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Chapter

# Sedation in TBI Patients

*Lorenzo Peluso, Berta Monleon Lopez and Rafael Badenes*

## Abstract

Sedation is an important topic in neurocritical patients. When compared with general intensive care unit and traumatic brain-injured patients, sedation has its therapeutic indications, such as management of intracranial pressure, treatment of status epilepticus, sedation for targeted temperature management patients and paroxysmal sympathetic activity. Nowadays, the assessment of sedation is done by neurological evaluation and new monitors based on electroencephalography signals that help the physician titrate the sedative agents. Therefore, the aim of this chapter is to discuss the main pharmacological properties of sedatives and analgesics, their proper indications related to pathophysiological issues and their titrations based on the abovementioned new technologies.

**Keywords:** TBI, sedation, sedative agent

## 1. Introduction

Traumatic brain injury is an acquired brain injury which occurs after a sudden trauma.

TBI is a major socioeconomic problem. It is an important cause of death and hospital admissions worldwide. The epidemiology in Europe is not well known, and more rigorous epidemiological studies are needed to fully quantify the effect of TBI society.

There are primary and secondary injuries. The primary injury is the trauma suffered by the patient itself, while the secondary injuries develop afterwards due to hypoxia, alterations in cerebral hemodynamic and metabolism and disruption of the blood brain barrier. Our aim is to avoid the secondary insults. Examples which can lead to worsen primary injury are convulsions, fever or intracranial hypertension.

TBI can be divided into different categories based on clinical examination or CT imaging. The most widely used is the Glasgow Coma Scale (GCS) based on neurological examination. Three categories can be found: mild, moderate, and severe. Other neurological scales used are based on time of loss of consciousness (LOC) (**Tables 1** and **2**) [1–3].

Many patients being admitted to the ICU are already under sedation due to neurological reasons. Nowadays, sedative agents are used either as a tool to apply other therapies (such as hypothermia) or as a treatment itself, for example, barbiturate coma for refractory hypertension.

Sedation and analgesia are practices that, all clinicians who provide care to patients affected by traumatic brain injury, have to face daily. These patients are usually excluded from randomized clinical trials, so the level of evidence in this setting is still low. The aims of sedation and analgesia can be divided into two main categories.

Firstly, general objectives are to ensure the patients' comfort, reduction of pain and agitation, improvement of patient-ventilator synchrony and facilitation of the nursing caring.

| Parameter | Response | Score |
|---|---|---|
| Best eye-opening response | -Spontaneously | 4 |
| | -To verbal request | 3 |
| | -To pain | 2 |
| | -No response | 1 |
| Best verbal response | -Oriented and conversational | 5 |
| | -Disoriented and conversational | 4 |
| | -Inappropriate words | 3 |
| | -Incomprehensible sounds | 2 |
| | -No response | 1 |
| Best motor response | -Obesity request | 6 |
| | -Appropriate withdrawal | 5 |
| | -Flexion withdrawal | 4 |
| | -Flexion decorticate | 3 |
| | -Extension | 2 |
| | -No response | 1 |

**Table 1.**
*GCS classification*

| | GCS | LOC |
|---|---|---|
| Mild | 14–15 | 0–30 min |
| Moderate | 9–13 | 30 min–24 h |
| Severe | 3–8 | >24 h |

**Table 2.**
*TBI classification: GCS and LOC time.*

Specific objectives focused on "neurotreatment" are the reduction of intracranial pressure (ICP), the management of status epilepticus (SE), the control of targeted temperature management (TTM), the management of paroxysmal sympathetic activity and the decrease of cerebral oxygen consumption [1, 2].

