Critical Analysis of Sedation and Analgesia in Severe Head Trauma

Análise crítica da sedação e analgesia no traumatismo craniano grave

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Abstract

Introduction Head injury is a direct determinant of morbidity, disability, and mortality in the young population. Sedatives and analgesics are commonly used in patients with brain injury to retrieve an ICP, CMRO2, and CBF, preserving the cerebral regulation system and self-avoiding hypotension.

Objective The objective of this paper is to review on this topic, linking the main drugs, side effects, costs, anxiolytic properties, anticonvulsants, and correlating them with complacency and brain metabolism.

Methods We perform a literature review using PubMed database, MEDLINE, EMBASE, Science Direct, The Cochrane Database, Google Scholar, and Clinical trials. We selected papers from the period between 1958 and 2014, which totaled 254 papers. Of these, we selected 129 papers based on keywords, inclusion, and exclusion criteria.

Evidence Review The volume of the brain decreases due to dislocation of the CBV out of the skull. The main sedatives and analgesics are propofol, midazolam, etomidate, ketamine, barbiturates, dexedetomedina, morphine, fentanyl, alfentanil, sulfenatil, and remifentanil. We hereby discuss the algorithm for a fast intubation sequence and the algorithm for intracranial hypertension treatment regarding the systematic sedation therapy. A range of sedatives and analgesic agents are available for sedation. Each class has its own positive and negative effects on neurotrauma patients.

Keywords
- brain injury
- intracranial hypertension
- sedation
- analgesia

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Conclusions The correct analysis of sedation and analgesia in neurotrauma, rapid sequence intubation, and management of medications in intracranial hypertension can lead to an ideal management of brain injury.

Resumo

Introdução Traumatismo Craniano (TCE) é determinante direto na morbidade, incapacidade e mortalidade na população jovem. Sedativos e analgésicos são comumente usados em pacientes com lesão cerebral com o objetivo de recuperar PIC, CMRO2 e FBC, preservando o sistema de autorregulação cerebral, evitando hipotensão.
Objetivo O objetivo deste trabalho é fazer uma revisão sobre este tema, correlacionando as principais drogas, efeitos colaterais, custos, propriedades ansiolíticas, anticonvulsivantes, correlacionando com complacência e metabolismo cerebral.
Métodos Revisão da literatura utilizando base de dados PubMed, MEDLINE, EMBASE, Science Direct, The Cochrane Detabase, Google Scholar, ensaios clínicos. Os trabalhos selecionados de 1958 a 2014. Somou-se 254 trabalhos. Foram selecionados 129, através de palavras-chave, inclusão e critérios de exclusão.
Evidência Revisão O volume do cérebro é reduzido devido o deslocamento do volume cerebral. Os principais sedativos e analgésicos são: propofol, midazolam, etomidato, cetamina, barbitúricos, a dexmedetomidina, morfina, fentanil, alfentanil, sulfato, remifentanil. Discute-se algoritmo para a sequência rápida de intubação e algoritmo para tratamento de hipertensão intracraniana. Uma série de sedativos e analgésicos agentes estão disponíveis para sedação. Cada classe tem seu próprio efeitos positivos e negativos em pacientes no neurotrauma.
Conclusões e Relevância O presente trabalho contribui com a análise correta da sedação e analgesia em neurotrauma, sequência rápida de intubação e administração de medicamentos para analgesia e sedação em hipertensão intracraniana, e um ideal manejo na lesão cerebral.

Palavras-chave
- lesão cerebral
- hipertensão intracraniana
- sedação
- analgesia

Introduction

Trauma is a leading cause of death in people between 1 and 44 years. Traumatic brain injury (TBI) is the main determinant of morbidity, disability, and mortality within this age group. Severe TBI is associated with a 30 to 70% mortality rate, and the recovery of survivors is marked by severe neurological sequels and a severely impaired quality of life. TBI means any aggression traumatic order that results in anatomic injury or functional impairment of the scalp, skull, meninges, the brain or its vessels.[1,2]

Brain injuries and their coverage occur in ~200 out of 100,000 people per year and account for 14 to 30 deaths among 100,000 people per year in the United States. The most common cause of TBI is through vehicles, followed by falls from heights (pediatric and geriatric predominates in this group), and by firearms. The incidence in men is two to three times higher than in women and the most common age range is from 15 to 24 years, with a secondary peak after 65 years. The seriousness of the problem is complicated by behavioral sequelae, even in relatively small head injuries.[3,4]

Sedatives and analgesics are agents commonly used in critically ill patients. The use of sedatives in neurotrauma patients in both the operating room and the intensive care unit is extremely important to know what effects these drugs or drug combinations have on brain metabolism and intracranial compliance. Cerebral vasodilation may result in increased intracranial pressure (ICP) or oxygen consumption ($CMRO_2$). In addition, these agents can affect the cerebral perfusion pressure (CPP), as many have potent effects on mean arterial pressure (MAP). Other concerns involving the use of these agents include time until wake-up after the interruption and the effects on patient outcome. Cost is also becoming an increasingly important factor to consider in the choice of drug therapy.[5]

Severe trauma patients present with risk of hypotension and cerebral vasodilation due to brain injury. Hypotension reduces cerebral perfusion pressure, cardiac output, and peripheral resistance. Self-regulation persists only in the blood pressure range of 60–150mmHg. Different values start to trigger the mechanisms of brain swelling and impaired cerebral metabolic physiology, like increases of cerebral vasodilation (CVS), cerebral swelling, $CMRO_2$ and ICP.[6]

Objective of this study is to perform a literature review on the main effects of analgesia and sedation in severe TBI, relate the main drugs and their effects, correlating with metabolism and brain compliance. We also propose algorithms for rapid sequence intubation in TBI and intracranial hypertension to systematize the sedation therapy.

