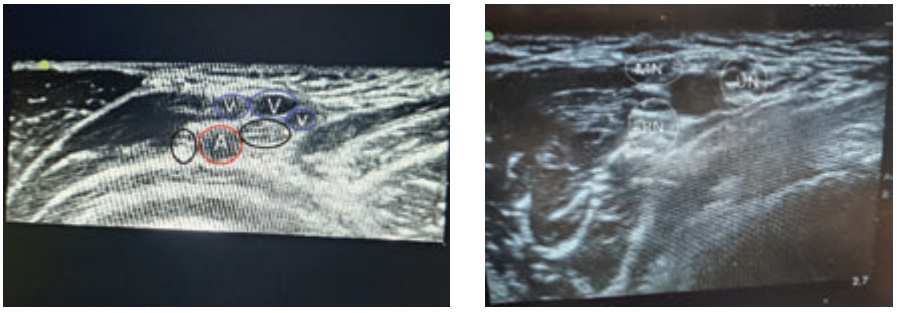

Figure 7. Ultrasound findings of axillary block: A- axillary artery, V – veins, MN – medial nerve, UN – ulnar nerve, RN – radial nerve. The first image is of a 7-year-old patient where the ulnar and medial nerves are located medially from the artery and the radial nerve is lateral to the artery. The second image is of a 15-year-old child with a different position of the nerves compared to the previous one.

Local anesthetic and dose. 0.2– 0.3 ml/kg bupivacaine 0.25% (max 2.5mg/kg) or 1% lidocaine (max 5mg/kg). 0.5 – 1ml for the musculocutaneous nerve (26).

Complications. Complications in this block are rare but may include accidental vascular puncture and, in that case, to prevent hematoma, pressure should be applied for at least 5min.

Clinical tips.

- Use color Doppler for improved visualization of the vessels in this area (usually there are more than one vein)
- For enhanced localization of the nerves, a neurostimulator may be of help.

Conclusion

Regional anesthesia as a part of the multimodal analgesia provides effective, opioid-sparing postoperative analgesia; improves comfort and hastens the recovery in children. Ultrasound imaging increases block safety, reduces complications and improves the block's accuracy. The choice of the block should be based on surgical procedure, anatomy and experience of the anesthesiologist. In order for regional technics to be fully implemented in pediatric anesthesia, the anesthesiologist needs to undergo structured education, continuous training in the acquisition of ultrasound imaging and needling skills, and gain knowledge of pediatric anatomy and physiology as well as familiarity with the latest guidelines.

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REVIEW ARTICLE *UDK: 616.714.1-089.85-009.7-089.5*

APPLICATION OF SCALP BLOCK AS A REGIONAL ANESTHETIC TECHNIQUE FOR ELECTIVE AND EMERGENCY CRANIOTOMY

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Abstract

Almost 90% of patients who undergo craniotomy experience postoperative pain that is poorly controlled in the early postoperative period. As many as half of them are considered to have moderate to severe headaches caused by the surgical procedure. The use of opiates in the intraoperative and postoperative period is the most common method for pain management. Scalp block is a regional anesthetic technique in which local anesthetic is infused near the nerves that innervate the scalp, thus providing quality intraoperative and postoperative analgesia. When applying the scalp block, 2 ml of local anesthetic is infiltrated at 5 sites on the side where the craniotomy will be performed. The scalp block blocks n.supraorbitalis and n.supratrochlearis; n.auriculotemporalis; n.occipitalis major and n.occipitalis minor. When applying the scalp block, long-acting local anesthetics such as bupivacaine or ropivacaine are used, while a combination of lidocaine and bupivacaine is also possible. Systemic application of corticosteroids prolongs the analgesic effect of the block for up to 48 hours, and according to some authors, up to 72 hours. The scalp block drastically reduces the need for opiates in the intraoperative period and provides complete hemodynamic stability (1). According to the meta-analysis by D. Taylor and colleagues, scalp blocks reduce opioid consumption in the first 24 and 48 hours postoperatively, and also significantly reduces pain by 2/10 in the first 24 hours after the surgical procedure, with the possibility of extending the analgesic effect for up to 48 hours (2)(3). Additionally, scalp block significantly or completely attenuates the hemodynamic effects of craniotomy, providing hemodynamic stability immediately after its application (2)(3). According to the ESAIC recommendations for the management of craniotomy-related pain issued in 2023, analgesia for craniotomy should consist of scalp block combined with intraoperative administration of paracetamol, with or without continuous infusion of dexmedetomidine, while opiates are considered only as salvage therapy when all other modalities have failed (4).