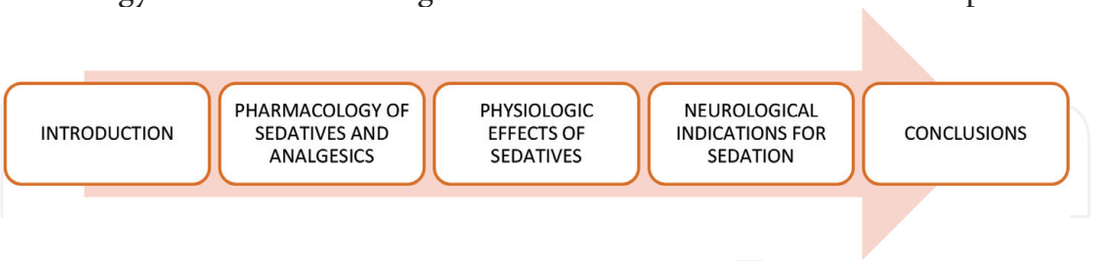
A variety of studies show the positive outcomes of an adequate sedation and analgesia in the general critical care patient as, for example, reduce time on the ventilator and decrease the length of stay in ICU and prevention of neurologic deterioration, amongst others.

The best way to assess these patients is with the physical examination, allowing a clinical monitoring and timely detection of warning neurological signs; thus, the removal of the sedative agent is required. However, this can lead to a cerebral and hemodynamic derangement when sedation is abruptly stopped [3]. Cerebral hypoperfusion and raised ICP might result in an imbalance of energy supply and demand, especially for the injured brain and, therefore, aggravate the risk for metabolic distress and brain tissue hypoxia. It might lead to significant ICP elevation and cerebral perfusion pressure (CPP) reduction, but it has been shown that, in patients with a stable ICP and CPP readings, the wake-up tests remain the gold standard for clinical monitoring and detection of neurological changes [4].

Available drugs used for sedation are analgesics and sedatives. Evidence shows that combining them both in order to achieve the optimal level of sedation leads to a reduction in the appearance of adverse effects.

Control patients' level of sedation plays an important role in what recently has been described as the "ABCDE bundle." An evidence-based clinical approach improves patients' outcome and recovery [5] such as duration of mechanical ventilation, brain dysfunction (i.e., delirium and coma), physical restraints, ICU readmission rates, and discharge disposition of ICU survivors.

In this chapter we will go over the basis of sedation in TBI patients, as well as the pharmacology of the different drugs used and the main indication for such patients.




## 2. Pharmacology of sedatives and analgesics

The ideal sedative drug for a neurocritical patient should have different properties. It should have a rapid onset and recovery for a prompt neurologic evaluation, a predictable clearance independent of end-organ failure to avoid the accumulation of the drug, and it should be easily titrated. It has to reduce ICP by reducing cerebral blood flow (CBF) or cerebral vasoconstriction, however maintaining the coupling between cerebral blood flow and cerebral metabolic rate of oxygen consumption ($CMRO_2$). Cerebral autoregulation should be preserved as well as normal vascular reactivity to changes in $PaCO_2$. Finally, the hemodynamic depression should be minimal to avoid deleterious effects on brain circulation.

### 2.1 Propofol

Propofol is a central nervous system depressant which directly activates GABA receptors and inhibits the NMDA receptor modulating calcium influx through slow calcium ion channels. It has a rapid onset (1–2 min) and a dose-related hypnotic effect. Its rapid onset is due to its high lipophilic property and a large volume of distribution, leading to a rapid recovery too (10–15 min). These characteristics made propofol one of the best alternatives for sedation in neurocritical patients allowing us to do wake-up test daily for neurologic evaluation. Some studies show that in patients requiring >48 h of mechanical ventilation [6], sedation with propofol results in significantly fewer ventilator days than intermittent lorazepam when sedatives are interrupted daily. Propofol has no active metabolites and does not produce significant drug interactions. It reduces ICP, $CMRO_2$, CBF and cerebral electrical activity. $CO_2$ vascular reactivity and cerebral autoregulation are also preserved. On the other hand, it has no analgesic effect, and it raises tolerance and tachyphylaxis. Side effects of propofol are dose-dependent hypotension which can decrease cerebral perfusion pressure even if it induces a decrease in ICP [6] and dose-dependent respiratory depression. Thus, invasive blood pressure and maybe cardiac output monitoring may be necessary.