Materials and Methods

We conducted a literature review using as a database PubMed, MEDLINE, EMBASE, Science Direct, the Cochran Database, Google Scholar, and Clinical Trials. We selected works from the period of 1958 to 2014. There were a total of 254 works, from which 129 were selected according to exclusion criteria. We also performed a manual search in medical journals and magazines regarding the brain metabolism in severe TBI. Articles with incomplete clinical data were not included in the work. We also deleted those focused on TBI approach, surgical types, and behaviors of cerebral injury. The main topics determined are presented below.

Sedation and Analgesia

Knowledge of brain metabolism is very important to understand the brains self-protection mechanisms in the face of acute brain injury. The brain volume decreases simply because of the partial displacement of the cerebral blood volume (CBV) outside the skull with head elevation (single measure for drainage of venous blood), control mean arterial pressure (MAP), cerebral perfusion pressure (CPP), cerebrospinal fluid drainage, stimulation of vasoconstriction inducers brain (hypercapnia), and decreased chest compressions. The mechanisms are centered in: maintenance of cerebral autoregulation, reduced cerebral consumption (cerebral metabolic rate for oxygen - $CMRO_2$), and cerebral blood flow (CBF).[7–20]

Agents that lead to cerebral vasoconstriction are benzodiazepines, etomidate, propofol, lidocaine, and barbiturates (from smallest to greatest effect). They can behave differently depending on the applied dosage. The following medications have the effect of (a) reducing cerebrospinal liquor: fentanyl, halothane isoflurane, pentobarbital, nitrous oxide; (b) increasing cerebrospinal liquor: enflurane and ketamine; (c) reducing the ICP: thiopental, etomidate, lidocaine, benzodiazepine, droperidol, and narcotics; and (d) increase ICP: halothanes, enflurane, succinylcholine, and isoflurane. ►**Table 1** shows the relationship of analgesia and sedation drugs with their pharmacological characteristics.[21–30]

Sedation has a significant effect on energy expenditure. In postoperative patients, an increase in the depth of sedation progressively decreased metabolism. There is a reduction in VO2 after the application of adequate diet in sedated patients.[31] The goal of controlled hypothermia with sedation and neuromuscular blockade (NMB) in patients with TBI is to reduce intracranial hypertension, avoiding coughing and agitation into the fan, and to eliminate tremors.[32–35]

Malnutrition has been associated with increased morbidity and mortality and prolonged length of stay. Providing optimal caloric intake is important, especially in intensive care units. Resting energy expenditure (REE) for patients with cerebral lesions was estimated between 40 and 200% higher than a person not injured. This energy expenditure can be reduced with appropriate sedation.[36–40]

Evidence suggests that continuous infusion of sedatives and opioids may increase the duration of mechanical ventilation (MV) and contributes to pneumonia and ventilator associated bloodstream infections. A strategy to prevent the accumulation of sedatives and opioids is the use of sedatives with daily interruptions and spontaneous breathing attempts to reduce the duration of MV and hospital time.[41–50]

The use of sedation protocols proved effective with a reduction in the duration of MV, hospital stay and use of drugs, but has been limited primarily to medical intensive care unit (ICU) patients. Therefore, a multidisciplinary team is required to develop a protocol for analgesia and sedation, aiming to standardize the process of keeping patients calm and cooperative.[26,27]

The benzodiazepines are central nervous system (CNS) depressants and anticonvulsants, which also increase seizure threshold; they are not painkillers. They stimulate the GABA receptors. This drug act in sedation, anxiolysis, and amnesia effect. The muscle relaxant property is via the spinal cord. It is lipid-soluble and quickly penetrates the blood-brain barrier. Onset of action is short, producing minimal cardiovascular effects that are contraindicated in hypovolemic patients.[51] Association of opioids and benzodiazepines are synergies in situations that require a vigorous sedation. If there is high left ventricular pressure, the association of diazepam and midazolam has a "nitroglycerin effect," lowering blood pressure and increasing cardiac output. Drugs in Neurotrauma can decrease the CBF as well as $CMRO_2$, ICP, and CBV. There is a plateau of maximal effect due to saturation of the receptors. Midazolam may reduce alpha activity, an increased theta and delta-® activity. In the EEG (electroencephalogram). This effect of midazolam will be represented with low voltage in EEG. Midazolam is unable to produce a standard surge suppression in the EEG. It does not affect responses in somatosensory-evoked potential. Midazolam provides greater protection against hypoxia than diazepam. The flumazenil decreases MAP, increases ICP, but has little effect on $CMRO_2$.[52–59]

