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THE ROLE OF ENTROPY IN ANESTHESIA MANAGEMENT DURING EMERGENCY SURGICAL INTERVENTIONS AND IN THE IMMEDIATE POSTOPERATIVE MONITORING OF COGNITIVE FUNCTION

RESUME

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Articles

- **Cotae, A.-M**.; Grinţescu, I.M. Entropy—The Need of an Ally for Depth of Anesthesia Monitoring in Emergency Surgery. *CEACR* 2019, *1*, 1. doi: 10.35995/ceacr1010001.
  Chapter 2, *Subchapter 2.4, Subpoint 2.4.2, page 49*

- **Cotae AM**, Ţigliş M, Cobilinschi C, Băetu AE, Iacob DM, Grinţescu IM. The Impact of Monitoring Depth of Anesthesia and Nociception on Postoperative Cognitive Function in Adult Multiple Trauma Patients. Medicina (Kaunas). 2021 Apr 23;57(5):408. doi: 10.3390/medicina57050408. PMID: 33922552; PMCID: PMC8146673.
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- **Ana-Maria Cotae**, Liliana Mirea, Cristian Cobilinschi, Raluca Ungureanu, Ioana Marina Grinţescu. Early postoperative cognitive decline—are there any preventive strategies for surgical patients in the emergency setting?. Signa Vitae. 2024. 20(1);1-7.
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- Cotae A.-M., Monitoring depth of anesthesia in major emergency surgeries and immediate postoperative cognitive dysfunction, SRATI 2018
- Dumitriu A.-M., Postoperative cognitive dysfunctions after regional anesthesia, ARAR 2024

The Importance of the Research Topic and Its Relevance to Current Concerns

The perioperative optimization of surgical patients remains a constant priority for the anesthetic-surgical team. The current trend is to extend the implementation of intervention sets, so-called care bundles, which can significantly improve the postoperative outcomes of patients.

Evaluating the surgical patient through pre-anesthetic consultation represents the first step in determining the current medical condition, medical history, and chronic treatment, assessing perioperative risk, and anticipating potential perioperative complications. The main goal is to develop an interventional plan that ensures the best postoperative recovery and outcomes for the patient.

Most published good practice recommendations to date primarily guide the perioperative management of patients scheduled for elective surgical interventions. The specialized literature abounds with recommendations for stratifying and managing cardiovascular and thromboembolic events, although there are more frequent postoperative complications that contribute to prolonged hospital stays and, implicitly, increased patient care costs. Among these, postoperative neurocognitive dysfunctions constitute a significant percentage of immediate or delayed postoperative complications in the general surgical population, with an overwhelming prevalence among the elderly. Cognitive decline that begins in the perioperative period is considered to increase the likelihood of unfavorable outcomes not only during hospitalization but also after discharge, having adverse effects on the patient's quality of life.

In emergency surgical interventions, the limited time for patient evaluation and optimization significantly reduces the possibility of implementing general or specific prophylactic therapeutic measures, thus increasing the risk of perioperative complications.

Regarding the prevention of postoperative cognitive dysfunctions, the few strategies described so far are mainly applicable in the context of scheduled surgical interventions.

Therefore, the subject of therapeutic measures with clinical applicability, which can prevent postoperative cognitive dysfunctions and can be implemented when the time for preoperative optimization is limited, remains open to research. Ideally, these measures should not hinder other essential preoperative preparations.

Although the etiology and pathophysiology of neurocognitive disorders in the postoperative period are still being studied, there are recognized risk factors acknowledged by anesthetists that can be intervened upon perioperatively to minimize the occurrence of these dysfunctions. The most frequently cited modifiable risk factors in the specialized literature, which have a major impact on the development of such neurocognitive disorders, are uncontrolled postoperative pain and excessive use of sedatives, especially benzodiazepines.

The introduction of neuromonitoring in clinical practice has, however, opened a new horizon regarding the possibility of modulating another presumed intraoperative risk factor: the inadequate control of anesthesia depth. Although the primary objective of intra-anesthetic neuromonitoring is to avoid awareness, given the low incidence of this event in the general population, routine use of neuromonitoring is more justified for avoiding too deep a level of anesthesia or sedation and for faster recovery from anesthesia at the end of the surgical intervention.

Currently, there is a significant number of validated devices for monitoring the depth of anesthesia at the European level, including static and response entropy derived from the spectral entropy of electroencephalography (M-Entropy module, GE Healthcare, Helsinki, Finland). Another advantage of this type of neuromonitoring is indicating insufficient analgesia and improving the intraoperative hemodynamic profile, secondary to reducing the consumption of sedative-hypnotics.

In the postoperative period, neurocognitive disorders can be differentiated based on their onset into early forms, such as postoperative delirium that can occur anytime after 24 hours postoperatively but no later than the first 72 hours, or late forms, such as postoperative cognitive decline, which is described weeks or months after the surgical intervention. In daily practice, we are more familiar with cognitive alterations associated with delirium, as the clinical picture of late cognitive dysfunctions is often hard to capture during hospitalization.

Most clinicians can identify the presence of postoperative delirium without a diagnostic test when the clinical picture is sufficiently expressive. However, there are several neurocognitive tests that can facilitate early diagnosis when clinical changes are subtle, differentiate the type of delirium, or classify the severity of symptoms. In addition to the established test for evaluating patients in intensive care, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), another confirmed test is the NEECHAM confusion scale (Neelon and Champagne confusion scale). Its main advantage is that it allows easy patient evaluation by nurses. Additionally, the scale incorporates not only elements of information processing or behavior but also data on the patient's physiological status.

Motivation for Choosing the Topic

Current recommendations and specialized protocols primarily address perioperative optimization of patients in the context of elective surgical interventions. However, it is known that emergency surgical interventions entail increased complexity, associated with a higher risk of severe perioperative complications, and represent a continuous challenge for the entire anesthetic-surgical team.

Alongside traumatic shock, hemorrhagic shock, fluid-coagulant balance disorders, or surgical wound infections, perioperative cognitive dysfunctions constitute a significant percentage of immediate or delayed postoperative complications secondary to progressive cognitive and functional decline. In emergency surgical intervention scenarios, there are a limited number of factors that can be intervened upon to prevent unfavorable cognitive outcomes. Although standard monitoring does not include anesthesia depth monitoring, this could become a central pillar in managing the prevention of cognitive decline since the main target of anesthetics is the brain, and through this type of monitoring, the hypnotic anesthetic can be titrated.

Currently, the results reported in the literature regarding the role of intraoperative neuromonitoring through entropy during major emergency surgical interventions are limited. This research aims to contribute to the completion of intraoperative anesthetic approaches and to improve strategies for preventing perioperative cognitive dysfunctions through the intra-anesthetic use of entropy in patients indicated for emergency surgery.

Research Hypothesis and Objectives The present study aims to identify the roles that depth of anesthesia monitoring through entropy occupies in the anesthetic management of patients undergoing emergency surgical procedures and in the immediate cognitive evolution during the postoperative period. In the scenario of surgical pathologies requiring emergency interventions, the main goals of the anesthetic-surgical team are both patient survival and the secondary prevention of complications. Even though unfavorable cognitive outcomes result from multiple factors, this research aims to provide clear results on how patients' postoperative immediate period can be improved. To monitor cognitive evolution within the first 72 hours postoperatively, we opted for the Neecham Confusion Scale. This score includes attention elements, evaluates executive function, memory, language, and also records physiological data and vital function stability during the postoperative period.

Content and Methodology of the Research The current research is structured into 6 chapters and concludes by synthesizing the main conclusions, as well as summarizing personal contributions. The general part of the work includes notions about validated systems for monitoring the depth of general anesthesia, the clinical impact, and limitations of the main neuromonitoring means. Subsequently, definitions, diagnoses, and pathophysiology elements of perioperative cognitive dysfunctions are presented, along with current prevention and treatment strategies. The original part of the research includes a randomized prospective study that tracked the evolution of patients with various comorbidities and ASA severity scores, who underwent major abdominal and orthopedic emergency surgeries and who were either monitored standardly intraoperatively or additionally benefited from entropy monitoring. The results revealed the possibility of better intraoperative optimization for patients who were neuromonitored, primarily due to the reduced amount of volatile anesthetic, crystalloid volume, and vasopressor support. Regarding cognitive evolution in the immediate postoperative period, it can be affirmed that the incidence of the confusion syndrome was lower within the first 48 hours in the case of patients intraoperatively monitored through entropy, even in the presence of certain risk factors.

