Sedatives in neuro-critical care: an update on pharmacological agents and modes of sedation

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Abstract

Purpose of review

In this paper, the specific and general indications for sedatives in the neuro-critical care unit are discussed, together with an overview on current insights in sedative protocols for these patients. In addition, physiological effects of sedative agents on the central nervous system are reviewed.

Recent findings

In the general intensive care unit population, a large body of evidence supports light protocolized sedation over indiscriminate deep sedation. Unfortunately, in patients with severe acute brain injury, the evidence from randomized controlled trials is scarce to non-existent, and practice is supported by expert opinion, physiological studies, and observational or small randomized trials. The different sedatives each have different beneficial effects, and side effects.

Summary

Extrapolating the findings from studies in the general intensive care unit population suggest to reserve deep continuous sedation in the neuro-intensive care unit for specific indications. Although an improved understanding of cerebral physiological changes in patients with brain injury may be helpful to guide individualized sedation, we still lack the evidence base to make broad recommendations for specific patient groups.

Keywords

Critical care; intensive care unit; brain injuries; sedation; sedatives and hypnotics;

Introduction:

In the general intensive care unit (ICU), light rather than deep sedation is recommended in mechanically ventilated patients [1], in combination with daily awakening trials. RCT's have demonstrated the short-term benefits of this policy, such as a reduced ICU length of stay (LOS) and a shorter duration of mechanical ventilation (MV) [2, 3]. Unfortunately, brain injured patients were excluded in these trials. In the neuro-critical care unit (NCCU), sedative agents are used for specific therapeutic indications, that do not exist in patients without intracranial pathology. On the other hand, sedatives interfere with clinical neurologic assessment of the patient [4]. This paper is a narrative review on the indications, sedation protocols, and depth of monitoring in the NCCU, as well as the pharmacologic properties of frequently used sedatives.

Specific indications in the NCCU for the continuous use of sedative agents.

Intracranial pressure (ICP) control is an important indication for continuous sedatives in the NCCU, even while the evidence for this practice is based on low-quality evidence [5]. The ICP is a warning sign for pending herniation and deranged perfusion. The relationship between elevated ICP and worse patient outcomes is determined by the degree of ICP elevation, as well as by the duration of the episode of intracranial hypertension [6]. Sedatives reduce ICP through multiple mechanisms. First, they suppress coughing or other forms of Valsalva. Second, they reduce agitation and motoric unrest. Third, they reduce brain metabolism ($CMRO_2$). Cerebral blood flow (CBF) is closely regulated by $CMRO_2$, and a reduction in CBF will reduce cerebral blood volume (CBV), bringing the patient in a less steep range of the ICP/volume curve. In addition, when cerebral perfusion is critical, the reduction in $CMRO_2$ can restore supply/demand mismatch to the brain. Fourth, they can treat seizures, as discussed below. Finally, sedatives can facilitate ICP-directed therapies, for instance P_aCO_2 control by MV. Specific properties of different sedatives are discussed below. Continuous sedation is also a rescue therapy for refractory status epilepticus (RSE), and should be considered in case of ongoing seizures for more than 40 minutes failing to respond to first- and second-line anticonvulsants [7]. For this indication, guidelines recommend anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol, under continuous electro-encephalogram (EEG) monitoring [8]. There is no clear evidence from RCTs for this rescue therapy. A third specific indication for sedation in the NCCU is allowing targeted temperature management (TTM). TTM is associated with shivering, leading to patient discomfort, increased $CMRO_2$ and increased ICP. Short acting sedatives such as propofol and remifentanil may be preferred here, over longer acting products such as midazolam and fentanyl [9].

