Anaesth Crit Care Pain Med 42 (2023) 101219

Contents lists available at ScienceDirect

Anaesthesia Critical Care & Pain Medicine

journal homepage: www.elsevier.com

Review article

Toward individualized sedation in patients with acute brain damage

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ARTICLE INFO

Article history:
Available online 16 March 2023

Keywords:
Sedatives
Opioids
Brain damage
Traumatic brain injury
Intracranial pressure

ABSTRACT

Sedation/analgesia in patients with acute brain damage, either traumatic or non-traumatic, is paramount to prevent alterations in brain perfusion secondary to the injury. Despite reviews on sedative and analgesic drugs, adequate sedation is an overlooked therapy in the prevention and treatment of intracranial hypertension. When to indicate continued sedation? How to guide the level of sedation? How to terminate sedation? This narrative review provides a practical approach to the individualized use of sedative/analgesic drugs in patients with acute brain damage.

Contents

1. Introduction

Guidelines have been published regarding the general clinical management of pain, sedation and delirium in critically ill patients [1] and others regarding the early management of patients with severe traumatic brain injury (TBI) [2,3]. Despite reviews on sedative and analgesic drugs in the neurointensive care unit (NICU) [4–6] and on the major role of sedation in controlling intracranial pressure (ICP) [7], it is not uncommon to see patients with high ICP and suboptimal dosing of sedatives and/or opioids in routine practice. In addition, there is a paucity of literature concerning the real-life management of sedation/analgesia in this setting. Questions remain unanswered on the decision for continued sedation, the level setting of sedation, or the termination of sedation. This narrative review will discuss drugs and step-by-step strategies of sedation/analgesia in adult patients with acute brain damage, either traumatic or non-traumatic. Our aim is to provide a practical approach to the personalized use of sedative/analgesic drugs in these patients.

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https://doi.org/10.1016/j.accpm.2023.101219

The goals of sedation and analgesia in general intensive care unit (ICU) are to provide comfort, prevent and treat any sources of pain, facilitate mechanical ventilation, and improve tissue oxygenation in critically ill patients. It should be noted that all recent randomized clinical trials on sedation/analgesia failed to find differences in survival rates between intervention and control groups when compared, for example, no sedation *vs.* light sedation [8], dexmedetomidine *vs.* usual care [9], and cisatracurium *vs.* usual care in acute respiratory distress syndrome [10]. This indicates that i) the survival rate is not an optimal endpoint when comparing drugs or strategies on sedation; ii) sedation/analgesia in the ICU should be viewed as an adaptable means to address each individual needs, *i.e.,* respiratory, pain and/or comfort, that may change all the times during the ICU stay. Individualized sedation/analgesia should be the future in the ICU. Although sedation/analgesia is more complex to manage in the NICU because of the interference between the injured brain and the direct effects of sedatives on neurological function, it is still possible to consider individualized approach in patients with acute brain damage.

2. Which sedative and analgesic drugs in the NICU?

One systematic review found no evidence of anyone sedative (hypnotic) or analgesic drug being more efficacious than another at improving outcomes of patients with TBI [6]. Apart from that concerning the treatment of refractory intracranial hypertension, *i.e.* barbiturates and high-dose propofol, no specific drugs are recommended, in either the French or US guidelines, for use in the sedation and analgesia of patients with TBI [2,3]. However, it is possible to consider all known effects, potential advantages and side effects, in order to determine the best use of sedative and analgesic drugs in these patients.

2.1. Sedative drugs

Propofol (1−4 mg/kg/h) is largely used for sedation and the control of ICP in the NICU. At higher doses, propofol can induce electroencephalogram (EEG) burst suppression to treat status epilepticus and refractory intracranial hypertension. However, poor tolerance in patients with hemodynamic instability has been reported, and an increased risk of propofol-related infusion syndrome (PRIS) occurring at high doses (>5 mg/kg/h) following more than 48 h exposure was found in TBI patients [11].

Midazolam (1−15 mg/h) is also used in the NICU, in particular in cases of hemodynamic instability. However, this drug is associated with tissue accumulation of metabolites that delays awakening and reliable neurological examination. In addition, midazolam may result in withdrawal syndrome and tachyphylaxis at higher doses. Although propofol and midazolam appear equally effective in patients with controlled ICP, midazolam is less effective than propofol in the treatment of intracranial hypertension [6].