Interdisciplinary Characteristics of the Thesis Improving perioperative care in emergency surgery remains a subject of ongoing research, and reducing preventable complications and facilitating recovery are priority measures for both the anesthesiologist and

any other surgical specialty. The results of the present research demonstrate that the intraoperative implementation of entropy neuromonitoring can bring benefits both intraoperatively and in the immediate postoperative period, at least in terms of cognitive evolution. Cognitive dysfunctions that begin in the perioperative period interfere with the adequate care of surgical patients, reduce their participation and compliance with care and treatment, and implicitly reduce their degree of independence and activity.

Materials and Methods The present research is based on a randomized prospective study conducted at the ATI I Clinic of the Clinical Emergency Hospital Bucharest, from 01.10.2018 to 01.10.2022. The study included patients with physical status ASA I-IV, aged ≥18 years, undergoing major abdominal and orthopedic emergency surgeries at the Clinical Emergency Hospital Bucharest. The surgeries were performed under general anesthesia with orotracheal intubation, balanced on a volatile pivot with Sevoflurane. The study involved the following exclusion criteria:

- Severe craniocerebral trauma,
- Untreated preoperative cognitive dysfunction or evolving psychopathological symptoms,
- Patients for whom intraoperative ketamine administration was chosen,
- Surgical intervention duration less than 60 minutes,
- Necessity of reoperation within the first 72 hours of the initial intervention,
- Presence of major perioperative complications such as neurological, cardiovascular, or metabolic,
- Inability to extubate in the immediate postoperative period for adequate neurological evaluation.

In the randomized prospective study, patients were consecutively assigned 1:1 into two groups. For both groups, data related to age, gender, nutritional status, comorbidities, and their types, as well as paraclinical data: hemoglobin level, lactate, serum Na and K, blood glucose level, and C-reactive protein (CRP) level, were collected. For one of the groups, general anesthesia was performed under standard monitoring: electrocardiography, non-invasive blood

pressure, pulse oximetry, expiratory carbon dioxide concentration (etCO2), and residual neuromuscular block monitoring. For the second group, in addition to standard monitoring, the depth of anesthesia was continuously recorded through non-invasive entropy monitoring during general anesthesia. Entropy monitoring was made possible by using specific sensors with three electrodes connected to the GE Entropy™ Module, and was initiated after securing venous access. Premedication consisted of administering 1-2 mg of midazolam in patients <65 years. In all patients, preoxygenation with 100% oxygen was initiated with a flow of 8l/min for 3 minutes, followed by rapid-sequence induction. Fentanyl 2μg/kg, Propofol titrated 1-2 mg/kg depending on the patient's response, and Succinylcholine 1mg/kg were administered. The airway was secured through an endotracheal tube. For maintaining muscle relaxation, rocuronium 0.4-0.5 mg/kg was administered. All patients were mechanically ventilated to maintain an ETCO2 between 35 and 45 mmHg. Anesthesia maintenance was achieved by administering a mixture of air-oxygen-sevoflurane with an FiO2 of 0.5-0.6, with the gas flow reduced to 2 l/min. The concentration of sevoflurane was adjusted using routine clinical parameters (MAC values and hemodynamic constants) in the control group, while in the entropy-monitored group, by maintaining an entropy value between 40 and 60.

For statistical analysis, values provided by static entropy (average value during monitoring), considered a more stable parameter estimating the hypnotic effect of anesthetics on the brain and not influenced by frontal muscle activity or the administration of neuromuscular blockers, were collected. Burst suppression events lasting at least 1 minute were recorded, noting the duration, number of events, and percentage representation of the recorded activity. For both groups, perioperative data on the amount of crystalloid, colloid, blood transfusion, vasopressor support, and at the end of the surgery: the amount of volatile agent, curare, and opioid used intraoperatively, were collected. Intraoperative hemodynamic events defined as:

- Arterial hypotension: decrease and maintenance of mean arterial pressure below 65 mmHg for two consecutive measurement cycles
- Arterial hypertension: increase of systolic blood pressure above 140-160 mmHg and/or diastolic blood pressure above 90-95 mmHg for two consecutive measurement cycles

- Bradycardia: ventricular rate <60 bpm
- Tachycardia: ventricular rate >90 bpm

Data on mean arterial pressure (MAP) and ventricular rate (VR) at the initial monitoring moment, induction, incision, end of surgery, and extubation were collected. Persistent MAP decrease below 65 mmHg (after two consecutive measurement cycles) was corrected in the following order: volume repletion with crystalloid (200ml), short-acting sympathomimetic, colloid (200ml), and continuous vasopressor infusion (norepinephrine). Postoperative analgesia control was evaluated using loco-regional analgesia or major opioid alone, and the level of analgesia obtained was evaluated using the Visual Analog Scale (VAS). Cognitive function evaluation in the postoperative period was performed using the NEECHAM Confusion Scale at 24, 48, and 72 hours postoperatively. Data on information processing capacity quantified by attention, ability to follow commands, orientation, behavior, control, and physiological measurements were collected.

Depending on the score obtained, postoperative cognitive dysfunction was interpreted as:

- 0-19 points: moderate to severe confusion, delirium
- 20-24 points: confusion syndrome,
- 25-26 points: at risk for developing confusion,
- 27-30 points: absence of confusion status.

Results

The final analysis included 168 surgical patients, both men and women, who required major emergency surgeries, both in general surgery and orthopedics-traumatology, under general anesthesia with and without assessment of anesthesia depth through entropy monitoring. In terms of the proportion of patients who benefited from monitoring anesthesia depth through entropy (52.4%), a small difference was observed compared to those for whom this type of control was not applied (47.6%), with the difference being statistically

insignificant. A higher proportion of neuromonitoring was observed in patients undergoing abdominal surgeries (63.9%) compared to those undergoing orthopedic surgeries (41.9%).

Analysis of independent factors

The analysis of independent factors included the following patient data: age, nutritional status expressed by body mass index (BMI), ASA score, comorbidities (type and number). The ages of the patients in the study ranged from 21 to 92 years, with a median value of approximately 60. Older patients required abdominal surgery in a proportion 1.5 times higher than orthopedic surgery. Nutritional status quantified by body mass index (BMI) ranged from 18.7 to 33.5 kg/m2, with a median value belonging to overweight nutritional status and was distributed almost uniformly among patients, regardless of the type of intervention. The two gender categories presented approximately equal proportions: female (46.4%) and male (53.6%), with no gender difference among patients based on the type of intervention. Patients included in the study groups had ASA scores as follows: ASA I in 3.6% of cases, ASA II in 36.1%, ASA III in the majority of cases at 46.7%, and ASA IV in 13.6%, with no possibility of differentiating the severity of ASA scores based on the type of surgical intervention. From the analysis of comorbidity distributions, a high proportion of their presence (83%) is observed, mainly represented by cardiovascular comorbidities (54%), metabolic (28%), neurological (16%), and, in the case of patients undergoing orthopedic surgery, associated traumas that did not require surgical intervention (27%). Very low proportions were represented by pulmonary (6%), renal (3%), and alcoholism (6%) comorbidities. Injuries (that did not require surgical sanction) were associated to a very large extent with patients who required orthopedic surgical interventions. For the other types of comorbidities considered, statistically significant differences in the type of intervention were not identified. For the other types of comorbidities considered, statistically significant differences in the type of intervention were not identified. Metabolic comorbidities had a higher prevalence both in cases of abdominal surgical intervention and in patients monitored by entropy, approximately twice as high as in non-monitored patients by entropy and in cases of orthopedic surgical intervention. 83% of the total patients had comorbidities, with the highest proportions belonging to cases with a single comorbidity (47%) and with two comorbidities (38.06%), while only 14.93% had at least three comorbidities. In the case of patients undergoing surgical

intervention, the presence of at least two comorbidities was approximately 0.63 times lower than in patients undergoing orthopedic surgery.