Opioids have properties similar to morphine. Each receiver has a function. The sigma receptor is related to dysphoria, hallucinations, and respiratory stimulation. The μ1 relates to analgesia and bradycardia urinary restraint; whereas the μ2 is responsible for analgesia, respiratory depression, physical dependence, and constipation. The Kappa receptor is related to analgesia, sedation and dysphoria. Finally the DELTA receiver is responsible for analgesia, respiratory depression, physical dependence and urinary retention. Agonists such as pethidine (meperidine), fentanyl and causes less gastric hypomotility, biliary spasm, and has little effect on the breathing pattern.[60] Synthetic (fentanyl) has high lipid solubility and rapid onset of action without cardiovascular damage. Meperidine increases heart rate. Morphine, fentanyl, sufentanil, alfentanil, remifentanil cause vagus-mediated bradycardia. Meperidine and morphine are histamine-inducing, leading to a decrease in blood pressure, systemic vascular resistance, and bronchospasm. Opioids lead to stiffness of the chest wall and increased progressive muscle tone mediated by the μ receptors in supraspinal muscles in the raphe nucleus and on the bridge.[61] It provides slower gastric emptying, reducing peristalsis, and biliary spasm.

Table 1 Drug ratio for analgesia and sedation and their pharmacological characteristics

Drug	Action	Neuro proportion	Advantages	Dose	Indicative	Side effects
Propofol (fenol derivative)	Na channel blocks and enhances GABA receptors	Decreases CBF, $CMRO_2$, ICP, MAP. Increases seizure threshold	Good effect of CBF, $CMRO_2$, ICP, MAP. Fast action, good brain penetration	Induction: 1–2.5 mg/kg, 0.5–1.5 mg/kg in elderly or low cardiovascular reserve. Maintenance: 1.5–5.4 mg/kg/hour	Inducing agent, hypotension sedation in brain injury, ICP control of refractory, seizures refractory	Hypotension, pancreatitis, increased liver enzymes, contraindicated in egg or soy allergies, increased cholesterol
Midazolam (chloro-methyl-imidazo-benzodiazepine)	GABA receptor agonist, opioid agonist Kappa activates chloride channels	Decreases CBF, $CMRO_2$, ICP, MAP. Increases seizure threshold	Half-life less than benzodiazepine, less hypotension than barbiturates and propofol	Induction: 0.1 mg/kg Maintenance: 0.01–02 mg/kg/hour	Induction of anesthesia om patients hypotension in injury cerebral	Accumulation of long-term metabolic, reduction of MAP, delirium, suppression of coughing reflex, tachyphylaxis over 72h, withdrawal syndrome
Etomidate (carboxylate imidazole)	GABA receptor agonist	Decreases CBF, $CMRO_2$, ICP, MAP. Increases seizure threshold	Good effect of CBF, $CMRO_2$, ICP, MAP. Fast action	Induction: 0.2–0.4 mg/kg	Induction of anesthesia, beware of adrenal suppression	Adrenal suppression, metabolic acids, myoclonic movements, nausea and vomiting, pain or injection
Ketamine (phencyclidine)	Agonist competitive NMDA receptor interacts with opioid and muscarinic receptor (Na channel)	Decreases glutamate	Preserve MAP and CPP	Induction: 2 mg/kg Maintenance: 50 mcg/kg/min	Hemodynamic instability	Increase ICP, epileptogenic, hallucinogen
Barbituric	Inhibits AMPA receptor and GABA receptor stimulates	Decreases CBF, $CMRO_2$, ICP, MAP. Increases seizure threshold	Good effect CBF, $CMRO_2$, ICP, MAP, fast action	Induction: 2–5 mg/kg Suppression: EEG 40 mg/kg followed by an infusion 4–8 mg/kg/hour titrated EEG	Beware of induction of anesthesia to prevent hypotension. PIC refractory and refractory epilepsy	Accumulation of drug, hypotension, gastroparesis, shakiness, immunosuppression, hypokalemia during infusion, hyperkalemia, arrhythmogenic
Dexmedetomidine	Selective α-2 adrenergic agonist	Reduces CBF and ICP	Minor respiratory depression, reduced delirium	Initial dose: 1 mcg/kg Infusion: 0.42–1 mcg/kg/h	Keeps sedation before and after the extraction management in agitation and delirium	Hypotension, bradycardia, arrhythmia (atrial fibrillation), high cost

Table 1 (*Continued*)

Drug	Action	Neuro proportion	Advantages	Dose	Indicative	Side effects
Morphine	μ-selective agonist	Increases ICP	Low cost hemodynamic stability, hypnotic, analgesic	0.05–0.1 mg/kg/hour	Long periods of analgesia	Hypotension, respiratory bradycardia, cough reflex depression, seizures, stiffness, constipation, nausea, itching and sphincter oddie spasm
Fentanyl	μ-selective agonist	Increases CBF and $CMRO_2$	Low hemodynamic stability, hypnotic, analgesic	Induction: 1–3 mcg/kg Maintenance: 0.5–2 mcg/kg/h	Inductor and infusion agent continues	Even morphine
Alfentanil	μ-selective agonist	Increases CBF and $CMRO_2$	Hemodynamic stability, hypnotic, analgesic	Induction: 10–50 mcg/kg Maintenance: 0.5–1mcg/kg/h	Inducer	Even morphine
Sufentanil	μ-selective agonist	Increases CBF and $CMRO_2$	Hemodynamic stability, hypnotic, analgesic	Induction: 4 mcg/kg	Inducer	Even morphine
Remifentanil	μ-selective agonist	Increases CBF and $CMRO_2$	Quick effect, little nausea, hemodynamic stability, hypnotic, analgesic	Bolus: 1 mcg/kg Infusion: 0.0125–1 mcg/kg/min	Inductor and infusion agent continues	Even morphine

Abbreviations: CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate for oxygen; ICP, intracranial pressure; MAP, mean arterial pressure; MBP, mean blood pressure.