Ketamine (1−3 mg/kg/h) is well tolerated regarding systemic hemodynamics and respiratory drive and is an opioid-sparing agent [12]. It can also be used safely in patients with TBI, showing no deleterious effect on ICP [13]. An inhibition of cortical spreading depolarizations (CSD) over a wide range of doses commonly used for sedation was found with ketamine [14]. However, in view of psychomimetic adverse events and dose-dependent hepatic dysfunction [15], its use should be considered in adjunction to other sedatives rather than as a first-line therapy in patients with acute brain damage. S-ketamine, which is twice as potent as the racemic mixture, could be a better alternative with fewer side effects [16] and was found to also significantly reduce CSD incidence in patients with aneurysmal subarachnoid hemorrhage (SAH) [17].

Dexmedetomidine (Dex) (0.3–1.4 mcg/kg/h) is a short-term selective alpha-2 adrenergic agonist with moderate sedative and analgesic properties. In patients with acute brain damage, Dex has been associated with reduced agitation [18], reduced doses of opioids and other sedatives [19], and fewer rescue therapies for intracranial hypertension [20]. Due to its potential impact on hemodynamics, Dex should be used in stable patients and is particularly indicated to facilitate the cessation of sedation (see below).

The inhaled agent isoflurane is emerging as an alternative sedative for use in ICUs equipped with specific systems for delivery and expertise although no study exists yet on patients with TBI. Isoflurane sedation permitted a reduction in opioid dose intensity compared to propofol along with a faster wake-up time in ICU patients [21]. In patients with SAH but no intracranial hypertension or cerebral vasospasm, isoflurane allowed a greater increase in regional blood flow with no difference in ICP levels compared to propofol [22]. Similar findings were shown in patients with hemorrhagic or ischemic stroke [23]. Isoflurane might therefore be considered in patients without high ICP in the event of tachyphylaxis or hemodynamic instability during intravenous sedation. The dose of isoflurane commonly used in the ICU corresponds to a minimal alveolar concentration (MAC) of 0.5−1. At higher doses (MAC > 1), isoflurane exerts brain vasodilation that could alter cerebral perfusion pressure (CPP) in a brain with low compliance. It should be noted that sevoflurane should be abandoned in the ICU setting because of the risk of drug-induced nephrogenic diabetes insipidus [24,25].

Barbiturates cannot be viewed as sedative agents in patients with acute brain damage because of their numerous side effects, *i.e.*, arterial hypotension, ventilator-associated pneumonia and immune depression. As a third-tier therapy for refractory intracranial hypertension, barbiturates can be tested (5−7 mg/kg bolus) if refractory intracranial hypertension is at least partly due to cerebral hyperhemia as assessed with transcranial Doppler (TCD). If the bolus has a positive effect on ICP, barbiturates will be administered through a continuous intravenous infusion (2−4 mg/kg/h). The optimal level of barbiturate coma is assessed using continuous electroencephalogram or bispectral index (2–5 bursts/min) [26]. Barbiturates can be beneficial on brain oxygenation for intractable intracranial hypertension [27]. In the RescueICP trial where no difference in neurological outcome was found between decompressive craniectomy and medical treatment in TBI patients with refractory intracranial hypertension, it should be noted that more than 85% of the medical group was receiving barbiturates [28].

2.2. Analgesic drugs

Alongside sedative agents, analgesics are mandatory in mechanically ventilated patients to remove any sources of nociception susceptible to increasing ICP, in particular during nursing. All opioids can be used through continuous intravenous infusion: fentanyl (0.7–10 mcg/kg/h), sufentanil (0.1–1 mcg/kg/h) and remifentanil (0.5–15 mcg/kg/h). However, excessive use of opioids is associated with side effects such as prolonged duration of mechanical ventilation, ventilator-associated pneumonia, gastrointestinal problems, opioid tolerance and withdrawal syndrome. A continuous opioid infusion was found as an independent risk factor for the development of delirium in mechanically ventilated patients with severe COVID-19 [29]. It is thus important to consider non-opioid analgesics including acetaminophen, nefopam, gabapentin, pregabalin, and non-steroidal anti-inflammatory drugs as opioid-sparing agents in critically ill patients [1].