Keywords: *Craniotomy; Scalp Block; Regional Anesthesia.*

Introduction

Craniotomy as a surgical procedure can be a cause for postoperative pain in approximately 80-90% of patients (1,2). Unfortunately, postoperative pain after craniotomy has been neglected and treated insufficiently worldwide due to clinical underestimation of the pain severity, as well as the risk of sedation when using opioids as a rescue technic in pain control. It is well known

that early postoperative pain control could be key to preventing chronic pain development and central sensitization. Therefore, perioperative pain management in either elective or urgent craniotomies is more than important, while at the same time, the patients are guided safely through the therapeutic process. The pain resulting from neurosurgical interventions is clearly somatic by origin, resulting from the skin, muscle and bone injuries that have occurred due to the surgical intervention. However, the pain is not visceral at all because it is well known that the pain is not caused by damaging the brain itself. It was reported that as many as half of previously mentioned 90% of patients are considered to have moderate to severe headache caused by the surgical procedure (1). Since, the percentage of patients experiencing severe postoperative pain is serious and clinically relevant, the discussion in this article will focus on the usage of regional anesthesia as a technique for pain control, providing precise data about the usage of scalp block in daily practice with careful review of latest recommendations with relevant clinical implications.

Craniotomy-related Pain

As previously said, the pain related to craniotomy is purely somatic, originating from the damage of the skin of the scalp, muscles, periost and the bone itself, as well as the dissection of the meninges. However, the pain is not visceral because the brain itself does not possess pain receptors. Regardless the type of craniotomy, the pain is usually concentrated around the incision site and not involving parts of the head which were not affected by the surgical incision. The pain stimuli are created usually because of incision, dissection and retraction of tissues involving dermatomes in the innervational area of the trigeminal nerve, as well as branches from the cervical plexus. Temporal craniotomy, long lasting surgeries, subtle nerve damage and implantation of osteosynthetic material were considered risk factors that could worsen the pain. Given that the pain itself is a negative postoperative experience that was left undertreated in daily practice, it is worth mentioning that the pain arising from craniotomy is related to surge of catecholamines due to activation of the stress responses related to pain. Actually, pain-related stress response and following catecholamine release are strongly unwanted, since the hemodynamic disturbances in the perioperative period could end with undesirable complications and hemorrhage leading to an unfavorable outcome. Evidently, the importance of strict perioperative pain management in patients undergoing craniotomy does not consist merely of pain control, rather securing a hemodynamic stability.

SCALP Block: How to Perform It?

The head possesses dual sensitive innervation, arising from the trigeminal nerve and cervical plexus. In fact, to provide full analgesia of the skin, muscles and the periost, the anesthetist must know the innervational area of each one of the nerves that provide sensitive innervation of the head. Therefore, performing a scalp block implies infiltrating local anesthetic in a well-known landmark guided point around the following nerves: supraorbital and supratrochlear nerve, zygomaticotemporal and auriculotemporal nerve, as well as minor and major occipital nerve, together with magnus occipital nerve. Providing successful intraoperative and postoperative analgesia is possible with infiltration of long-lasting local anesthetic on a few sites guided by well-known anatomical landmarks without the need of ultrasound. Application of 2ml of plain bupivacaine or ropivacaine at each site provides immediate analgesia. The first application

site is located above the orbit in the middle where the exit of the supraorbital nerve is located. Anatomically, it is recognized by the incisura on the upper edge of the orbit, which should be palpated. The 2ml of local anesthetic should be infiltrated immediately above, thus blocking the supraorbital nerve. Using the same puncture, but only by changing the direction of the needle medially towards the nose, another 2ml of local anesthetic should be infiltrated, thus blocking the supratrochlear nerve. With one puncture and two different infiltrations, analgesia is provided for the frontal and parietal regions. Then, just before the tragus, the pulse of the auriculotemporal artery is palpated preauricularly and carefully, without injuring it, while another 2 ml is applied around the artery, thus blocking the auriculotemporal nerve. Then, through the same puncture, the direction is changed to the medial area, where 2 ml is applied, thus blocking the zygomaticotemporal nerve. By blocking these two nerves, analgesia of the temporoparietal part of the scalp is provided. Next, at a distance of 2-3 cm lateral to the external occipital protuberance, another 2 ml of local anesthetic is infiltrated, to block the greater occipital nerve. The lesser occipital nerve is blocked by infiltrating 1-2 ml of local anesthetic medial to the mastoid and at the posterior border of the sternocleidomastoid, which blocks the lesser occipital nerve. The lesser and greater occipital nerves provide sensory innervation of the occipital part of the scalp. The same application sites apply to the application of this block in pediatric neuroanesthesia, so it is necessary to pay great attention to the dose of local anesthetic and adjust it according to the patients' weight and the reduced level of acid alpha glycoprotein.