Hypertriglyceridemia may appear after high-rate infusions; clinicians should also be aware of the propofol infusion syndrome (PRIS) to detect it as soon as possible. PRIS manifests as metabolic acidosis, hyperkalemia, rhabdomyolysis, hypoxia and progressive myocardial failure [7–9].

### 2.2 Benzodiazepines

Benzodiazepines such as midazolam, lorazepam and diazepam are sedatives widely used in the ICU. They have anxiolytic, sedative and hypnotic properties. Midazolam is

a GABA receptor agonist. Systemic effects of these drugs are anxiolysis, sedation, muscle relaxation, anterograde amnesia, respiratory depression and anticonvulsant activity. It decreases $CMRO_2$ and CBF and has a slight effect on lowering ICP too. As with propofol, vascular reactivity to $CO_2$ and cerebral autoregulation is preserved. Midazolam produces amnesia and has a rapid onset of action, and it produces less hemodynamic instability than propofol. However, they also produce tolerance and tachyphylaxis. Their metabolism is impaired when hepatic failure because of its oxidation via CYP450 enzyme system producing active metabolites excreted in the urine, leading to accumulation in renal dysfunction. It can prolong duration of mechanical ventilation, and the appearance of delirium in the ICU patients is increased. A continuous infusion of midazolam for more than 24 h will lose the rapid recovery properties due to the accumulation of active metabolites. Therefore, it is recommended only for short-term infusions. The Society of Critical Care Medicine consensus guidelines state that midazolam should be used only for short-term (<48 h) therapy [10]. High doses of benzodiazepines can cause respiratory depression and apnea, leading to an increase in ICP caused by hypercapnia. Benzodiazepines' reverser is flumazenil.

### 2.3 Opioids

Morphine, fentanyl and remifentanil are the most frequently used opioids in the ICU [11]. These drugs stimulate mu, kappa and delta receptors, distributed all along the central nervous system (CNS). They have a fast onset when given intravenous (iv), and they are more easily titrated. Morphine and meperidine are not the ideal sedative agent for ICU because their active metabolite can precipitate seizures [12]. Moreover, morphine has a long-lasting effect. Fentanyl with its high lipid solubility has a very rapid onset and a short duration of action when given as a bolus; however, the pharmacokinetics change when administered in perfusion. It may increase ICP and decrease CPP (decrease in MAP) transiently after a bolus. Remifentanil is more powerful than morphine, and it is metabolized directly in the plasma by nonspecific esterases, thus avoiding drug accumulation. Due to its very short duration of action, it requires a continuous perfusion [13–17]. This makes this drug very suitable for neurocritical patients because it facilitates frequent awakening for the neurologic evaluation [18]. Remifentanil is eliminated by the kidneys, and it does not have to be adjusted if kidney failure. On the other side, as they act as respiratory depressants, they may cause hypercapnia with consequent increase in ICP. They can induce histamine release, causing urticaria and flushing, somnolence respiratory depression, chest wall and other muscle rigidity, dysphoria or hallucinations, nausea and vomiting, gastrointestinal dysmotility and vasodilation with hypotension. The reverser is naloxone, which should be given slowly and be titrated.

In order to reduce and minimize the use of opioids, it is possible to add other categories of analgesics as gabapentin and/or acetaminophen [19].

### 2.4 Dexmedetomidine

Dexmedetomidine is an alpha-2 agonist which has been recently introduced into clinical practice. It has sedative, analgesic and anxiolytic properties, and it is widely starting to spread through the neurointensive care unit (NICU). It has a short-acting effect, and it does not accumulate, thus being very appropriate for frequently wake-up test for neurological evaluation. The respiratory depression is minimal, and it has been reported that it may reduce the incidence and severity of delirium. On the other side, it is a very expensive drug, and there have been reported cases of dose-dependent bradycardia, hypotension, arrhythmias and hyperglycemia. Deep sedation is not possible with this drug [20–24]. The pharmacokinetics is influenced by liver rather than renal function. Dexmedetomidine is metabolized in the liver by

CYP450 enzyme system, and there are no active or toxic metabolites. Sedation with volunteers showed a decrease in regional and global cerebral blood flow, but the ratio with $CMRO_2$ and flow metabolism coupling is maintained [25]. The neuroprotective effect in animal studies has also been studied, and they showed a preconditioning effect and attenuation of ischemia-reperfusion injury [26].