Analysis of anesthesia duration and the main intra-anesthetic substances used

The duration of anesthesia ranged between 75 and 260 minutes, with the distribution showing significant positive skewness, expressed by a mean duration of 144.63±41.44 minutes and a median of 135. A significant mean difference was observed in anesthesia durations grouped by the type of surgery, with a difference of 43 minutes for patients requiring abdominal surgery. The presence or absence of entropy control resulted in only about a 3-minute mean difference. The amount of Fentanyl (μg) ranged from 250 to 750 μg, distributed approximately symmetrically, with a mean quantity of 450.89±97.66 μg and a median of 450. An 85 μg higher Fentanyl dose was identified for patients undergoing abdominal surgery. The Fentanyl dose was lower for those who underwent entropy control regardless of the type of surgical intervention, approximately 68 μg. The amount of Sevoflurane (ml/h) ranged from 6.2 to 13.5 ml/h, with a mean quantity of 9.53±1.76 ml/h and a median of 9.30. The presence of neuromonitoring led to a mean difference of approximately 2.3 ml/h, with the quantity being lower for those who underwent entropy control for any type of surgical intervention. The intra-anesthetic Rocuronium quantity ranged from 35 to 130 mg, with a median of 70 mg. A significant mean difference was identified between the Rocuronium quantities (mg) grouped by the type of surgery, with a difference of 38 mg, more pronounced in patients requiring abdominal surgery. Entropy control also had a significant effect, resulting in a mean difference of approximately 5 mg, with the quantity being lower for those undergoing surgical intervention with entropy control and undifferentiated for those undergoing orthopedic intervention. The volume of Crystalloid (ml) ranged from 1000 to 6000 ml, distributed with positive skewness, expressed by a mean of 2869.82±935.85 and a median of 3000. The analysis demonstrated a significant mean difference between Crystalloid volumes (ml) grouped by the type of intervention, with a difference of 546 ml higher in patients undergoing abdominal surgical intervention. The implementation of entropy resulted in a reduction in Crystalloid volume by approximately -310 ml regardless of whether orthopedic or abdominal surgical intervention was required. Vasopressor support with Noradrenaline was used in 72 (≈43%) cases. Patients undergoing abdominal surgical intervention required Noradrenaline in

a proportion approximately 3.6 times higher. The average dose of Noradrenaline was 0.35±0.30, with a median value of 0.30, and the quantity was on average lower by -0.14 µg/kg/min in patients who underwent entropy control. Regarding analgesic modalities, locoregional analgesic techniques were identified in 44% of cases, with patients undergoing orthopedic interventions benefiting from this to a greater extent compared to those undergoing abdominal interventions.

Analysis of intra-anesthetic hemodynamic, hypoxic, and metabolic events

The proportion of patients who initially presented with hypotension was 46%. Patients who required abdominal surgical intervention exhibited initial arterial hypotension 2.36 times more frequently than those with orthopedic intervention. The proportion of cases without intraoperative arterial hypotension was approximately 29% (28.8%). Most patients had 2 hypotensive events (33.3%), while 22% of patients had only 1 event, and 16.1% had 3 or more intra-anesthetic hypotensive events. The absence of neuromonitoring resulted in a higher number of events, with a probability approximately 5 times greater, and patients with orthopedic surgical interventions had 0.4 times fewer intraoperative hypotensive events. Bradycardia events were observed in a lower proportion of 32.7%. In 17.3% of cases, 1 case of intra-anesthetic bradycardia was recorded, and in 13.7% of cases, a higher number of 2 events were recorded. The absence of neuromonitoring resulted in a higher number of events, with a probability approximately 2.3 times greater than those who benefited from this type of control, and patients with orthopedic interventions had 0.49 times fewer events. Tachycardia events were recorded in approximately 29% of the studied population, with higher proportions in cases with a maximum of 2 events, approximately 23%. The proportion of hypoxia events in the two study groups was very low, approximately 12%, with a maximum of 2 events in about 4% (3.6%) of cases. For these last two types of events, no differences were identified based on the presence or absence of entropy monitoring or the type of intervention.

Metabolic acidosis was present intraoperatively in 43% of cases. The proportion of perioperative metabolic acidosis cases was lower in patients who underwent entropy control during anesthesia, with those who benefited from control showing metabolic acidosis at a rate 0.33 times lower than those who did not have this additional type of monitoring. Patients with

abdominal surgical intervention showed metabolic acidosis approximately 2 times more frequently than those with orthopedic intervention.

Analysis of the main paraclinical data in the perioperative period.

Pre-operative hemoglobin levels ranged between 6.0 and 14.0 g/dl, with a mean of 9.97±1.54 g/dl and a median of 10.0 g/dl. The need for transfusions did not reach statistical significance. A significant difference of 0.55 g/dl was observed between the mean pre-operative hemoglobin values, with lower values in patients undergoing abdominal surgery. Regardless of the type of surgical intervention, there was an average hemoglobin level difference of approximately 0.67 g/dl in patients who were monitored with entropy. A mean difference of 0.63 g/dl was identified between the mean post-operative hemoglobin values based on the type of surgery. Thus, the values were lower in patients undergoing abdominal surgery. Regardless of the type of surgery, there was an average hemoglobin level difference of approximately 0.58 g/dl in the neuromonitored group, a statistically significant difference.

CRP (C-reactive protein) values ranged from 60 to 128.30 mg/l, with a mean of 32.06±28.59 mg/l and a median of 23.40 mg/l. Regardless of the type of surgery, there was an average CRP level difference of 20.72 mg/l, with CRP levels being lower in patients who were monitored with entropy.

Perioperative sodium levels ranged from 124 to 147 mEq/L, with mean values of 135.35±5.00 pre-operatively, 136.17±3.88 intra-operatively, and 137.70±3.32 post-operatively. Blood glucose levels during the perioperative period ranged from 75 to 310 mg/dl, with mean values of 154.33±49.50 pre-operatively, 143.85±43.26 intra-operatively, and 131.21±31.07 post-operatively.

Patient outcome based on the Neecham confusion scale at 24, 48, and 72 hours.

The Neecham score at 24 hours ranged from 17 to 30 points, with a mean score of 24.51±2.78 and a median of 25, indicating a borderline value between the risk of early confusion syndrome and the development of delirium. 43.2% of patients had Neecham scores ≤24 points.

At 48 hours, the Neecham score ranged from 18 to 30 points, with a mean score of 25.56±2.86 and a median of 26, indicating a borderline value for the risk of confusion syndrome. 32.5% of patients had Neecham scores ≤24 points.

At 72 hours, the Neecham score varied between 21 and 30 points, with a mean score of 27.9±2.1 and a median of 28, indicating the absence of confusion syndrome for the majority of patients, with only 8% of patients having Neecham scores ≤24 points.

In the first 48 hours, the main deductions from the final score calculation were due to minor or inadequate information processing (46.3%), slowed response to commands (15.2%), inappropriate motor behavior, disorientation, and inconsistent orientation (21.3%), as well as vital function instability (17.2%). At 72 hours, the deductions were still primarily due to inadequate information processing or inappropriate motor behavior, while vital function instability played a limited role in the score composition.

Entropy monitoring is a statistically significant predictor in predicting the occurrence of a Neecham score ≤24 points, with a predictive capacity that ranged from 15.7% to 24% up to 48 hours, significantly reducing to only 5.2% at 72 hours.

Entropy monitoring was a negative predictor at 24 hours, reducing the chances of patients developing a Neecham score ≤24 points by 0.18 times at 24 hours and 0.16 times at 48 hours. For the Neecham score measured at 72 hours, entropy monitoring represents a marginal predictor.