3. First step: an early neurological reassessment?

By definition, the neurological assessment of a sedated patient with brain lesions is unreliable. The in-charge physician must then

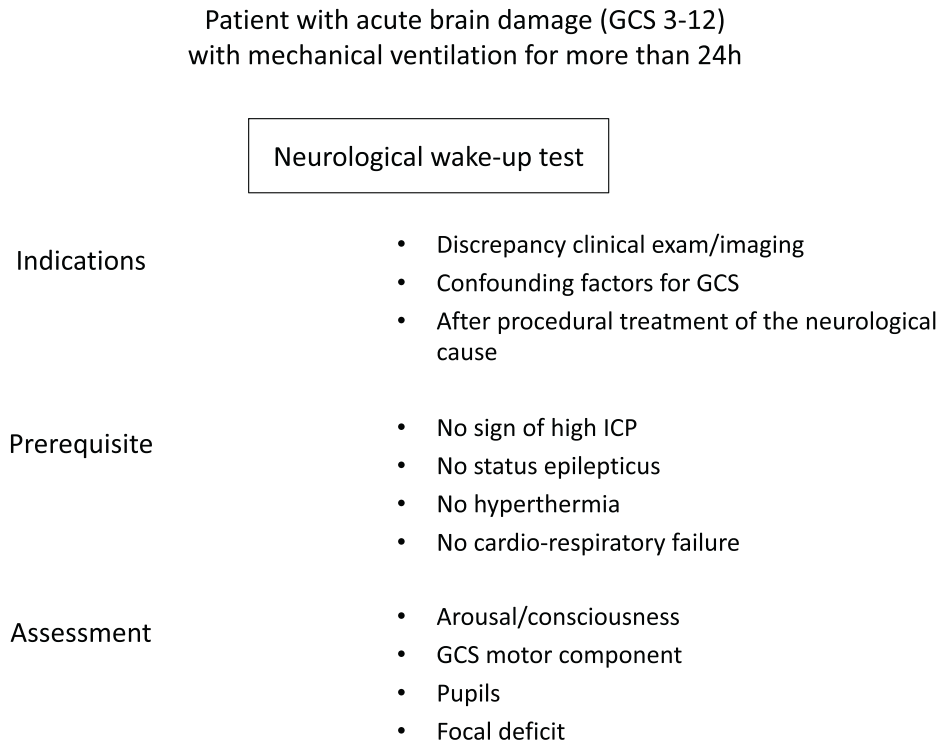

Figure 1. Conditions to perform a neurological wake-up test in mechanically ventilated patients with acute brain damage.

decide between two alternatives: to interrupt the sedation in order to obtain information about the neurological status, *i.e.*, perform a neurological wake-up test (NWT), or to continue the sedation to control ICP and prevent secondary brain lesions. This choice constitutes the first step for personalized sedation in the NICU (Fig. 1).

Clinical situations in which an NWT is indicated include the discrepancy between severe clinical data and normal brain imaging on CT scan, or confounding factors for Glasgow Coma Scale (GCS) score due to hypothermia, alcohol intoxication, seizures, or metabolic disorders. An NWT may also be indicated after treating the cause of a neurological degradation, *e.g.*, ruptured aneurysm or compressive epidural or subdural hematoma. Once temperature-target management is terminated after cardiorespiratory arrest, a neurological reassessment is mandatory. The NWT will provide useful information for detecting changes in neurological status some of which may require more active management, *i.e.,* additional therapy, new imaging and/or brain monitoring, or discussing end-of-life procedures if the responses to clinical examination are very poor. The NWT may also reduce the duration of mechanical ventilation and the incidence of secondary complications such as nosocomial infections and delirium [30].

However, any discontinuation of sedation exposes head-injured patients to a stress response with agitation, increased oxygen consumption and energy expenditure, and cerebral hyperemia. A 30-50% increase from baseline in energy expenditure and global oxygen consumption (VO2) was found following cessation of sedation in TBI patients [31]. In a brain with low compliance (or reduced volume-pressure compensatory reserve), these changes result in increased ICP and cerebral hypoperfusion [32]. Episodes of brain hypoxia were found during inappropriate NWT procedures [33]. This illustrates that sedation is closely linked with ICP level in patients with low brain compliance, meaning that ICP value will drive the management of sedation level in these patients (see below). When decided in a patient with no high ICP (or indirect signs of high ICP), no status epilepticus, no marked hyperthermia and no cardiorespiratory instability, the NWT includes sedative interruption, the maintenance of a low dose of opioid and, if available, careful monitoring of ICP and CPP. The patient is then assessed regarding signs of arousal and consciousness, the motor component of the GCS, pupillary reflexes and focal neurological deficits.