Finally, paroxysmal sympathetic hyperactivity (PSH), is a rare but striking clinical syndrome

following severe acquired brain injury, with paroxysmal tachycardia, arterial hypertension, tachypnoea, hyperthermia, and spasticity in response to afferent stimulation [10]. Continuous infusions of sedatives are often used to suppress the manifestations of PSH. GABA-acting agents such as propofol or midazolam are not preferred, but opioids, and α-2-agonist like clonidine or dexmedetomidine, can be effective temporary therapeutic options while the patient is still in the ICU. An excellent and more elaborate review on the specific indications for sedatives in the NCCU can be found in Oddo *et al*. (11). Outside these specific indications, the sedation strategy of NCCU patients, regardless of the admission diagnosis, should aim at light rather than deep sedation, to allow neurological evaluation and to avoid the side effects of continuous sedation, as explained in the sections below.

Assessment of the depth of sedation

Guidelines recommend to titrate to light sedation, and use a clinical scale to set the therapeutic goal and assess the depth of sedation [1]. When sedating for a NCCU-specific indication, therapy should be titrated to a therapeutic goal as well with appropriate monitoring: ICP-monitoring when ICP-control is the goal, continuous EEG monitoring when seizures are treated, clinical scales for TTM and PSH. In particular, it is important to monitor when withdrawing sedation. The Bi-spectral index (BIS) monitor uses a processed EEG signal to quantify depth of sedation and could be useful in the general ICU for deep sedation combined with neuromuscular blockade, or for light sedation when a sedative scale cannot be used [1]. In TBI, the BIS has been shown to be prognostic [12]. A small prospective RCT in a tertiary NCCU, including mainly hemorrhagic stroke patients, demonstrated a reduction in propofol-dose used in a 12-hour period, when BIS-guided sedation was compared to sedation-scale-guided sedation, but these findings need to be confirmed in a larger trial before they can be widely recommended [13].

Sedative protocols, and neurological wake-up tests.

The clinical neurological examination (neuro-exam) is crucial in the evaluation patients admitted to the NCCU, with 3 main goals: first, to detect the presence of neurological abnormality; second, to formulate a differential diagnosis, and establish the possible anatomical location of the problem; third, to assess the evolution of the neurological condition by serial assessment [4]. Sedation interferes with many aspects of the neuro-exam. Therefore, it is essential to avoid unnecessary sedation, titrate to therapeutic goals, stop sedation as soon as the indication is no longer present, and to monitor carefully during withdrawal [11]. Protocolized sedation may reduce hospital LOS, in general ICU patients [14]. Only one study has examined the effectiveness of protocolized analgo-sedation, specifically in the NCCU [15]. Using a before-after design, protocolized sedation led to more adequate pain control, a

reduced use of propofol and midazolam, and faster awakening when daily neurological wake-up tests (NWTs) were performed. In the general ICU, NWTs have been shown to reduce the number of unnecessary technical exams because of unexplained prolonged unconsciousness [16]. Performing NWTs in patients sedated for ICP-control is still controversial, because of the risk of neuro-worsening, while the probability to detect a new neurological finding appears to be low [17-18]. A recent review identified in total 1 retrospective and 4 prospective observational trials on NWTs in brain-injured patients, as well as one small non-predefined subgroup of a RCT [19]. In 5 studies, NWTs were associated with worsening of neuro-monitoring parameters, and/or had to be interrupted. In summary, there are no data to support the indiscriminate use of NWTs in severe brain injury. When performing a NWT, it should be done with appropriate monitoring.

Specific sedatives in the NCCU

The advantages and drawbacks of different sedatives are summarized in table 1. Figure 1 is a schematic graphical representation of their differential effects on ICP, cerebral perfusion pressure (CPP), CBV, CBF, $CMRO_2$, and glucose metabolism (CMR_{gluc}).

Propofol

Propofol is a GABA-receptor agonist, and the most frequently used sedative in the ICU. It has an interesting pharmacokinetic profile, with fast recovery even after prolonged sedation. Propofol is highly effective in reducing the ICP, and is in fact the first choice sedative for the treatment of intracranial hypertension [19], even while there are concerns because of the prominent hemodynamic suppression and CPP reduction. Propofol has a dose-dependent EEG-suppressive effect, and is used as third-line treatment for RSE as explained above [8]. In addition, propofol preserves cerebrovascular autoregulation, and CBF-$CMRO_2$-coupling [20]. In the NCCU, long-term high dose propofol infusions have been associated with propofol infusion syndrome (PRIS). This is a rare phenomenon characterized by massive muscular energy failure due to the effect on mitochondria, leading to rhabdomyolysis, cardiac arrhythmia, and asystole [21]. PRIS is in most cases fatal.