At 24 hours, systolic arterial pressure (TAs) ranged from 92 to 189 mmHg, with a mean value of 126.67±20.51 mmHg and a median value of 124 mmHg. Diastolic arterial pressure (TAd) ranged from 44 to 110 mmHg, with a mean value of 67.98±13.91 mmHg and a median value of 65 mmHg. For 27% of patients, it was necessary to continue vasopressor support in this postoperative period, with an average dosage of 0.3±0.05 μg/kg/min. The ventricular rate (AV) in the first 24 hours ranged from 60 to 123 bpm, with a mean value of 88.72±16.07 bpm and a median value of 89 bpm.

At 48 hours, TAs ranged from 101 to 176 mmHg, with a mean value of 126.89±16.73 mmHg and a median value of 124 mmHg. TAd ranged from 51 to 99 mmHg, with a mean value of 70.83±9.66 mmHg and a median value of 69 mmHg. For 21% of patients, it was necessary to continue vasopressor support during this postoperative period, with an average dosage of 0.15±0.025 μg/kg/min. AV at 48 hours ranged from 62 to 121 bpm, with a mean value of 82.00±12.96 bpm and a median value of 79 bpm.

At 72 hours, TAs ranged from 105 to 164 mmHg, with a mean score of 128.46±10.02 and a median value of 128 mmHg. TAd ranged from 53 to 92 mmHg, with a mean value of 69.45±7.64 mmHg and a median value of 69 mmHg. For 11.6% of patients, it was necessary to continue vasopressor support during this postoperative period, with an average dosage of 0.1±0.02 μg/kg/min. AV at 72 hours ranged from 62 to 114 bpm, with a mean value of 79.14±10.83 bpm and a median value of 78 bpm.

Regarding the evolution of TAs in the first 72 hours, no statistically significant differences were identified. For TAd, the differences identified are statistically significant but at a low level. Only the difference between 24 and 48 hours is statistically significant, indicating an increase in TAd at 48 hours. The evolution of ventricular rates recorded shows statistical significance with a high effect, with mean values in the first 72 hours being significantly different from each other.

For 43.6% of patients, it was necessary to continue oxygen therapy via mask or nasal cannula, with a flow of 4-6 l/min in the first 48 hours, and at 72 hours the percentage decreased to 27.4%.

The main notable complications in the first 72 hours in the study groups were emetic syndrome, atrial fibrillation, and urinary incontinence, but these events were isolated and without statistical significance.

The type of surgical intervention did not influence the cognitive evolution of patients in the first 72 hours.

Analysis of the evolution of the Neecham score in the postoperative period based on electrolyte levels and perioperative blood glucose values.

The Na values consistently remained higher, regardless of the perioperative monitoring time, in patients who had a postoperative Neecham score greater than 24 points. In patients with a Neecham score of ≤ 24 points at 24 hours, the perioperative Na values consistently remained lower, with average values of 132.99±5.59, 134.27±4.05, and 136.26±3.30, respectively. Additionally, it can be observed that blood glucose values remained consistently higher, regardless of the perioperative monitoring time, in patients who had a postoperative Neecham score ≤ 24 points. For patients with a Neecham score of ≤ 24 points at 24 hours, perioperative blood glucose values remained consistently higher, with no variability within the group, with average values of 197.85±33.83, 177.79±32.75, and 153.79±26.80.

The final model obtained for a Neecham score of ≤ 24 points at 24h and 48h consists of the intraoperative Na factor and blood glucose (pre, intra, and postoperative). The final model obtained for the Neecham score at 72h consists of the intraoperative Na factor and postoperative blood glucose, with good predictive capacity. In this context, neuromonitoring does not represent a predictive factor for a Neecham score of ≤ 24 points at any of the time points (24h, 48h, 72h).

Evolution of the Neecham score in neuromonitored patients based on the presence of burst suppression episodes

Of the 87 patients monitored by entropy, only 39 patients had at least one burst suppression episode lasting at least 1 minute. The 49 patients who did not have any burst suppression episodes (BS) and had a burst suppression ratio (BSR) of 0 did not show a postoperative Neecham score of ≤ 24 points at any evaluation point (24h, 48h, or 72h).

According to the descriptive analysis of burst suppression events, it appears that the distribution of the percentage of BS (BSR%) and the duration (time) during which burst suppression signals were recorded was almost uniform, with reduced variability, with a BS percentage of 18 and an average burst suppression duration of 6 minutes.

Following the comparative analysis of the BSR(%) level and the duration of the BS episode on the presence or absence of at least one degree of confusion (Neecham ≤ 24 points), a high level of intraoperative BSR % (m=27.05 – 30.38) or a prolonged duration of BS (m=8.70 – 10.31) was identified in those who later developed confusion compared to those who did not show adverse cognitive changes.

Evolution of the Neecham score based on intraoperative Mean Arterial Pressure

The analysis of mean arterial pressure (MAP) at the five defined intraoperative moments—initial monitoring, anesthetic induction stage, surgical incision, end of the surgical intervention, and extubation—identifies differences between the group with a postoperative Neecham score at 24, 48, and 72 hours > 24 points and the group with a Neecham score at 24, 48, and 72 hours ≤ 24 points. Additionally, it was observed that MAP values consistently remained higher, regardless of the defined moment for measuring MAP, in neuromonitored patients who had a postoperative Neecham score greater than 24 points. However, there were no significant differences in MAP values within the group with a Neecham score > 24 points. In patients with a Neecham score ≤ 24 points within the first 72 hours, MAP values consistently remained lower, with no variability in MAP values within the group, and these corresponded mainly to patients who did not benefit from neuromonitoring.

The evolution of the Neecham score in relation to the Visual Analogue Scale (VAS)

According to the descriptive analysis, the VAS score ranged from 2 to 10 points, with a mean value of 5.38±2.3 and a median value of 5. In the first 48 hours, a high VAS score along with intraoperative entropy monitoring reduced the chance of patients developing a confusion syndrome. Regarding the predictive capacity of the VAS score for the evolution of patients with a Neecham score >24 or ≤24 points at 72 hours postoperatively, the predictive capacity is very low.

The evolution of the Neecham score in relation to independent factors

The proportion of cases that evolved with a Neecham score ≤24 at 24 hours can be determined based on independent factors. Among these, the following had a statistically significant effect: gender, with a 0.44 times reduced chance for women to develop a Neecham score ≤24; ASA score, with a 4.40 times higher chance for higher ASA scores to evolve with a Neecham score ≤24; entropy monitoring, with a 0.10 times lower chance of presenting Neecham ≤24 in those who benefited from entropy monitoring. Additionally, marginal predictors included nutritional status with a 0.60 times reduction in the presence of Neecham ≤24 in overweight cases and metabolic comorbidities increasing the chance by 2.44 times to present a Neecham score ≤24 points.

The proportion of cases that evolved with a Neecham score ≤24 at 48 hours based on independent factors identified the following independent factors: ASA score, with a 3.68 times higher chance in patients with high ASA scores to evolve with a Neecham score ≤24 points; as well as entropy monitoring, with a 10 times lower chance of presenting a Neecham score ≤24 points in those who benefited from entropy monitoring. The presence of other factors in the predictive model did not reach the threshold of statistical significance.

For cases that presented a Neecham score ≤24 at 72 hours, high ASA scores increased the chance by 3.59 times. Gender reduced the chance by 0.21 times for women to present a Neecham score ≤24, while entropy monitoring reduced the chance by 0.18 times to present a confused score ≤24 points in those who benefited from entropy monitoring.

The evolution of the Neecham score based on the main anesthetic substances.

The proportion of cases that evolved with a Neecham score ≤24 at 24h and 48h can be determined based on the quantities of anesthetic substances administered. Among these, Fentanyl showed a statistically significant effect with a 1.59, respectively 1.56 times higher chance of presenting a Neecham score ≤24 with high quantities, and Sevoflurane showed a 1.67, respectively 1.38 times higher chance of presenting Neecham ≤24 in those who received high quantities.

For the evolution at 72h, the model does not allow predicting a Neecham score ≤24.