Moreover, it reduces $CMRO_2$, cerebral blood flow, and ICP (intracranial cerebral pressure), reduces MAP and CPP. Sufentanil, alfentanil, and fentanyl in ICP has transient increase in ICP after peak five minutes, returning to normal in 15 minutes.[62] This transient increase in ICP can lead to muscle stiffness and opioid-induced histamine release. There are few studies on remifentanil, which has significant effects on ICP, with no change in brain metabolic dynamics with rapid awakening.[63–67]

Barbiturates have anticonvulsant properties and cause CNS depression. They activate the GABA receptors and inhibit AMPA excitatory receptors. Thiopental or pentobarbital acts by decreasing ICP, refractory epilepsy, and ischemic protection. These agents are lipophilic, metabolized in the liver by the cytochrome P450. They have a short duration and rapid distribution to fat. Constant EEG monitoring is necessary until there is a pattern of suppression outbreak in EEG.[68–75]

Propofol has high lipid solubility, rapid onset of action, and short half-life of 2 to 8 minutes. Promotes profound decrease in MAP, fall in systemic vascular resistance, cardiac contractility, deep brain depression. Decreases $CMRO_2$, CBF, and ICP in patients with brain injury. Propofol decreases the release of L-aspartate and L-glutamate. They are plasma antioxidant, useful in neurosurgery patients. Diprivan™ (Astrazeneca, London, UK), is a special propofol, it contains EDTA as a preservative while the generic product uses sulfides. EDTA is a chelating calcium, which is neuroprotective in combination with propofol.[76–86]

Etomidate has better metabolic behavior in cerebral than barbiturates. Unlike these, etomidate little changes the cardiovascular metabolism. It is lipophilic, with rapid penetration to the brain and other tissue.[87] The drug is metabolized in blood and liver and excreted in urine (75%), stool (13%), and bile (10%). Its effect on ventilation is minimal. The medication is associated with myoclonus incidence, however, reduce endogenous cortisol production. Supplementation of vitamin C can restore the cortisol levels. It has low solubility in water, resulting from the use of a propylene glycol vehicle, which leads to hyperosmolarity, intravascular hemolysis, renal insufficiency, acidosis, and lactate accumulation. There are records of complications such as thrombophlebitis, phlebitis, and pain on injection. The effect on EEG is equal to that of thiopental. It prolongs survival during hypoxia or ischemia. Glycine and glutamate levels were reduced in the group treated with etomidate.[88–91]

Ketamine interacts with N-methyl-D-aspartate (NMDA) receptor, similar effects can mediate analgesia, inhibiting dorsal horn of spinal cord. This medication of sedative action, amnesia, and analgesic properties increases heart rate, MAP, pulmonary artery pressure increases, hear attack chance and myocardial oxygen consumption, and potent bronchodilator.[92] Ketamine also increases $CMRO_2$ and ICP. This increase can be blocked by the administration of thiopental or diazepam; combinations are an option in patients with TBI. Midazolam and ketamine association provides small increases in CBF, ICP, and $CMRO_2$; whereas, propofol provides no increase. Ketamine can also lower the seizure threshold.[93–97]

Neuroleptics are of great importance for the control of sedation, anxiolysis, and analgesia. Haloperidol is widely protein binding ($> 90\%$) and metabolized by hepatic glucuronidation that induce ventricular arrhythmias (i.e., Torsade de Pointes), QTi increases, as well as reductions in the relationship between the CBF, CMRO2, and ICP.[98] The clonidine and dexmedetomidine have neuroprotective effects in cerebral ischemia.[99–102]

The halothanes have vasodilatory effect mitigated when associated with intravenous anesthetics that cause cerebral vasoconstriction.[103]

The isoflurane increases CBF less than halothane does. Barbiturates reduce total peripheral resistance, lowering blood pressure, and consequently also decreasing CBF, $CMRO_2$, and ICP, which may depress electrical and ischemic activity.[104]

Lidocaine (1 mg/kg) reduces the ICP and the reflection of tracheal intubation. Although it reduces $CMRO_2$ and CBF, in larger doses it becomes toxic and causes seizures, greatly increasing CBF and $CMRO_2$.[105]