### 2.5 Barbiturates

Nowadays, these drugs are used only for a specific goal. They are a GABA receptor agonist leading to a decrease in ICP and CBF that is proportional to the decrease in $CMRO_2$ (up to 60%) during burst suppression. Barbiturates have been associated with a high incidence of systemic complications, such as hemodynamic instability and immune suppression with an increased risk of infections, such as pneumonia. Indication for barbiturates is limited to refractory intracranial hypertension and refractory status epilepticus [27]. They accumulate in the tissues after long-term infusions leading to slow recovery from sedation.

### 2.6 Ketamine

Ketamine is an NMDA receptor antagonist with a relatively good hemodynamic stability. It has a fast onset and a short action. Sedation, analgesia and anesthesia can be induced with this drug, and it does not depress the respiratory system. Potential side effects of ketamine are increase of $CMRO_2$, CBF and ICP (due to an increase in cerebral blood volume). However, some reports have shown to decrease CBF and ICP in head trauma patients sedated using both ketamine and propofol or with a $PaCO_2$ maintained constant [28], and in an experimental setting ketamine even had neuroprotective properties [29]. Main advantages of using ketamine are the hemodynamic stability as well as CPP and the opportunity to reduce the excessive use of some sedative drugs as it reinforces them.

In a recent study, the use of ketamine was associated with a lower incidence of cortical spreading depolarization (CSD) when compared with propofol, midazolam and opioids [30].

### 2.7 Inhalation sedatives

Inhalative sedation in the ICU is starting to spread all over Europe and has been recommended as an alternative in a German consensus guideline [31]. However, it has historically been considered unsafe in the NICU around the world. Isoflurane, sevoflurane, and desflurane have shown some benefits compared with intravenous sedation. They have a low metabolism and, due to their low solubility, are eliminated quickly and offer shorter and more predictable wake-up times than intravenous agents. They give also a better hemodynamic stability. Some volatile anesthetics abolish cerebral autoregulation at high doses; it has been reported that with sevoflurane at MAC 1.0, the autoregulation of cerebral blood flow remained intact, but it was impaired at MAC 2.0. They have also a dose-dependent neuroprotective effect; sevoflurane at MAC 0.5 does not have this effect [32].

In a prospective study, it was seen that sufficient sedation levels without clinically relevant ICP increases were achieved in 68% of the patients. However, MAP had to be maintained actively to preserve the CPP. Therefore, it was concluded that the neuroprotective effect did not outweigh the risk of adverse events, and sedation with this agent should not be carry out in these patients [33].

A summary table can be found at the end of the chapter.