Evolution of the Neecham score based on hemodynamic events, hypoxemia, and perioperative metabolic acidosis

For the first 24 hours, statistically significant effects were observed with intraoperative hypotension, indicating a 1.74 times higher chance of developing a Neecham score ≤24 with a high number of events, bradycardia showing a 1.66 times higher chance of presenting a Neecham score ≤24 in those experiencing a high number of events, and perioperative metabolic acidosis, suggesting an approximately 5 times higher chance of presenting a Neecham score ≤24 in those experiencing this adverse event. At 48 hours, the presence of intraoperative hypotension increased the chance of confusion syndrome by 1.95 times with a high number of events, and perioperative metabolic acidosis increased the chance by approximately 3.88 times for patients to evolve with a Neecham score ≤24. For the evolution at 72 hours, the model does not allow the prediction of a Neecham score ≤24.

Evolution of the Neecham score based on the main predictors

The proportion of cases evolving with confusion syndrome at 24 hours can be determined based on the number of BSR events, with a 269.5 times higher chance in case of a high number of BSR events, PCR showing a 1.10 times higher chance of presenting a Neecham score ≤24 in those with a high PCR level. Perioperative metabolic acidosis represents a marginal predictor, with an approximately 13 times higher chance of presenting a Neecham score ≤24 in those who experienced perioperative metabolic acidosis. At 48 hours, the duration of BSR events increased the chance of confusion syndrome by 1.65 times with a high duration, PCR increased the chance by approximately 1.10 times of presenting a confusion score in those with a high PCR level. Additionally, preoperative Hb represents a positive predictor, with an approximately 10 times higher chance of presenting a Neecham score ≤24 in those with low preoperative Hb values, while postoperative Hb represents a negative predictor, with an approximately 0.07 times lower chance of presenting a Neecham score ≤24 in those with high postoperative Hb values.

Prediction model of Neecham score ≤24 points at 24h and 48h

The proportion of cases evolving with a Neecham score ≤24 at 24 hours can be determined based on: the administration of noradrenaline, with a 3.37 times higher chance when used, and entropy monitoring, with an approximately 5 times lower chance of presenting a Neecham score ≤24 in those who underwent entropy monitoring.

At 48 hours, the administration of noradrenaline increased the chance of evolving with confusion syndrome by 4.95 times, entropy monitoring reduced the chance by approximately 3 times for patients to present a Neecham score ≤24, and the amount of crystalloid represents a positive predictor, with a 1.7 times higher chance of presenting a Neecham score ≤24 with an increase in crystalloid quantity.

Length of hospital stay

The length of hospital stay in the ICU was reduced on average by -3.45 days for patients who underwent entropy control. The type of intervention determined a longer hospital stay on average by 2.7 days for patients undergoing abdominal surgery. The total duration of hospitalization indicates a shorter duration on average by -2.81 days for patients who underwent entropy control, and in the case of patients undergoing abdominal surgery, a longer hospital stay on average by 3 days. The 30-day mortality rate was 12% of the total number of patients included in the study, and all these cases evolved with delirium in the first 72 hours postoperatively, regardless of the type of surgical intervention. Higher proportions were observed in patients who did not undergo entropy control.

Discussions

The benefits of neuromonitoring during emergency surgeries have been insufficiently researched to date, although there are already numerous recommendations for preparing and optimizing the status of patients even in the preoperative period for elective surgeries. Patients undergoing emergency surgeries present additional risks and are more vulnerable to acute pathology requiring surgical intervention. The present research focused on the effect of monitoring the depth of general anesthesia through entropy on the intraoperative evolution of patients and its immediate effect on cognitive function.

The results presented in various studies and meta-analyses published to date are conflicting regarding the reduction in anesthesia duration for patients monitored intraoperatively, ranging from 0.6 to 12 minutes [1][2,3]. These differences found in the literature may also be the result of different definitions of the end of anesthesia, with some authors recording either the opening of the eyes to verbal stimulation, extubation of the patient, or even the moment when the patient becomes oriented. In this study, entropy control resulted in a difference of 3 minutes until extubation of patients, but this difference was not significant. However, the result of the analysis is not unique in the literature. Vance and colleagues reported the absence of a significant difference until extubation of patients in the group that underwent neuromonitoring compared to the standard monitored group [4]. On the other hand, both exposure to volatile anesthetic and opioids and muscle relaxant substance were significantly reduced in patients who benefited from entropy control, regardless of the type of emergency surgical intervention performed. Similar results regarding the consumption of volatile anesthetic can be found in the literature, although the vast majority of studies focus on elective surgeries [5][6]. This study identified a reduction of 2.3 ml/h in sevoflurane consumption in patients who underwent neuromonitoring, compared to the 1.4-2.2 ml/h reported in the literature [3][7]. Additionally, neuromonitoring allowed a significant reduction in the dose of fentanyl by approximately 68 μg, similar to the dose presented by Recart et al. [8]. Regarding the consumption of rocuronium, there was a reduction of 5 mg in the neuromonitored group in patients undergoing abdominal surgeries. Although the primary role of entropy is to titrate the hypnotic, the main reason why the neuromonitored group also showed a reduction in opioid and muscle relaxant dose may be due to the synergistic effect

these substances can have. Additionally, in patients who underwent entropy monitoring, locoregional analgesia techniques were more frequently implemented, although not significantly. It is well-known that regional analgesia techniques have multiple advantages in multimodal pain management. These techniques are safe, effective, and reduce perioperative opioid consumption [9]. The most well-known type of block used in the emergency department is the femoral nerve block for femoral fracture, while data on the performance of trunk blocks for emergency abdominal surgery are limited, although Enhanced Recovery After Surgery (ERAS) protocols encourage the implementation of these techniques [10].

Regarding the differences in fluid consumption between abdominal and orthopedic surgical interventions, as well as how entropy can modulate intraoperative crystalloid consumption, current data are limited. Both types of surgical interventions differ in terms of operating time, complexity, intercompartmental fluid transfer, or bleeding risk, so maintaining euvolemia can be a challenge especially for patients operated on in emergency conditions [11][12]. Lima et al. demonstrated that the total volume of crystalloid and colloid can be significantly reduced, indirectly through neuromonitoring [13]. In this study, only crystalloid consumption was more significant in patients with abdominal surgical interventions, but regardless of the type of surgical intervention, there was a significant reduction of approximately 300 ml of crystalloid in the neuromonitored group. Although neuromonitoring does not have a direct role in fluid management strategy, this consequence may primarily result from the reduction in the amount of volatile anesthetic in patients monitored by entropy and implicitly from the systemic vasodilatory effect [14]. Similarly, the reduced need for intraoperative vasopressor support in neuromonitored patients can be interpreted. This hypothesis can also be supported by the results of the study by Nitzschke et al., which demonstrated a direct association between sevoflurane plasma levels and the need for norepinephrine [15].

Specialized literature reports better hemodynamic evolution in patients undergoing depth of anesthesia monitoring, as a result of reducing intraoperative hypotension and sinus bradycardia events [7][16][17]. It must be noted, however, that defining better hemodynamic profile and arterial hypotension concepts are not uniform in the literature. Defining arterial hypotension by a relative reduction in blood pressure of more than 20% from the baseline

level is mainly based on opinion and historical precedent, and the introduction of cut-off values has not always justified perioperative adverse effects [18]. The new recommendations formulated by the European Society of Cardiology to minimize organ injury include avoiding reducing mean arterial pressure by more than 20% from the baseline level or dropping below 60-70 mmHg for at least 10 minutes in the perioperative period [19]. However, the recommendations are general and do not include additional data on cerebral protection. Also, intraoperative events such as arterial hypertension, bradycardia, or sinus tachycardia are vaguely defined in specialized publications [16].

In this study, arterial hypotension was defined as a decrease and maintenance of mean arterial pressure below 65 mmHg. To be able to define the severity of the event, two consecutive measurement cycles were chosen. Most patients had one or two intraoperative arterial hypotension events, and the occurrence of events was lower among neuromonitored patients and in patients who required orthopedic surgical intervention. Additionally, entropy monitoring reduces by almost 5 times the likelihood that patients will experience an episode of arterial hypotension. Also, the hemodynamic profile judged by the variability of mean arterial pressure presented reduced variability in the entropy-monitored group at the initial moment of monitoring, after anesthetic induction, after surgical incision, at the end of the surgical intervention, as well as at the moment of extubation.