Neuromuscular blockers are used during mechanical ventilation in patients with severe respiratory insufficiency and in the treatment of patients with intracranial hypertension, avoiding the use of succinylcholine as it may induce increase of intracranial hypertension. They should only be used after adequate sedation and analgesia. The pancuronium curare is preferable for patients with renal function, normal liver, and cardiac and hemodynamic stability.[106] The vecuronium, on the other hand, should be reserved for patients with heart disease or hemodynamic instability, in which the tachycardia may be deleterious. To avoid tachycardia, it can be used for vecuronium loading dose and pancuronium maintenance. Atracurium should be reserved for patients with renal impairment ($CrCl < 10$ mL/min), and hepatic impairment. (30x greater than the cost of pancuronium). The lock must be monitored with Train-of -Four (TOF). Prophylaxis should be adjusted to high risk of deep venous trombosis (DVT). In curarized patients, the only signs of inadequate sedation can be hypertension, tachycardia, sweating, lacrimation, and mydriasis. In cases that occur with severe intracranial hypertension, the decision to use neuromuscular blockers is still possible. In this case, nondepolarizing is indicated, preferably with less hemodynamic action, such as vecuronium (attack from 0.06 to 0.08 mg/kg, maintenance 0.02 to 0.03 mg/kg/hour) and atracurium ($\sim$0.3 to 0.5 mg/kg, maintenance 0.2 to 1 mg/kg/ hour), although other agents may be used, such as pancuronium (attack from 0.06 to 0.08 mg/kg, maintenance 0.02 to 0.03 mg/kg/hour). When using neuromuscular blockers, it is important to monitor the EEG to avoid convulsive states and, whenever possible, use t a peripheral nerve stimulator.[105]

Nitric oxide (N_2O) is used to reduce the consumption of intravenous hypnotic agent and promote patient awakening after surgery, discrete high levels of CBF. Commits brain complacency, increasing this effect in the brain, especially when used with halogenated agent.[107,108]

Dosages and associations can generate their own effects. Thiopental further reduces the $CMRO_2$, 50% of CBF. Fentanyl

above 200 mcg/kg increases $CMRO_2$, CBF, $PaCO_2$, aside from being epileptogenic. Etomidate in large dosages can lead epileptic seizures. The etomidate and fentanyl association form spicules in the EEG, which may increase seizures. Halogenates reduce $CMRO_2$ and CBF, increase vasodilation, and increase CBV, ICP, which may in turn reduce CPP.[109] Propofol and midazolam association are beneficial in cerebral hemodynamics, ICP, and CPP. Propofol, however, may lead to hypertriglyceridemia. When reducing bleeding hypotension is required, thiopental or isoflurane decrease total peripheral resistance and blood pressure. Fentanyl, morphine, sufentanil, ketamine, and sufentanil increase the ICP, decreases MAP and CPP. Ketamine and sufentanil have no effect on the MAP. Phenobarbital and etomidate reduce ICP. Propofol and morphine synergistically decrease ICP. Propofol and midazolam has good association. Drugs such as calcium channel blockers, triazole antifungal, and erythromycin inhibit midazolam metabolism. ►**Table 2** lists the major drugs used for sedation and analgesia in trauma and their relationship with the cerebral dynamics and metabolism.[110–112]

Drug of Choice for Induction for Each Injury

In neuroanesthesia not just fill the basic requirements such as analgesia, hypnosis, neurovegetative protection and muscle relaxation, should carefully examine each disease.[111,112]

Cerebral aneurysm, ischemia may occur by vasospasm should be careful with hypotension. When autoregulation is compromised will be difficulties in reducing CBV with hearing impairment. If necessary blood temporary occlusion, cerebral protection measures are necessary. if not clipped all aneurysms should be careful with hypertension, because the risk of rerupt.[97]

In brain tumor resections may have alteration of cardiovascular, respiratory and level of consciousness. When extensive peritumoral area with compromised edema or self-regulation, there may be difficulty in reducing brain volume through anesthetic maneuvers. The bleeding in the tumor area after resection, we need mild hypotension regime in the immediate postoperative period.[113]

If the ICP is high, there may be cardiovascular changes at the decompression. [114] Traumatic brain injury as the worst Glasgow more likely to be little vascular reactivity.[114]

In spinal cord injury may experience difficulty ventilatory due to lack of movement of the chest muscles, indicating immediate endotracheal intubation and mechanical ventilation to prevent hypoxemia. The friendly spinal injury high level exacerbates the parasympathetic activity and at the time of tracheal intubation may occur reflex bradycardia and cardiac arrest. The total peripheral vasoplegia, due to the sympathetic injury, causing significant hypotension. In this situation hypotension should be corrected with volume infusion associated with vasopressor drug titrated way, and should avoid the use of anesthetics that cause depression of the cardiovascular system.

With the exception burnt, intravenous drugs reduce the CBF and $CMRO_2$, which is a good indication for patients with high ICP because they reduce CBV. On the other hand fully intravenous anesthetic technique choice may hinder the early awakening of the patient difficult neurological evaluation.[115–117]

Resection of AVM (arterial venous malformation) produces a reduction in bleeding on the bed where he was the AVM, this is achieved by hypotension. Resection causes the blood flow before passing the AVM passes by passing pathological vessels that do not have effective self-regulation. This increased supply, increases the flow of pathological vessels and may have brain barrier break and brain swelling and increased ICP. In this situation the barbiturate is well indicated, until it can awaken without hypertension and bleeding. The barbiturate coma reduce the consumption of oxygen brain and will contract non pathological brain vessels, reducing ICP. Barbiturate large dose (4-5 g / 24 hours), depress the cardiovascular system that reduces cardiac output and the total peripheral resistance, causing hypotension arterial.[118]