| | Mechanism of action | Rapid onset | Fast recovery | Metabolism | IV Bolus dose | Continuous IV infusion | ICP reduction | CBF reduction | $CMRO_2$ reduction | Map reduction | Main advantages | Main disadvantages | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Propofol** | GABA R agonist | +++ | +++ | Hepatic | 1.5–2.5 mg/kg | 5–200 mg/kg/min | ↓↓ | ↓↓ | ↓↓ | ↓↓ | Clearance independent of renal or hepatic function. Rapid onset and fast recovery | No analgesia. Tolerance and tachyphylaxis. Increases triglycerides. | PRIS. Hypotension |
| **Midazolam** | GABA R agonist | +++ | ++ | Hepatic | 0.02–0.08 mg/kg | 0.04–0.3 mg/kg/h | ↓ | ↓↓ | ↓ | ↓ | Amnesia. Rapid onset | Tolerance. Tachyphylaxis. Accumulates in renal dysfunction. Active metabolites | Hypotension. Apnea. Delirium |
| **Morphine** | MU-R agonist | + | + | Hepatic | 0.8–10 mg/h | Max 80 mg/h | ↓/= | = | ↓ | ↓/= | Less peripheric accumulation than fentanyl. Analgesia | Hypotension | Apnea. Hypotension. Pruritus. Nausea. Active metabolite can produce seizures. Muscle rigidity |
| **Fentanyl** | MU-R agonist | +++ | ++ | Hepatic | 25–125 mg | 10–100 mg/h | ↓/= | = | ↓ | ↓ | More potent analgesic than morphine | Accumulation with hepatic impairment. Apnea | Pruritus. Nausea. Muscle rigidity. |
| **Remifentanil** | MU-R agonist | +++ | +++ | Plasmatic esterases | | 0.05–0.25 mg/kg/min | ↓/= | = | ↓ | ↓ | 500× more potent than morphine | | Hyperalgesia after infusion. CV depressant. |
| **Dexdor** | ALPHA 2 agonist | ++ | ++ | Hepatic | Not recommended | 0.2–1.4 mg/kg/h | ↓/= | ↓ | ↓ | ↓ | Sedative, anxiolytic, analgesic. Minimal respiratory depression. Reduces delirium | Limited experience in ABI. | Arrhythmias. Hypotension. Bradicardia. |
| **Thiopental** | GABA R agonist | +++ | + | Hepatic | 2–5 mg/kg | 1–5 mg/kg/h | ↓↓ | ↓↓ | ↓↓ | ↓↓ | Second-line treatment for refractory intracraneal hypertension | Accumulates in peripheral tissue. Adjust dose in renal failure. | HD instability. Immunosuppression. |

| | Mechanism of action | Rapid onset | Fast recovery | Metabolism | IV Bolus dose | Continuous IV infusion | ICP reduction | CBF reduction | $CMRO_2$ reduction | Map reduction | Main advantages | Main disadvantages | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ketamine** | NMDA R agonist | +++ | +++ | Liver | 1–4 mg/kg | (0.5–2 mg/kg) | ↑/= | ↓ | ↓ | ↑/= | Sedation, anesthesia, analgesia. No respiratory depression. HD stability. | Increases secretions. | Hallucinations. Nystagmus. Increases IOP, IAP |
| **Sevorane** | Not clear. GABA R agonist + glutamate receptor agonist | +++ | ++ | 5% Hepatic. 95% inhalatory pathway | 2% MAC | 0.5–3% of sevorane in | May increase after increase in CBF | ↑ | ↓ | ↓ | Fast elimination. Increases CBF in cerebral ischemia. | Hypotension. MAC 2 autoregulation impairs. | Toxic metabolite (compound A). Malignant hyperthermia |

## 3. Physiologic effects of sedatives on cerebral blood flow and cerebral metabolic rate of oxygen consumption

Sedation is one of the pillars in the management of patients with TBI. It is a treatment itself when used to prevent the secondary insult, and it allows other measures to be implemented which could not be applied otherwise, such as hypothermia.

The physiologic effects of sedatives are different, and they can be divided into effects on CBF and $CMRO_2$.

### 3.1 Effects on cerebral blood flow (CBF)

One of the main goals when treating these patients is to maintain a sufficient cerebral blood flow. Therefore, our drugs should have little or no effect on this matter.

The effects of intravenous sedatives on CBF have been investigated for diazepam, midazolam and propofol. All these iv agents cause a dose-dependent decrease in $CMRO_2$ and CBF. CBF reduction is an adaptative phenomenon to minimize brain metabolism. They usually have a systemic effect decreasing mean arterial pressure (MAP), inducing myocardial depression and peripheral vasodilation. Therefore, in patients with impaired autoregulation, such as those with TBI, decreasing the MAP can lead to a critical lowering in cerebral perfusion pressure and oxygen delivery to the brain. This can lead or worsen the secondary brain insult (ischemia/hypoxia) [34, 35]. If autoregulation is intact, this reduction on MAP will produce reflex cerebral vasodilation and may lead to an increase in intracranial pressure [36]. The hemodynamic effects are usually dose dependent, so it is important to assess the preload status of the patient in order to predict the hemodynamic response to the sedative agent, particularly in those with previous cardiac dysfunction.