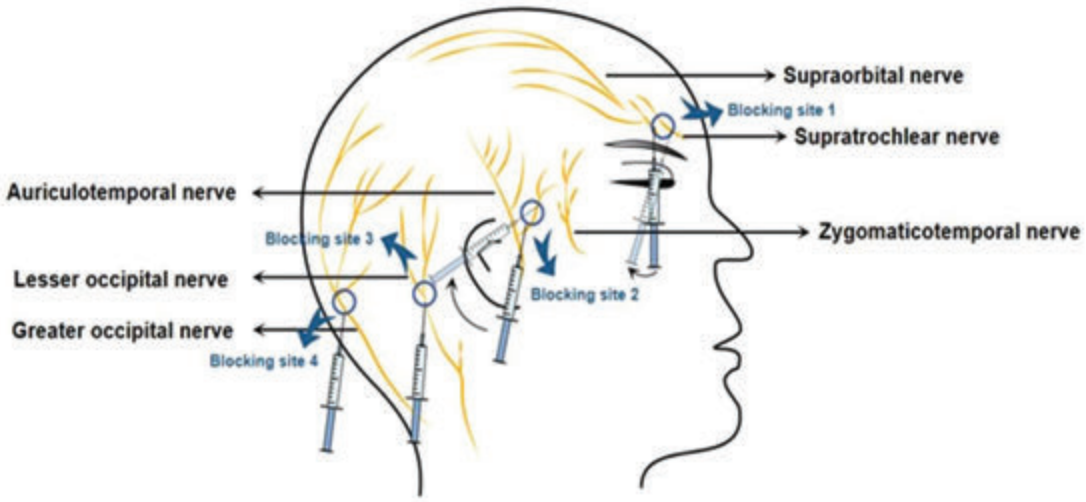

Figure1 Injection sites according to the anatomical dispersion of nerves

The Science Behind Scalp Block

In the past, craniotomy-associated pain in the intraoperative and early postoperative period was most often managed with the use of opioids. The modern approach involves reducing opioids to the minimum possible level, taking into account their adverse effects such as drowsiness, impaired consciousness, respiratory depression, nausea and vomiting, as well as the presence of miosis, which can interfere with early and timely recognition of signs of increased intracranial pressure or the occurrence of brain edema. Hence, the application of regional anesthetic techniques in everyday neurosurgical technique overshadows opioids as the first line of choice in the treatment of craniotomy-associated pain. Hence, scalp block is defined as a sovereign, modern, safe, easy to perform, and simple regional anesthetic technique for providing adequate intraop-

erative and postoperative analgesia. If a long-acting anesthetic is used for the block in combination with dexamethasone or dexmedetomidine, they will prolong the effect of the block (3). The superiority of scalp block in managing craniotomy-related pain is also confirmed by the results of a meta-analysis, according to which patients who received scalp block had significantly lower opioid requirements in the first 24 hours after surgery and less pain compared to patients who did not receive scalp block (4). Also, according to the authors of the same meta-analysis, scalp block provided significantly better hemodynamic stability during the intraoperative period, from the moment of the first incision until the end of the operation, with significantly lower heart rate and mean arterial pressure values and without strokes. These effects were observed in the intraoperative period in patients who received scalp block therapy (4). The positive effects of scalp block are confirmed by another meta-analysis based on data from 1500 patients, which came to a clear conclusion regarding the usefulness and the impact of scalp block on the occurrence of pain and on the stress response. Namely, patients who received scalp block had satisfactory analgesia up to 48 hours after surgery, but also a delayed time to require rescue analgesia after the end of the surgery, compared to the control group where scalp block was not applied (5). This meta-analysis comes to much more precise conclusions about the impact of scalp block on the occurrence of stress response during craniotomy. The reviewed studies determined intraoperatively and postoperatively much lower levels of cortisol and angiotensin in patients where scalp block was applied compared with the control group. These findings explicitly highlight the effect of regional anesthesia on systemic hemodynamics (5). Numerous authors point to the analgesic power of scalp block in the early postoperative period, but limit it to 24 hours, while Duda and colleagues in their meta-analysis conclude that scalp block provides analgesia for up to 72 hours and that it significantly reduces opioid consumption 24 and 48 hours after surgery (6). In that context, in regards to postoperative pain, another meta-analysis found superiority of scalp block application only in the early and the middle period of the first 24 hours, but not in the late first 24 hours, with patients who received the block having significantly lower pain scores only in the early and middle hours after the intervention compared to the control group, which was not the case in the late hours of the first postoperative day (7). The difference between one and the other meta-analysis may be due to the heterogeneity of the results incorporated in the second meta-analysis, according to which the use of scalp block was associated with lower pain scores only in the first half of the first 24 hours after surgery. Another meta-analysis also confirms the analgesic effect of scalp block in the first 24 hours, noting that it is associated with lower VAS in the first 24 hours, lower overall analgesics usage, and a significantly longer time for administration of rescue analgesia, compared to the control group where scalp block was not applied (8). In order to provide sufficient and successful analgesia when applying scalp block long lasting anesthetics as bupivacaine, levobupivacaine and ropivacaine are recommended. Howerver, some authors state that ropivacaine is superior when compared with others (9). Compared with local anesthetic infiltration, scalp block provides better analgesia according to one randomized trial (9). Previously, other authors have also published results according to which the application of scalp block is superior to the application of local anesthetic only to the incision site. It is likely that the selective blockade of the trigeminal and occipital nerve fibers provides deeper and longer-lasting analgesia and also appears to have anti-inflammatory properties. It is also probable that the selective blockade has a suppressive effect on the stress response, which likely plays an important role in the development of postoperative pain following craniotomy. It is also important to note that when it comes to pain control the application of the block before surgical incision is superior to its application postoperatively. Additionally, but no less important, the application of the scalp block significantly reduces the intraoperative use of opioids regardless of whether it is fentanyl or remifentanil, which is a significant fact that