After blood temporary arterial occlusion brain for a long time, with the use of hypothermia, the patient may experience respiratory difficulty in the immediate postoperative period. This difficulty may be caused by temporary ischemia due to arterial occlusion or metabolic changes inherent to

Table 2 Drug ratio most used for sedation and analgesia, and the effects on the cerebral metabolism

Drug	ICP	CPP	$CMRO_2$	CBF	MAP	Epilepsy action	ICP prevention	Sedation	Analgesia
Morphine	≥	≤	=	0	−	0	+	+	+++
Benzodiazepine	≥	≤	=	≤	−	+	+	+++	+
Propofol	≤	≤	<	≤	- -	+	+	+++	++
Barbituric	- -	≤	<	- -	- -	+	+	+++	−
Etomidate	≤	=	<	−	0	0	+	+++	−
Curare	≤	=	0	0	0	0	+	+	+
Ketamine	≤	=	=	0	0	0	+	+	+

Abbreviations: CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate for oxygen; ICP, intracranial pressure; MAP, mean arterial pressure; CPP, cerebral perfusion pressure; 0, without contributions; +, increase; ++, significant increase; ++ + , more significant increase -, reduction; - -, significant reduction; - - -, more significant reduction.

hypothermic, dehydration and the use of anesthetic large quantidade.[118]

Tumors in the hypothalamus region of stem and bulb, near lower cranial nerves, usually have cardiorespiratory problems in the postoperative period.

Patients with pulmonary disease, obese, with breathing difficulties and patients with multiple associated diseases that increase postoperative morbidity, should be kept intubated. Should choose drugs that have fast metabolism and excretion, as propofol, etomidate and analgesics short duração.[118]

Ideal Sedation for Neurocritical Patients

The medications for optimal sedation of neurocritical patients must start and end fast, as well as provide predictability of action to target organs, be easily titrated, and able to reduce ICP by reducing blood volume or cerebral vasoconstriction, reducing CBF and $CMRO_2$. At the same time, they must keep the CBF / $CMRO_2$ combination, maintain cerebral autoregulation, allowing cerebrovascular reactivity variations of $PaCO_2$, minimal cardiovascular depression, brain tissue recovery, and prevent secondary neuronal damage. This allows neurological evaluation, limiting the stress response to critical illness, protecting the brain during ischemia by metabolic depression, attenuating the release of catecholamines induced by ischemia, increasing vascular resistance of non-ischemic areas, increasing glucose plasma a2-adrenergic inhibition by insulin. Patients using these drugs need to be monitored through the use of capnography, ICP, MAP, CPP, transcranial Doppler. The level of sedation and adaptations to fan can be monitored by clinical parameters such as SAS, RASS, Ramsay, and Glasgow scales. Use of BIS