Aimé and colleagues reported the occurrence of bradycardia events as similar between the groups monitored by BIS or entropy and the group that did not benefit from depth of anesthesia monitoring [20]. It must be mentioned, however, that their study followed patients scheduled for surgical interventions. In this study, bradycardia events were noted if the ventricular rate dropped below 60 bpm. By this definition, 32.7% of bradycardia cases were identified, and in the case of patients monitored by entropy, the occurrence of the event could be reduced by at least 2 times.

Regarding the presence of arterial hypertension events, these were defined by an increase in systolic blood pressure above 140-160 mmHg and/or diastolic blood pressure above 90-95 mmHg for two consecutive measurement cycles. No statistical differences were identified between the neuromonitored group and the group that did not benefit from

neuromonitoring. Comparable results were recorded for tachycardia events defined by an increase in ventricular rate above 90 bpm.

Absence of variations between groups has been reported by Nair et al. in a prospective observational study, as well as by Karaca et al. [21][22].

According to the literature, monitoring the depth of anesthesia cannot prevent the occurrence of hypoxia during general anesthesia with endotracheal intubation. The analysis of hypoxia events in the present study demonstrates the presence of a small and nonsignificant number of hypoxia episodes. However, there are reports in the literature of higher peripheral oxygen saturation values in neuromonitored patients, most likely due to a better hemodynamic profile [22].

In this study, the number of patients who presented intraoperative metabolic acidosis was lower among patients who benefited from entropy monitoring. Although no general anesthesia monitoring device can directly influence the acid-base balance, the reduced presence of metabolic acidosis may be a consequence of a lower volume of crystalloid and a smaller need for vasopressor support with norepinephrine among patients monitored by entropy [23].

Another indirect consequence of reducing intraoperative crystalloid consumption is the higher hemoglobin levels in the postoperative period in the entropy-monitored group. Thus, hemoglobin levels in the preoperative period were on average 0.55 mg/dl higher, and in the postoperative period, they were on average 0.58 mg/dl higher. Transfusion requirements were similar in both groups.

Research on the relationship between inflammation and depth of anesthesia monitoring is ongoing. To date, alterations in EEG accuracy have been described with progressive inflammation, but without establishing a cutoff value. On the other hand, the literature mentions that the immunomodulatory role of anesthetics in patients undergoing emergency surgery is secondary, so surgical stress plays a central role. C-reactive protein (CRP) is considered a reliable indicator of trauma and surgical stress, and Fengling et al. demonstrated

a decrease in CRP levels in intraoperatively neuromonitored patients. In the present study, CRP levels were reduced by 20.72 g/dl in the intraoperatively neuromonitored group.

Regarding the cognitive evolution of patients in the postoperative period, I believe it is dictated by the entire perioperative period, and in the context of emergency surgeries, measures to prevent cognitive decline remain limited.

The first publication about cognitive changes after anesthesia and surgery appeared over 100 years ago. Research on cognitive changes during the perioperative period only became a priority in the 1980s and evolved separately from cognitive studies in the general population. There are current initiatives to standardize the definition of different types of cognitive dysfunction that may occur during the perioperative period, while multiple diagnostic tests with varying sensitivity and specificity are validated for diagnosis.

In this study, we chose to assess early cognitive function at 24, 48, and 72 hours postoperatively using the Neelon and Champagne Confusion Scale (NEECHAM) due to its high sensitivity and specificity in detecting not only patients with hyperactive delirium but also patients with hypoactive delirium or at risk. Currently, there are limited reports in the literature regarding the use of this score for detecting delirium in the postoperative period following emergency surgeries [7]. A confusion score ≤24 points indicated the presence of a confusion syndrome or a mild form of delirium. From the screening form analysis, 43.2% of patients had NEECHAM scores ≤24 points at 24 hours, 32.5% had scores ≤24 points at 48 hours, and at 72 hours, only 8% of subjects had scores ≤24 points. The incidence of postoperative delirium cases was similar to reports in the literature on the incidence of postoperative delirium after emergency surgeries. The type of surgical intervention (abdominal or orthopedic) did not influence the cognitive evolution of patients at any point during postoperative assessment. Patients who had a confusion score ≤24 points in the first 48 hours mainly presented minor or inadequate information processing deficits, slow response in executing commands, inappropriate motor behavior, disorientation, and inconsistent orientation. At 72 hours, the main deficits were still inadequate information processing or inappropriate motor behavior, while the contribution of vital function instability was diminished. It should be noted that for 27% of patients, vasopressor support was necessary at

24 hours, which decreased to 21% at 48 hours and to 11.6% at 72 hours. Additionally, 43.6% of patients required ongoing oxygen therapy in the first 48 hours, and 27.4% required ongoing oxygen therapy at 72 hours. According to the analysis, entropy monitoring reduced the chance of patients evolving with a score ≤24 points in the first 48 hours, while at 72 hours, it becomes a marginal predictor. Specialized literature offers conflicting data regarding the ability of neuromonitoring to prevent postoperative delirium. Recent studies and meta-analyses such as those by Chen Chen Y., Evered L., or Perez-Otal. and their colleagues have reported that processed EEG depth of anesthesia monitoring contributes to reducing the incidence of postoperative delirium, whereas the working group coordinated by Miao M. rejects this hypothesis. The latest guideline elaborated by the European Society of Anesthesiology and Intensive Care recommends intraoperative depth monitoring, giving it a grade B recommendation due to a low level of evidence.

I believe that patients' postoperative evolution cannot be judged solely based on the presence or absence of depth of anesthesia monitoring.

So far, the causal association between cognitive changes and the anesthesia-surgical act remains uncertain, although an impressive number of precipitating and predisposing factors have been described. Ormseth and colleagues' recent review identified 112 precipitating factors and 33 predisposing factors. Among these, emergency surgeries by definition carry an increased risk.

Advanced age is often cited in the literature as a predisposing factor. In this study, patients' ages ranged from 21 to 92 years, and almost 50% of patients were at risk age for postoperative cognitive decline according to literature data. However, the results obtained in this research show that age was not a risk factor, regardless of the type of emergency surgical intervention performed.

A higher body mass index (BMI) is considered to have protective effects on immediate postoperative cognitive evolution, although obesity is associated with long-term cognitive decline. In the studied population, only 37.3% of patients had a normal nutritional status, while 62.7% were overweight or had grade I obesity. Following the analysis, only overweight status had a marginal effect on reducing unfavorable cognitive evolution.

Published data are conflicting regarding gender predisposition to unfavorable cognitive evolution, although it leans toward male gender. As for gender categories, in this study, they were distributed roughly evenly between the study groups and regardless of the type of surgical intervention. Only the female gender conferred a protective effect and reduced the chance of female patients developing delirium.

The ASA score contributes to defining the risk for unfavorable cognitive evolution in the postoperative period. Most patients had a severity ASA score of at least III, with 83% of them having comorbidities. In this research, a high ASA score exposed patients to a fourfold higher risk of unfavorable cognitive evolution. Traumas that did not require surgical sanction were more frequently associated with patients who required orthopedic surgeries. The presence of metabolic comorbidities was approximately twice as common in patients who benefited from neuromonitoring and in those with abdominal surgical interventions. According to trials published so far, their presence increases the risk of patients developing delirium in the postoperative period.

Following the analysis of independent factors and their association with acute surgical interventions, it can be assumed that in the present study, patients exhibited multiple non-modifiable risk factors to evolve with at least a confusion syndrome in the immediate postoperative period. Entropy neuromonitoring reduced the likelihood of patients evolving with a Neecham confusion score $\leq$24 points at both 24 and 48 and 72 hours postoperatively, demonstrating a limited effect even in patients with ASA score $\geq$3 and in the presence of metabolic comorbidities.