Midazolam

Midazolam, as compared to propofol, has less pronounced reductions of $CMRO_2$, CBF and ICP, which is one of the reasons it is not the recommended first-line drug of choice for the treatment of intracranial hypertension [19], even when it has more favourable hemodynamic profile. Like all benzodiazepines, it has anticonvulsive properties, but does not produce an isoelectric EEG. A systematic review identified 4 studies including in total 187 patients that compared propofol with midazolam for the sedation of patients with TBI, and found a similar efficacy and safety of both drugs, with no differences in controlling ICP and CPP [22]. Another

systematic review found more hypotension and lower CPP with propofol compared to midazolam [23]. An important drawback of prolonged midazolam infusions, in particular in the NCCU, is the unpredictable prolonged awakening, due to tissue accumulation and an active metabolite [24]. In a recent multicenter before-after study, switching from a midazolam-fentanyl based regimen to propofol-remifentanil, resulted in significantly earlier awakening and more ventilator-free days [25]. A single center observational cohort study found an association between delayed awakening and midazolam use [26]. Because of this possible delay in neuro-prognostication when using midazolam, it might be advisable to avoid benzodiazepines in post-cardiac arrest patients. In addition, the use of midazolam, in particular by infusion, is an independent risk factor for the development of delirium and posttraumatic stress disorder [27, 28].

Ketamine

Ketamine is an N-methyl-D-aspartate receptor antagonist, producing amnesia, psycho-sensory and analgesic effects. The combination of analgesic and sedative properties, hemodynamic stability, and pulmonary vasodilation, makes ketamine an appealing agent in anesthesia and critical care [29]. It has an opioid-sparing effect [30]. Unfortunately, data on safety in long-term ketamine infusions are lacking, but they are associated with liver failure and haemorrhagic cystitis.

Ketamine has long been banned in patients at risk for intracranial hypertension after two small studies in the seventies reported an increase in cerebrospinal fluid pressure in non-ventilated patients [31,32]. However, a recent systematic review of 7 studies (in 101 adult and 55 pediatric sever TBI patients) [33] has provided low-level evidence that ketamine does not increase, and might even lower ICP, provided patients are ventilated and sedated. A second systematic review in non-traumatic neurological illness, found the same [34]. Due to the known psychotomimetic effects of ketamine, clinicians are apprehensive of the risk of delirium. However, a retrospective cohort study comparing ketamine- and non-ketamine-based sedation, found no significant differences in delirium incidence, or number of delirium days [35].

There is some evidence pointing towards a possible neuroprotective role. Ketamine reduces glutamate-induced inflammatory cytokine production in isolated human glioma cells in vitro [36], and reduces MRI-spectroscopy-measured frontal glutamate concentrations in children [37]. Cortical spreading depolarizations (CSDs) are large, propagating waves of mass neuronal and glial depolarization and important contributors to the progression of brain injuries in patients with acute neurological injury. Findings from preclinical data suggesting that ketamine might decrease CSDs, have recently been confirmed in a small prospective RCT in 10 SAH

and TBI patients, where even sub-anesthetic doses of ketamine inhibited CSDs [38], providing the first evidence that CSDs are not mere an epiphenomenon of the suffering brain.

Ketamine has differential regional effects on $CMRO_2$: frontal regions, the insula, and the anterior cingulate gyrus show an increase, while a decrease is observed in pons, cerebellum, and temporal lobe. These changes in regional $CMRO_2$ are not entirely followed by changes in regional CBF, pointing to a dose-dependent uncoupling [39, 40].