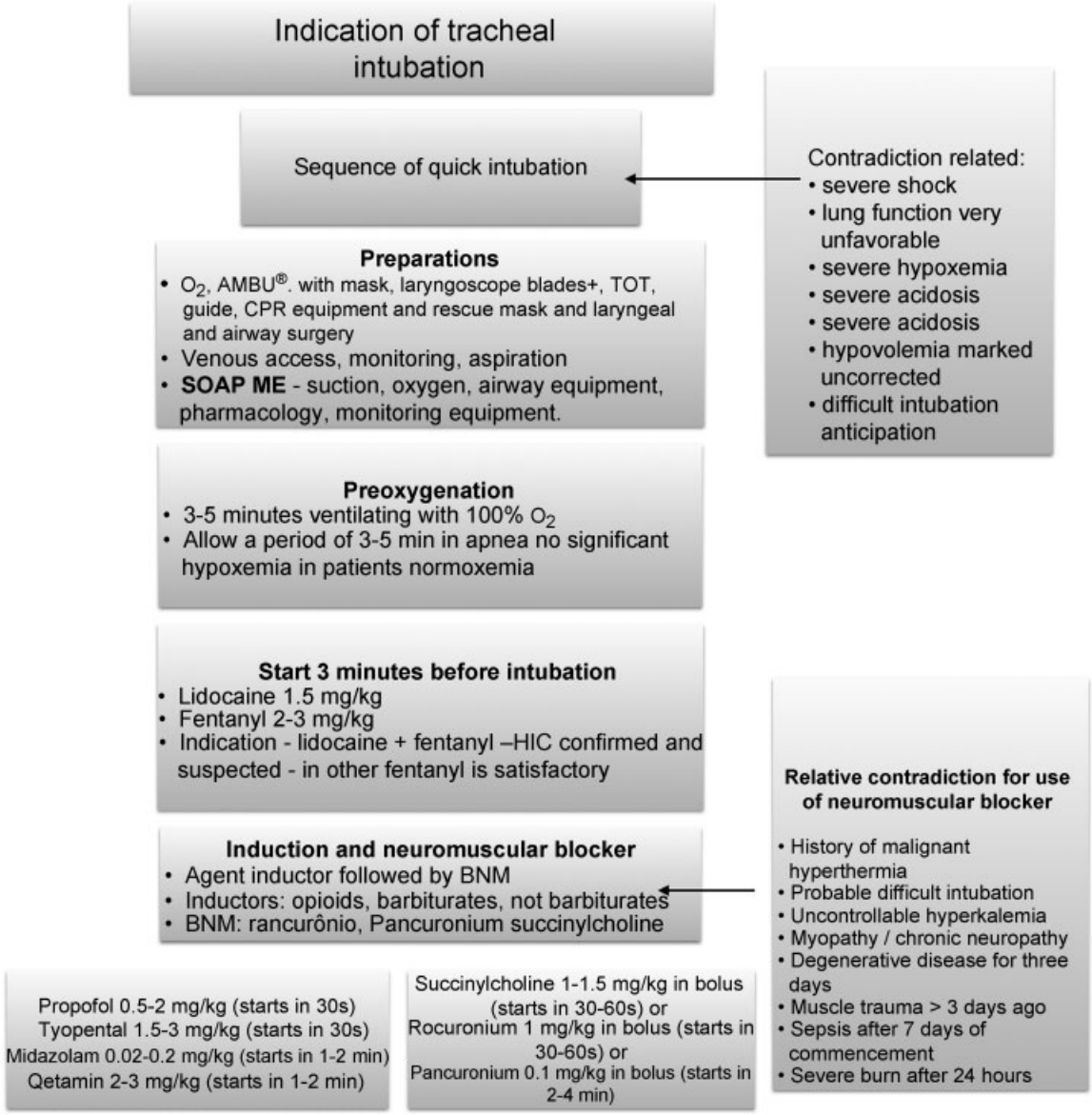

Fig. 1 Algorithm intubation in the emergency room. Abbreviations: AMBU®, bag valve mask; BNM, neuromuscular block, CPR, cardiopulmonary resuscitation; TOT, endotracheal intubation.

(Bispectral index) has been of great value for monitoring sedation since it encodes the EEG traces into digital values ranging from 0 to 100. Values between 90 and 100 mean the patient is awake and between 45 and 60 means the patient is adequately anesthetized.[113–120]

The pharmacokinetics of drugs depends of absorption, distribution, metabolism or biotransformation, and excretion of drugs. In brain injury, disruption of the blood-brain barrier and changes in the binding protein can modify the drugś pharmacokinetics. Perfused organs receive disproportionately large amounts of the drug compared with poorly perfused organs. The elimination of the drug occurs in two stages. First occurs through oxidation and reduction reactions, cytochrome P-450 and hydrolytic reactions. Second is through conjugation reactions of the drug or its metabolite with an endogenous substrate, such as D-glucuronic acid. The drugs cross biologic membranes. The kidney is the main excretor.[119–121]

One study found that pre-hospital intubation may increase mortality. Mortality of intubated patients in trauma scene was 93%, compared with 67% mortality that were intubated in hospital. This statistic persists even when adjusted for age, Glasgow score, associated injuries, and injury mechanism. The increased mortality pre-hospital is due to lower staff training regarding the rapid sequence intubation procedure and the greater frequency of more severe patients in pre-hospital care. The bias of this study is the selection bias of patients since patients scene end up being worse.[118,119]

The anticonvulsant action of sedatives is widely used in clinical practice. Risk factors for early posttraumatic seizures are: Glasgow below 10, injury, subdural or epidural hematoma, penetrating injury, and convulsions in the first 24 hours. The drugs with superior results were barbiturates, propofol, and benzodiazepines. Early prevention of seizure does not diminish late epilepsy after trauma. Phenytoin and carbamazepine are also very effective in the seizure post early trauma prevention.[121–125]

Neurological patients often present autonomic disorders. Sedatives and analgesics, as well as neuroleptics, can