### 3.2 Effects on the cerebral metabolic rate of oxygen consumption ($CMRO_2$)

The $CMRO_2$ and CBF are nicely connected. In TBI patients, our target is to maintain an adequate oxygen availability and energy balance; thus, we aim to increase oxygen delivery by optimizing cerebral and systemic hemodynamic, as well as attenuating metabolic demands [2, 37, 38].

Patients in coma or suffering from secondary brain insults have their cerebral metabolism decreased globally by one-third to one-half of normal levels.

Sedative agents act by reducing CMRO2, improving cerebral tolerance to ischemia and limiting the supply/demand mismatch in conditions of impaired autoregulation [34, 35]. Beyond the level of isoelectric EEG, no further suppression of cerebral oxygen consumption can take place; a minimal oxygen consumption is, indeed, due to cells' homeostasis.

## 4. Neurological indications for sedation

Continuous infusion of sedative agents is contemplated during the first 48 h, in order to prevent secondary brain injury by decreasing oxygen consumption, as well as to reduce pain, anxiety and agitation to tolerate mechanical ventilation.

Apart from the general indications due to patient's agitation and pain control, there are specific situations in these patients that require sedation as therapy.

### 4.1 Control of intracranial pressure (ICP)

The effect of sedatives on ICP is due mainly to reduction in $CMRO_2$ that leads to a decrease in cerebral blood flow. This effect can be seen as a decrease in cerebral blood volume that leads to a decrease in ICP. As well, sedation reduces pain and agitation and improves the tolerance to the endotracheal tube. These effects lead to a decrease of sympathetic activity with a reduction of arterial pressure and less ventilation asynchronies leading to a decrease of jugular venous resistance and a better venous outflow.

Sedation is a first-line therapy that should be integrated with other specific interventions as hyperventilation, osmotic agents and head-of-bed elevation. Bolus of opioids needs caution for the transient decrease in mean arterial pressure and increase in ICP due to autoregulatory cerebral vasodilation [36]. When compared with opioids, propofol showed an association with a lower ICP and less ICP treatments in patients with severe traumatic brain injury (TBI) [6].

### 4.2 Targeted temperature management (TTM)

The effects of hypothermia on the brain are multiple. First, the cerebral metabolic rate decreases leading to a decrease in CBF and, consequently, a reduction of cerebral volume. Moreover, cooling procedures suppress many of the pathways that lead to cell death, including apoptotic mechanisms (programmed cell death).

Sedation is recommended during TTM to prevent shivering, to reduce the stress response and to allow the patient-ventilator synchrony. To avoid shivering a lot of drugs are available, but they could engender side effects. One of the most used drugs is propofol that has a dose-dependent antishivering effect.

An excess in sedation can lead to an increase of mechanical ventilation time and a delay in neurological response [39].

### 4.3 Treatment of status epilepticus (SE)

Status epilepticus is a quite common neurologic condition with an overall incidence of 41–61 cases per 100,000 patients/year [40].

The emergency therapy consists in benzodiazepines for the emergency, followed by one or more anti-epileptic drugs (AED). When both categories fail, it is necessary to begin a deep sedation with anesthetic agents for at least 24 h of effectiveness [41].

Different studies showed and reported the effectiveness of propofol or midazolam as therapy for refractory SE.

The traditional barbiturate (phenobarbital), due to its side effects, is being replaced by the newest propofol and midazolam.