4. Second step: which target level of continued sedation?

If the conditions to interrupt sedation after severe brain injury are not met, the sedation/analgesia must be continued and adjusted to prevent episodes of high ICP during nursing. The control of ICP keeping it below 20−25 mmHg *via* the maintenance of optimal CPP is paramount to prevent alterations in brain perfusion secondary to the injury and poor outcome [34]. The removal of any source of nociception during nursing interventions, the maintenance of normocapnia during mechanical ventilation, the prevention of seizures, a reduction in brain oxygen consumption rate with concomitant metabolic vasoconstriction and reduced cerebral blood volume are sedation-related mechanisms involved in the prevention and/or treatment of episodes of high ICP. An appropriate level of sedation/analgesia along with other first-tier therapies, *i.e.,* osmotherapy, cerebrospinal fluid (CSF) drainage, and mild hypocapnia, was effective at controlling ICP in more than 70% of patients after severe TBI [35].

In sedated patients with no possibility of clinical examination, neurological function is assessed using multimodal monitoring including continuous measurements of ICP and/or brain tissue oxygen pressure ($PbtO_2$), repeated measurements of TCD and brain CT imaging. Target values to initiate therapies in TBI patients have been recently proposed: ICP $>$ 25 mmHg, CPP $<$ 50 mmHg, $PbtO_2$ $<$15 mmHg [34]. A reduced diastolic blood flow velocity (FVd $<$20 cm/s) and high pulsatility index (PI $>$ 1.4) on TCD can be also used as indices of brain hypoperfusion [36]. However, because sedation may impact ICP in brains with low compliance (see above), ICP should be prominent to guide the level of sedation. The prerequisite is the absence of nociceptive responses to painful procedures as reflected with a Behavioral Pain Scale (BPS) score $<$5

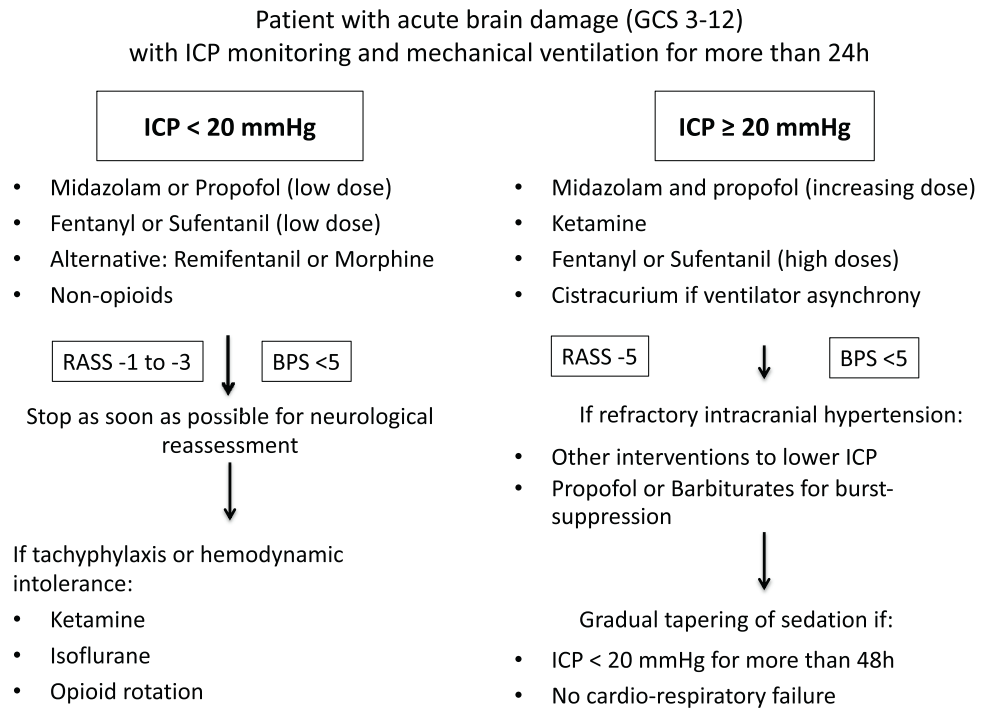

Figure 2. A practical algorithm for using sedatives and analgesics for mechanically ventilated patients with acute brain damage and continued sedation. GCS, Glasgow Coma Scale; ICP, intracranial pressure.