completely changes the concept of the use of fentanyl anesthesia in neurosurgery. Moreover, patients who were anesthetized with a scalp block not only received a smaller amount of opiates compared to patients who did not receive a scalp block, but also had identical or even better hemodynamic stability compared to the opioid group (9). Hence, it seems that the introduction of this regional anesthetic technique into everyday neuroanesthesia can not only reduce everyday opiate usage, but can also contribute to faster and easier awakening from anesthesia without the presence of opioid side effects.

Guidelines and Recommendations

According to the PROSPECT study recommendations that are the newest official document published by ESAIC, the management of postoperative pain after elective craniotomy may be complex and should be multimodal. They specify each of the available medications and their effect when dealing with postoperative pain after craniotomy. According to the PROSPECT study, application of the scalp block is the foundation in providing quality perioperative analgesia and preventing central sensitization of the pain. The study strongly recommends preincisional application of the scalp block in order to provide sufficient analgesia. According to PROSPECT study team, the application of scalp block offers long lasting analgesia from 2-48 hours after surgery with significantly reduced postoperative opioid consumption (10). Despite the clearly stated opioid sparing effects of scalp block, according to the study team, its application is related to less frequent postoperative nausea and vomiting. Finally, according to the PROSPECT recommendations, scalp block should be routinely used in patients that undergo elective craniotomy in combination of paracetamol, NSAID and dexamethasone and/or dexmedetomidine, while opioids should be used only as a rescue analgesia (10).

Conclusion

The scalp block is a simple to perform, easy, safe and sovereign regional anesthetic technique that provides adequate intraoperative and postoperative analgesia in elective and emergency craniotomies. The use of this technique is associated with significantly reduced perioperative opioid use and reduced incidence of opioid-associated complications. The scalp block is part of a modern multimodal approach to the treatment of craniotomy-associated pain and is recommended by ESAIC as the technique of choice and first line of treatment before opioid use.

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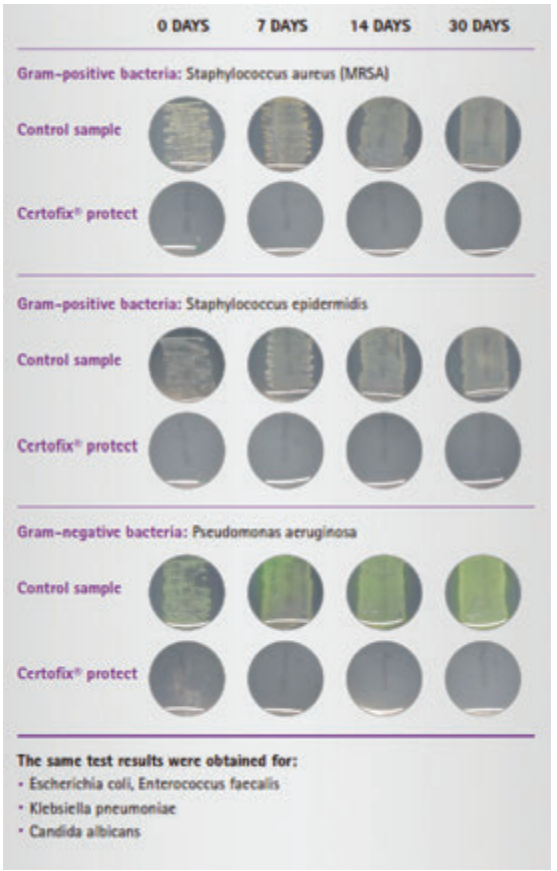

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