### 4.4 Paroxysmal sympathetic activity

This syndrome has been recognized in a subgroup of survivors of severe acquired brain injury, characterized by simultaneous, paroxysmal transient increases in sympathetic (elevated heart rate, blood pressure, respiratory rate, temperature, sweating) and motor (posturing) activity. This syndrome has been observed for the last 60 years. It affects 8–10% of patients suffering from acute brain injury, and it is associated with greater morbidity, higher healthcare costs, longer hospitalization and poorer outcomes. However, it is a potentially treatable contributor to secondary brain injury. In patients surviving traumatic brain injury, it has been associated with severe anoxia, subarachnoid and intracerebral

hemorrhage and hydrocephalus. There are many theories dealing with the pathophysiology of this entity. Disconnection of the inhibitory efferent pathways (malfunctioning pathways) from cortical areas of the brain is one of the possible theories. It is also thought that alterations in the excitatory nucleus of the brainstem can cause this syndrome; excitatory centers are then upregulated, increasing sympathetic activity. There is no accepted treatment for this entity. The objective is to mitigate signs and symptoms to avoid the adverse effects such as dehydration, muscle wasting or delayed recovery. Dopaminergic agents have shown to decrease body temperature and sweating. Alpha agonists can decrease heart rate and blood pressure. When medication fails, the use of hyperbaric oxygen therapy (HBOT) to control autonomic discharges and posturing in the subacute TBI phase has been reported. In this condition, sedation should be considered to reduce sympathetic activation [42].

## 5. Monitoring sedation in the neuro-ICU

Monitoring the depth of sedation is essential in the management of the patient in the ICU, and it influences their outcomes. Oversedation increases the risk of infections by delaying weaning from mechanical ventilation and increases length of stay and, thus, costs. On the other side, undersedation can cause agitation and anxiety of the patient, increase the risk of self-extubating and develop asynchronies between the patient and the ventilator. In NICU patients, assessing routine level of sedation is really important both for the daily wake-up tests that should be done for neurologic evaluation and, in comatose patients, to avoid oversedation.

There are various scales available for ICU patients. The Ramsay Sedation Scale evaluates consciousness, while the Richmond Agitation-Sedation Scale (RASS) examines cognition. The Motor Activity Assessment Scale (MAAS) and the Sedation-Agitation Scale (SAS) monitor sedation and arousal. Both RASS and SAS are reasonable to use in TBI patients [43]. Moreover, RASS is usually integrated with a delirium assessment performed with Confusion Assessment Method for the ICU (CAM-ICU). However, in deeply sedated patients and with muscular blockade, these scales become useless. EEG monitoring has therefore become a very investigated topic to titrate sedation in these patients. Simplified EEG tools like BIS, based on Fourier transform, have shown significant correlation with RASS and SAS in ABI [44]. However, BIS was developed to monitor sedation in the operating room (OR) setting in patients with no acute brain injury (ABI) due to the possible changes in EEG because of the brain lesion; it is often used in the ICU setting.

The possible confounders of such method are shivering, temperature fluctuation, increased muscle tone, grimacing and catecholamine levels. To assess the adequacy of pain relief, it is useful to assess autonomic signs of activation such as tachycardia, hypertension, ICP increase and diaphoresis.

## 6. Conclusions

Sedation and analgesia are widely used in NICU and all clinicians who provide care to neuropatients' face daily with such practice. The indication for sedation in NICU could be general or properly neurologic that is considered as a therapy in the acute brain injury patient. Sedation, indeed, allows a better control of cerebral hemodynamic and is part of control of intracranial pressure.

The knowledge of basic principles of pharmacology, neurophysiology, and neuropathology remains, therefore, essential to manage such kind of therapy.

Propofol and midazolam seem to be the most used drugs in such patient due to their security profile; ketamine appears to be interesting for its neuroprotective role.

To target sedation properly, it is possible to use different approaches; the use of score (RASS, SAS) in the awake patient remains a good tool that can be integrated in comatose patient, knowing their limits, with the newest EEG-derived methods.

## Conflict of interest

We declare no conflict of interest.

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