or a Pupillary Pain index <5 assessed with quantitative pupillometry [37]. Therefore, there exist two ICP-dependent clinical situations in sedated and mechanically ventilated patients (Fig. 2):

- For an ICP below 20 mmHg, light-to-moderate sedation can be continued using low doses of sedatives and opioids until the patient meets all the criteria to terminate sedation. The Richmond Agitation Sedation Scale (RASS) score is maintained between −1 (eye contact >10 s) and −3 (move to voice). This situation may correspond to comatose patients with post-TBI diffuse axonal injuries, anoxo-ischemic lesions, status epilepticus and/or cerebrovascular vasospasm where the risk of subsequent intracranial hypertension is limited. A functioning external ventricular drainage or decompressive craniectomy can drastically change brain compliance, then the need for deep sedation. In case of tachyphylaxis or hemodynamical instability, the introduction of low-dose ketamine, isoflurane or another opioid (opioid rotation) can be considered.
- For an ICP persistently equal or above to 20 mmHg, deep sedation should include increasing doses of midazolam and propofol, high doses of opioids, ketamine and the adjunction of cisatracurium if adaptation of the patient to the ventilator is needed. The RASS score should be -5 (unresponsive to physical stimulation). This situation may correspond to comatose patients with large traumatic contusions, large intraparenchymal hematoma, malignant stroke or diffuse brain edema. In case of intractable intracranial hypertension, third-tier therapies will be considered such as therapeutic hypothermia (34−35 °C), metabolic suppression with barbiturates or high-dose propofol, moderate hypocapnia ($PaCO_2$ 30−35 mmHg) and decompressive craniectomy.

5. Third step: how to detect patients with reduced brain compliance?

Intracranial compliance refers to the ability of the brain to tolerate increases in the volume of the brain's three components, *i.e.*, brain tissue, CSF, and blood volume, without a corresponding increase in ICP. A normal ICP value does not mean that the patient is exempted from episodes of high ICP during nociceptive stimuli, episodes of agitation, and/or secondary expansion of brain lesions. The accurate measurement of dynamic ICP is complex because ICP is influenced by intra-cranial factors and extra-cranial factors (respiratory, hemodynamics, metabolism, head elevation), and has inter- and intra-individual variability. Discussing the best marker of volume-pressure compensatory reserve (brain compliance) is thus beyond the scope of this review (see reviews [38–40]). Nevertheless, there are indirect elements from the brain multimodal monitoring that may indicate reduced brain compliance.

Post-trauma cerebral contusions represent lesions with the highest potential of expansion. Age, subdural hematoma, multiple contusions with fuzzy signs, contusion volume and coagulation abnormalities were found associated with contusion expansion in TBI patients [41]. The presence of traumatic bifrontal contusions of more than 65 cm^3 on Day 2 was at high risk of brain lesions expansion and neurological degradation [42]. The analysis of ICP waveform components can inform on intracranial compliance: reduced brain compliance is reflected with peak P2 wave amplitude (intracranial amplitude) greater than peak P1 (arterial pulsation) and peak P3 (aortic valve closure) [38]. The development of A waves, or plateau waves following a sharp rise of ICP from normal value up to 50 mmHg or more, indicate reduced brain compliance. Similarly, an ICP that takes more than 5 min to return to baseline values after a stimulus such as endotracheal suctioning may indicate low brain compliance. Taken together, these elements should be accounted for prior to taking the decision to terminate sedation.

A comprehensive picture of how to consider step-by-step tailored sedation/analgesia in patients with acute brain damage is shown in Fig. 3.