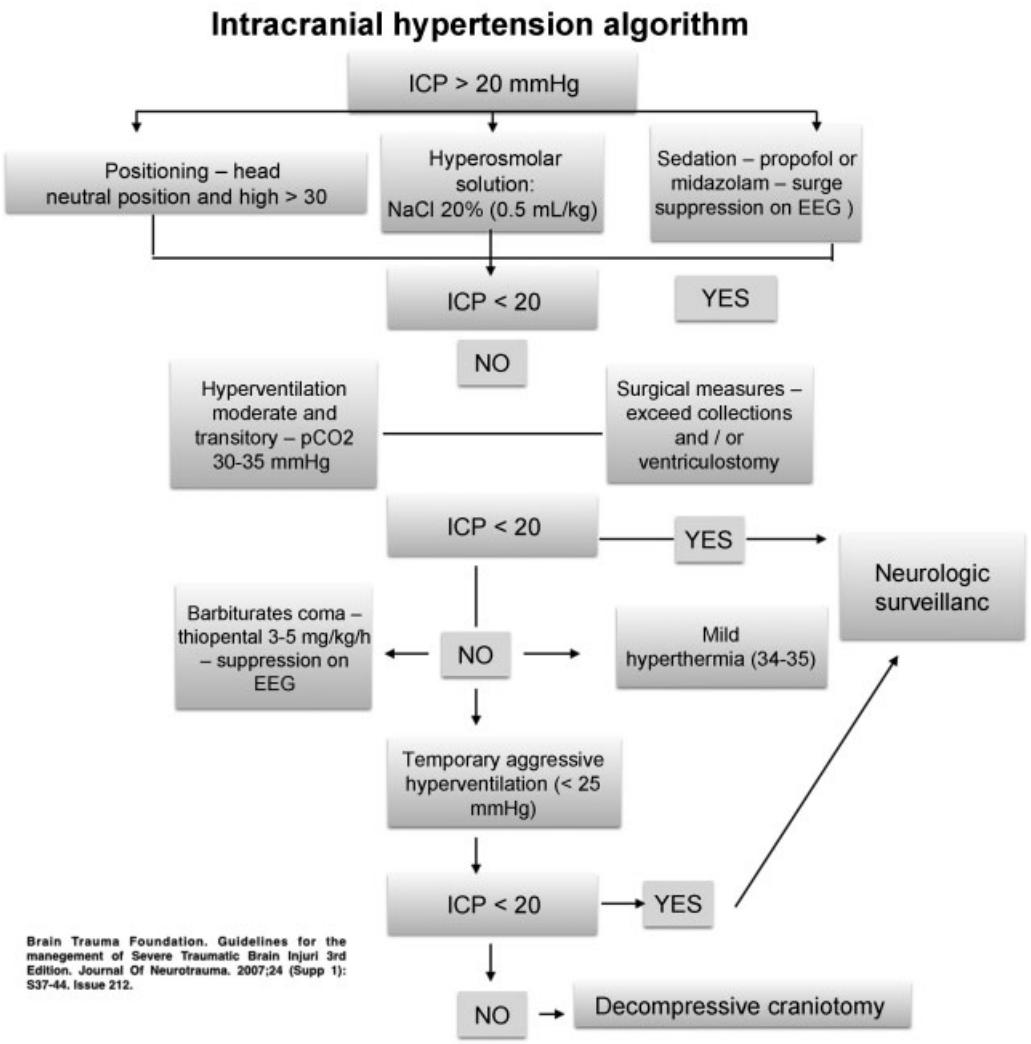

Fig. 2 Algorithm for treatment of patients with intracranial pressure in the emergency room. Abbreviations: EEG (electroencephalogram); ICP (intracranial pressure). Source: Brain Trauma Foundation. Guidelines for the management of severe traumatic brain injury. J Neurotrauma 2007; 24(Suppl1):s37-s44.

contribute for treatment. The main usage of medications that avoid hypertension, tachycardia, tachypnea, hyperthermia, sweating triggered by autonomic disorders, and their effects on the central nervous system.[126]

Discuss in this paper the non-pharmacological sedation procedure to help these patients. It involves respect family / patient / staff. Decreased volume monitoring equipment, active and passive mobilization of the patient, respecting the circadian cycle, family stay with patient and even use personal songs in hospital.[127]

The reversal of drugs frequently occurs in neurological patients. Neuromuscular blockers reverse with Prostigmine® (0.25 to 0.35 mg/kg) and atropine (20 mg/kg), which can increase the ICP. The flumazenil (0.1 to 0.4 mg/kg) used to reverse the benzodiazepines may cause tachycardia, hypertension, and increase $CMRO_2$. The naloxone (0.4 to 2 mg) to reversal opioids. Benzodiazepines may lead to reactive bilateral mydriasis. The treatment uses up morphine or methadone or clonidine associated to treatment with anxiolytics and sedatives.

Neuronal activity and apoptosis are stimulated by electrical activity of the brain on NMDA receptors in two ways depending on the receiver's position in the cell. Synaptic are neuroprotective, related to neuronal activity. The extrasynaptic NMDA receptors are related to cell death or reduction of neuronal activity and decrease of CPP and MAP.[89] Deep sedation reduces neuronal activity, loss of neurons, and functional neurological impairment. Tissue repair after acute brain injury occurs when there are activation mechanisms of brain development. Deprivation of neural activity with anticonvulsants also had adverse effects after brain injury with stimulation of extrasynaptic receptors. Pretreatment with midazolam or isoflurane can lead to cell death and worse results in rats acutely brain injury.

This paper contributes to the literature with two algorithms, presented in ►**Figs. 1** and **2**, regarding the medications used in rapid sequence intubation and management of intracranial hypertension.

Conclusion

A range of sedative and analgesic agents are available for sedation. Each class has its own positive and negative effects in critically ill neurotrauma patients. There are few studies, which are limited to tests performed during elective neurosurgical procedures or in healthy volunteers in the brain metabolism works on physiological thresholds. Thus, data must be applied cautiously for neurocritical patients. The preference for certain agents should be based on a thorough understanding of the effects on brain metabolism and intracranial compliance. The ideal medication is one that combines reduced LCR, increase less CBF and CBV, increase CPP, and decrease the IPC without much decrease to MAP. It is best to avoid the use of inhaled halogenates since they vasodilate the brain, which worsens the brain hemodynamics. It is preferable to use intravenous sedatives. The target for the use of these agents is to optimize the care of critically ill patients in neurotrauma without affecting the ability to assess the patient clinically to limit the secondary neuronal damage due to pain agitation and sedation. The correct analysis of sedation medications and analgesia in neurotrauma, with rapid sequence intubation and management of medications in intracranial hypertension, provide a correct handling in the brain.

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