Regarding the duration of surgical intervention and implicit anesthesia duration, the literature data categorize it as a potential modifiable risk factor for the development of immediate postoperative cognitive dysfunction, although the level of evidence is moderate. Therefore, it is assumed that monitoring the depth of anesthesia can bring significant benefits by significantly reducing anesthesia duration in elective surgical interventions. However, in the present work, entropy control resulted in a non-significant difference regarding the reduction of anesthesia duration for emergency surgical interventions. In this context, the following hypothesis can be formulated: even though anesthesia duration was not significantly

reduced in the neuromonitored group compared to the other group, better optimization of anesthesia depth could be ensured, as well as a reduction in unwanted hemodynamic effects such as arterial hypotension.

The consumption of volatile anesthetic was significantly reduced in patients who underwent entropy control, regardless of the type of emergency surgical intervention performed. The specialized literature provides contradictory evidence regarding the role volatile anesthetics play in the etiopathogenesis of postoperative delirium. While Taylor and colleagues reject the hypothesis that the Sevoflurane dose is directly implicated in delirium onset, there are studies demonstrating the protective effect of neuromonitoring by reducing minimum alveolar concentrations and delirium incidence. Regarding systemic opioid administration, ERAS protocols promote reducing the use of this class of analgesics. Although opioids play a central role in pain management, they have multiple side effects and are recognized as one of the main precipitating factors of cognitive dysfunction in the perioperative period. In the present study, Fentanyl consumption was significantly reduced in patients monitored through entropy. It should be noted that some of these patients also benefited from locoregional analgesia and morphine during the perioperative period. As for the morphine dose, it was administered judiciously, following the recommendations of Morrison and colleagues, without exceeding a dose of 10 mg/day in subjects exposed to confusion syndrome. The analysis of intraoperative Sevoflurane and Fentanyl consumption from the present research suggests a reduced likelihood of patients evolving with a Neecham confusion score $\leq$24 points in the first 48 hours following dose reduction, while reducing volatile anesthetic consumption only becomes a marginal predictor at 48 hours postoperatively.

In the group that benefited from neuromonitoring, crystalloid volume and vasopressor support utilization were significantly reduced. These results are in line with published data. It is known that both hypovolemia and hypervolemia can have unfavorable consequences on the cognitive evolution of patients in the postoperative period, but regarding the effect that intraoperative reduction of vasopressor dose can have on this, the data are uncertain. Following the analysis from the present research, it is evident that both increasing noradrenaline dose and increasing crystalloid volume are associated with the development of

at least a confusion syndrome in the first 48 hours postoperatively, although entropy monitoring represents a protective factor in both scenarios.

The cognitive evolution of patients is dictated by hemodynamic events, and among these, episodes of arterial hypotension, especially if prolonged, as well as tensional variations, play a major role. Maheshwari et al. report an increased incidence of complications, especially when prolonged arterial hypotension is associated with too deep anesthesia. Another multicenter study reports the occurrence of postoperative delirium regardless of the duration of the arterial hypotension event (< or > 15 minutes), if the mean arterial pressure value was lower than 55 mmHg. In this context, Brady K. and colleagues introduce the concepts of arterial tension personalization for cerebral protection and redefinition of hypotension based on cerebral blood flow autoregulation, as a normal mean arterial pressure may actually have a lower value than the lower limit of autoregulation. Non-invasive and continuous intraoperative assessment of cerebral autoregulation is currently in the experimental stage. Parameters such as mean velocity index have shown negligible effects until now. Therefore, mean arterial pressure remains a faithful parameter for the hemodynamic optimization of patients. As previously mentioned, in the current research, entropy monitoring significantly reduced the number of arterial hypotension events and variations in mean arterial pressure. According to the analysis performed, arterial hypotension during the intraoperative period increases the risk of patients developing confusion syndrome within the first 48 hours. Patients who developed a Neecham confusion score > 24 points within the first 48 hours consistently had higher intraoperative mean arterial pressure values, although differentiable by the presence of entropy, regardless of the chosen moment for blood pressure monitoring. Additionally, mean arterial pressure values at a specific intraoperative moment, combined with entropy monitoring, influence the cognitive evolution of patients within the first 48 postoperative hours and may reduce the probability of progression to a Neecham score ≤ 24 points. Cognitive evolution at 72 hours was influenced by intraoperative variations in mean arterial pressure, regardless of the presence of entropy monitoring. Another hemodynamic event within the first 24 hours that significantly contributed to the development of confusion syndrome was sinus bradycardia.

Another significant contributor to the increased incidence of confusion syndrome was metabolic acidosis during the perioperative period. Specialized literature notes the presence of metabolic acidosis as a predictive factor for confusion syndrome or delirium. At the same time, confusion syndrome and disorientation can be expressions of metabolic imbalances and dyselectrolytemias. In this study, perioperative variations in sodium and glucose levels resulted in differences between subjects who developed a Neecham confusion score > 24 points and those with a score ≤ 24 points. In the latter case, perioperative sodium values remained consistently lower, within the range of mild hyponatremia, while glucose values remained consistently higher, indicative of moderate hyperglycemia. For the first 72 hours, intraoperative sodium levels and perioperative glucose levels were identified as high-risk factors for unfavorable cognitive evolution, while neuromonitoring had a limited role in the presence of dyselectrolytemias.

A significant number of publications have attempted to identify the role of biomarkers in the etiopathogenesis of postoperative delirium, but recent guidelines specify that no biomarker described to date is sufficiently specific or sensitive to confirm or predict the evolution of patients with postoperative delirium. In the present study, although neuromonitoring reduced the chance of patients developing confusion syndrome, the measured systemic inflammatory biomarker (PCR) increased the chance of patients developing a Neecham score ≤ 24 points within the first 48 hours after surgery. The possible interaction between systemic inflammatory syndrome and EEG alteration has not been definitively established to date, although in neuroinflammation, the EEG trajectory undergoes changes and can influence EEG-derived parameters.

The low concentration of hemoglobin during the perioperative period is prevalent in patients undergoing emergency surgeries and negatively influences patients' outcomes in both the short and long terms. Myint's audit and colleagues report the absence of an association between anemia and cognitive evolution in elderly patients after emergency surgeries, but caution in interpreting the data is recommended as the analysis is retrospective. Many other randomized studies report anemia as an independent risk factor for postoperative delirium and cognitive decline, although the reported cutoff values in the literature differ. In the present study, hemoglobin values in neuromonitored patients were 0.55 mg/dl higher during the

preoperative period compared to the mean value of 9.21 mg/dl and 0.58 mg/dl higher during the postoperative period compared to the mean value of 8.05 mg/dl, most likely due to reduced crystalloid volume in this group. For the first 48 hours, perioperative hemoglobin values increased the chance of patients developing a confusion score ≤ 24 points. Similar results have been reported for abdominal surgery by Raats et al.

Neuromonitoring offers another advantage besides monitoring the depth of general anesthesia, namely the identification of the burst suppression ratio (BSR), defined as a period of profound cerebral inactivity within an epoch, which can be another precipitating factor for postoperative delirium. Soehle and colleagues concluded that patients who developed confusion syndrome had prolonged burst suppression episodes compared to those with normal cognitive evolution. Similar reports come from studies including a significant number of patients scheduled for surgeries. Fritz et al. report that a suppression duration of over 4.5 minutes was associated with a higher incidence of postoperative delirium compared to a shorter duration (< 4.4 minutes). A retrospective analysis conducted by Pedemonte JC. demonstrated that the duration of the burst suppression episode, correlated with age, exposes patients scheduled for cardiac surgery to a higher risk of postoperative delirium. However, in the context of advanced age, EEG signals are diminished, so the indices provided by the parameters may be falsely elevated during an anesthetic overdose. A secondary analysis after the ENGAGE trial demonstrated that burst suppression episodes can negatively influence cognitive evolution, including in patients with pre-existing cognitive pathologies. It should be noted that none of the significant studies published to date have targeted patients undergoing emergency surgery. In the present study, 39 of the neuromonitored patients recorded at least one burst suppression episode lasting at least 1 minute, with an average duration of 6 minutes and a BSR of 18. Both BSR and the duration of BS events were identified as significant predictors for the onset of confusion syndrome or delirium within the first 48 postoperative hours. Additionally, the ASA severity score contributed to a limited extent in this context, while age, unidentified as a precipitating factor in the present study, was not a contributing factor. For the other 49 patients monitored through entropy, no burst suppression episodes were recorded. For these patients, at no point during the postoperative evaluation (24h, 48h, or 72h) was the Neecham confusion score ≤24 points.