6. Fourth step: how to manage the termination of sedation?

One challenging situation in the ICU is weaning off from sedation. Surprisingly, this phase has almost never been discussed

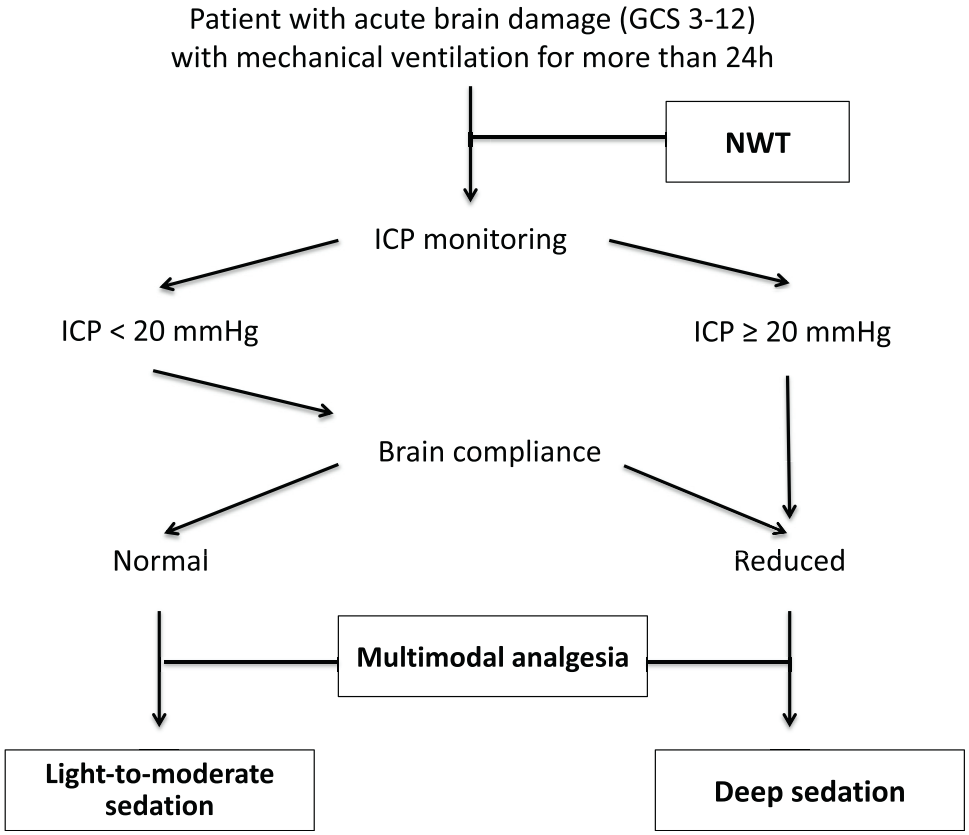

Figure 3. A comprehensive picture of tailored sedation for mechanically ventilated patients with acute brain damage. GCS, Glasgow Coma Scale; ICP, intracranial pressure; NWT, neurological wake-test.

in reviews on patients with acute damage [4,5]. Liberation techniques from invasive mechanical ventilation in the NICU will not be discussed here (see recommendations [43]). Before considering stopping sedation in patients with TBI, certain criteria must be fulfilled: no elevation in ICP over the last 48 h, no new CT findings or midline shift >10 mm on a recent brain imaging, no TCD and $PbtO_2$ abnormalities, no cardiorespiratory failure, and no status epilepticus. A possible rebound in the ICP during this phase should not indicate the need to restart sedation if the patient shows clinical signs of awakening. Schematically, there are three unexpected scenarios that may occur during this phase: persisting coma, severe agitation and delirium.

6.1. Persisting coma

The persistence of a poor response to clinical examination is not uncommon in the NICU. Specifically, elderly and/or obese patients, or those with renal/liver impairment can become over-sedated with sedatives and/or opioids; this complicates the neurological assessment of such "slow to wake" patients. However, this situation may also reflect a neurological complication such as hydrocephalus, new brain lesions, or non-convulsive seizures, and a brain CT scan and/or EEG recording should be considered. Measuring the blood concentrations of midazolam and its glucuronide metabolites was found useful in distinguishing between over-sedation and neurological damage among patients for whom coma persisted after the termination of sedation [44].

6.2. Agitation

Agitation, defined as a RASS score of +2 or more, is common on the awakening of patients with acute brain damage, with an incidence of 11–70% [45–47]. An agitated patient is exposed to the life-threatening risk of accidental device removal and the continued use of sedatives with prolonged duration of mechanical ventilation and ICU-related complications. Causes of agitation are numerous in the ICU and can be medical-related (sepsis, metabolic disturbances, respiratory dysfunction, hepatic encephalopathy, stroke, and non-convulsive seizures), or not (urinary retention, fecal impaction, pain, hyperactive delirium, withdrawal from drugs or substances, drug-induced agitation, and sleep deprivation) [48]. In addition, agitation in patients with acute brain damage may also reflect hidden neurological complications such as cerebrospinal fluid infection, cerebral vasospasm, and extended or new intra-cerebral lesions. The use of amantadine may increase the risk of agitation in this population [46].

Once treatable causes of agitation have been eliminated, pharmacological agents are often used, although there is no consensus on the most efficacious and safest therapeutic strategy for agitated patients with TBI [47]. We recently proposed to distinguish between the treatment of withdrawal syndromes and that of agitation symptoms in critically ill patients [48]. Clonidine, buprenorphine, methadone and benzodiazepines are validated options for withdrawal syndromes [49–51]. The pharmacological treatment of agitation symptoms preferably comprises short-acting drugs to prevent any interference with the neurological assessment: neuroleptics (loxapine, tiapride, haloperidol, cyamemazine, risperidone), alpha-2 agonists (clonidine, Dex) and benzodiazepines (clorazepate, diazepam) [48]. We successfully tested 48-h infusions of clorazepate and buprenorphine to prevent withdrawal-related agitation in severe TBI patients when prolonged sedation was stopped [52]. Using Dex to minimize the use of benzodiazepines and antipsychotic drugs was also suggested to reduce confusion, amnestic effect and impairment of motor recovery [19].

6.3. Delirium

Delirium is defined as a state of acute confusion with disturbance in attention, awareness or cognition that develops over hours or days and that cannot be explained by sedation. It is associated with increased mortality and long-term cognitive impairment. There are numerous causes for the development of delirium in patients with acute brain injury, including primary and secondary brain damage, hyperosmolar therapy, seizures, drugs, organ failure, sepsis, sleep deprivation, sensory deprivation and pre-existing pathology [53]. The use of sedatives has been established as one cause of delirium with long-term cognitive impairment [54]. As with the general ICU population, brain-injured patients can be assessed for delirium using the Confusion Assessment Method for the ICU (CAM-ICU) or Intensive Care Delirium Screening Checklist (ICDSC). According to a systemic review of 7 studies including patients with stroke or TBI, the pooled prevalence rate was 12−43% [55]. The ICDSC showed better diagnostic performance than CAM-ICU in detecting delirium in a cohort of assessable NICU patients, *i.e.*, RASS score of -2 or above [56]. However, testing for delirium is not always possible in patients with acute brain injury due to their decreased level of consciousness relating either to the primary injury itself or to the deep sedation (RASS of -3 or below) to treat high ICP.

Among the general population of patients in the ICU, non-pharmacological approaches aimed at optimizing the patient's environment and improving levels of comfort can be considered to reduce the occurrence of delirium: cognitive stimulation, minimizing light and noise, reducing sedation, reducing hearing and/or visual impairment [1]. The routine use of physical restraint to prevent agitated patients from self-extubation was associated with a higher risk of delirium [57]. However, these multicomponent interventions are more difficult to implement in patients with acute brain damage due to their presentation and/or requirement for deep sedation. In addition, there is no evidence that antipsychotics improve their clinical outcomes [58,59]. Beta-blockers, anticonvulsive drugs or Dex can be considered to treat patients with delirium [53,60].

7. Conclusion

Although overlooked in routine practice, adequate sedation/analgesia plays a central role in preventing and treating episodes of intracranial hypertension in patients with acute brain damage. While analgesia should always be maintained, the levels of sedation required should be individually adapted according to the need to perform neurological clinical assessment and the level of ICP and brain compliance. The most challenging issue for the in-charge physician is choosing the best strategy of sedation and the best moment to permit its cessation in patients with acute brain damage.

Disclosure of interest

Dr. Payen declares having received personal fees from Sedana Medical and IDD-CDM Lavoisier. The other authors declare having received no fees.

Funding

This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

Study design/planning: JFP
Study conduct: JFP
Data analysis: JFP, CS, BB and AB
Writing the paper: JFP, CS, BB and AB
Revising the paper: all authors

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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