I believe that, in addition to the aforementioned points, the occurrence of confusion syndrome cannot be judged in the absence of pain evaluation. Suboptimal pain treatment further increases the risk of unfavorable cognitive evolution. In this study, pain was evaluated postoperatively using the VAS score. Ma et al. described unfavorable cognitive evolution within the first 72 postoperative hours in patients whose pain was inadequately treated. According to the analysis obtained, an increase in the VAS score correlates with an increased risk of the patient developing confusion syndrome within the first 48 postoperative hours. The correlation between pain intensity and the risk of presenting confusion syndrome has been described after variable periods of the anesthetic-surgical act and by other publications. Furthermore, in this study, multivariate analysis demonstrated that both at 24 and 48 hours, entropy monitoring represented a protective factor.

Specialized literature notes that intraoperative anesthesia monitoring and avoiding a deep level of anesthesia reduces the hospitalization duration for patients both in the Intensive Care Unit and the total hospitalization duration. In the present research, hospitalization duration was, on average, 3 days shorter in the entropy-monitored group and in patients requiring orthopedic surgeries. However, I consider that in the case of surgical patients, these data can be influenced by several other factors such as comorbidities, age, and recovery capacity.

Studies have also reported a reduction in mortality among patients who were intraoperatively neuro-monitored. The explanation for the lower mortality among patients benefiting from neuro-monitoring lies in the fact that in the case of monitoring the depth of anesthesia, a too deep level of anesthesia and especially tensional oscillations, as well as episodes of arterial hypotension, can most often be avoided. The data from the present study demonstrated a 30-day mortality rate of 12%, with the risk being significantly reduced in patients who benefited from entropy monitoring. I note that all these patients presented postoperative delirium at 72 hours, and the causes of death were not a consequence of the depth of anesthesia (multiple organ dysfunction due to septic/hemorrhagic/cardiogenic shock).

Research limitations: The present research is a single-center study conducted in a tertiary referral center, on a population of patients who underwent emergency abdominal or orthopedic surgeries, so the results cannot be generalized to all surgical centers or patients.

This work did not aim to validate the utility of entropy in monitoring the depth of anesthesia in emergency surgery, but rather the potential benefits on optimizing anesthesia and on the cognitive evolution of patients in the immediate postoperative period.

Although entropy monitoring has demonstrated its usefulness in perioperative patient care, it has several limitations. The index displayed by the monitor has a latency degree, it results from the processing of EEG signals whose patterns can be modified in certain clinical scenarios, by the presence of artifacts, as well as by patient characteristics (age, comorbidities, pharmacokinetics, sensitivity to drug interaction). Since studies regarding these patterns are limited, integrating the information provided by entropy monitoring into anesthetic management must be adapted to the clinical context and cannot replace the clinician's judgment.

I consider that due to the multifactorial etiopathogenesis of postoperative delirium, intraoperative entropy monitoring cannot represent the sole intervention in the perioperative period in the scenario of emergency surgery. In this sense, I consider a better understanding of the pathophysiological mechanisms and the clinical entity represented by postoperative delirium necessary in order to adjust the anesthetic act and improve the quality of life of patients after surgery.

General conclusions:

The main objectives of this work were to evaluate the role of entropy neuromonitoring on anesthetic management during major emergency surgeries and its effect on cognitive evolution in the immediate postoperative period.

Based on the analysis of the study results, the following conclusions can be drawn:

1. Exposure to volatile anesthetic, opioids, and muscle relaxant was significantly reduced in patients monitored by entropy, regardless of the type of emergency surgical intervention performed.
2. The total volume of crystalloid was significantly reduced in the neuromonitoring group.
3. Vasopressor support was decreased in intraoperatively entropy-monitored subjects.
4. The group that benefited from intraoperative entropy control presented a better hemodynamic profile, with a significant reduction in episodes of arterial hypotension and mean arterial pressure variations, as well as a reduction in sinus bradycardia events.
5. Cases that evolved with intraoperative metabolic acidosis were fewer in the neuromonitoring group.
6. The postoperative level of hemoglobin was higher among patients in the entropy-monitored group.
7. Entropy monitoring significantly reduced the chance of patients developing delirium in the first 48 postoperative hours, including patients with ASA severity scores ≥3 and in the presence of metabolic comorbidities.
8. Patients who presented delirium at 24 and 48 hours exhibited information processing deficits, slowed response in executing commands, inappropriate motor behavior, disorientation or inconsistent orientation, as well as instability in vital functions (continuation of oxygen therapy and vasopressor support).
9. At 72 hours postoperatively, entropy monitoring became a marginal predictor for postoperative delirium;

10. Patients who developed delirium at 72 hours demonstrated inadequate information processing or inappropriate motor behavior, but showed better vital signs stabilization;

11. Reduction in Sevoflurane and Fentanyl consumption secondary to neuromonitoring decreased the risk of unfavorable cognitive outcomes in the first 48 hours;

12. Patients who showed good cognitive evolution in the first 48 hours had fewer episodes of arterial hypotension, consistently higher mean arterial pressure values intraoperatively, differentiable by the presence of entropy monitoring, regardless of the chosen moment for blood pressure monitoring;

13. In neuromonitored patients, Burst Suppression Ratio (BSR) and the duration of BS events were identified as significant predictors for the onset of postoperative delirium in the first 48 hours, independent of ASA severity score or age;

14. Better pain control in the postoperative period, correlated with intraoperative neuromonitoring, reduces the occurrence of postoperative delirium;

15. Perioperative hemoglobin levels correlated with the presence of entropy monitoring reduce the likelihood of delirium evolution in the postoperative period;

16. In the presence of moderate intraoperative hyponatremia, moderate perioperative hyperglycemia, and systemic pro-inflammatory status, entropy monitoring had a limited role in preventing postoperative delirium;

17. Length of hospital stay and mortality were reduced in patients monitored through entropy.

Importance and Originality of Thesis Results

This research demonstrates the importance of implementing depth of anesthesia monitoring through entropy in emergency surgical patients in an attempt to individualize intraoperative anesthetic management. In the scenario of emergency surgeries, preoperative evaluation is often succinct and primarily addresses the cardiovascular and respiratory systems; thus, cognitive evaluation and possible proactive interventions to improve cognitive status play a marginal role. The results of this study recommend the use of this type of neuromonitoring to prevent cognitive decline in the immediate postoperative period, although due to the multifactorial etiopathogenesis of cognitive disorders in the perioperative period, it cannot represent the sole intervention.

For this reason, in this thesis, the role of neuromonitoring was analyzed in the context of the presence of other predictive or precipitating factors for unfavorable cognitive evolution. Although shortening the duration of anesthesia is often cited in the literature as a beneficial factor for cognitive evolution in the postoperative period, the results of this research demonstrate that this aspect has limited contribution and possibly more important is the intraoperative titration of anesthetic substances and fluids. In contrast, entropy monitoring allowed for a better hemodynamic profile during the intraoperative period, as well as the identification of burst suppression events that can precipitate the onset of delirium independent of age. However, the presence of electrolyte disturbances and the inflammatory syndrome reduced the potential role of entropy monitoring in preventing postoperative delirium.

The literature on the role of entropy in optimizing anesthetic management in emergency surgical patients is limited, so the results of this work complement the therapeutic strategy in this context. Research on perioperative measures whose implementation can lead to increased precision in anesthetic management remains open, requiring additional robust evidence to contribute to the improvement of postoperative outcomes for patients undergoing emergency surgery.

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