During prolonged seizures, the number and activity of postsynaptic GABA-A receptors decreases, leading to decreased effectiveness of GABA-acting agents, while concurrently, the number and activity of NMDA receptors increases. In this perspective, whether using ketamine earlier on could facilitate early seizure control or improve outcomes, is an interesting hypothesis, currently not supported by evidence from RCTs. Nowadays, ketamine is mainly used after 5-6 anticonvulsants have failed [41], In a retrospective study, the introduction of ketamine contributed to the permanent control of refractory or super-refractory status epilepticus in 1/3 of patients [42].

Dexmedetomidine

Dexmedetomidine, an alpha-2 agonist, provides sedation without inducing unresponsiveness or coma and has analgesic properties without effect on respiratory drive. A recent Cochrane review concluded that dexmedetomidine shortens the time to extubation and discharge compared to more conventional agents such as propofol [43]. During neurosurgery, dexmedetomidine allowed for a better neurological evaluation including detection of focal neurological deficits, compared to midazolam or propofol [44]..Despite the surge in interest the past years, only limited literature exists about the safety and efficacy of alpha-2 agonists in NCCU patients, as evident from 2 recent systematic reviews [45, 46]: there was no safety issue with using dexmedetomidine in this population, although the available evidence was of low quality. No evidence for efficacy could be found. Currently, no studies have compared dexmedetomidine to clonidine in the NCCU.

Volatile anaesthetics

The development of new anaesthetic reflectors ‘AnaConDa’ and ‘Mirus’, revamped interest in the use of volatile anaesthetics for sedation in the ICU [47]. Potential benefits include rapid onset, bronchodilation, a decreased $CMRO_2$ and easy titration through end-tidal gas monitoring. When administered for a long time, volatile agents also improved sedation stability with fewer dose adjustments [47, 48]. In a recent meta-analysis, volatile anaesthetics had significantly shorter awakening and extubation times compared to propofol and midazolam, but no difference in LOS [49]. Nonetheless, sedative agents are still not routinely used in the

NCCU,because of the risk of an increased ICP due to a rise in CBF, even though the study of Villa in 2012 showed no difference ICP levels compared to propofol [50]. Some concerns still exist, including the potential environmental contamination, which urges the need for scavenging [51]. Epidemiological data on prolonged volatile anaesthetics administration demonstrate a strong association with long-term cognitive deficits [52], in particular in children [53]. Although confounding by indication remains an important concern in interpreting these studies, these potential neurotoxic effects cannot be ignored and uncertainty about safety, in particular in young and brain injured patients, preclude their use in the NCCU, even though a study on rats in 2014 showed a decrease of CSD when using isoflurane compared to propofol [54].

Opioids

Fentanyl is associated with a moderate [55] or no [56] reduction in CBF and $CMRO_2$. The same holds for sufentanil, where a small increase in ICP was found in one study, most likely as a consequence of the normal autoregulatory response to a temporary reduction in blood pressure [57]. Remifentanil can cause minor clinically negligible increases in CBF [58]. In view of their very similar and small effect on ICP, CBF and $CMRO_2$, the choice of opioid should be determined by the pharmacokinetic profile: remifentanil permits faster and more predictable awakening for neurological assessment. However, if prolonged deep sedation is required, fentanyl or sufentanil might be preferred [59, 60].

Barbiturates

Barbiturates cause a dose-dependent suppression of EEG, up to an almost total suppression of all cortical activity above basal metabolism, with a concomitant decrease in $CMRO_2$, CMR_{gluc}, and CBF. At high doses, there is important hemodynamic suppression. Other side effects, such as ileus, loss of ciliary transport, nefro- and hepatotoxicity, adrenal suppression, and profound immunosuppression, make the patient under barbiturate coma highly vulnerable for potentially lethal complications [61, 62]. In addition, barbiturate infusions have an unfavourable pharmacokinetic profile with prolonged awakening. In view of these important side-effects, barbiturates are mainly used as rescue therapy, for refractory seizures and control of intracranial hypertension where lower tier therapies are insufficient. Other rescue therapies for refractory intracranial hypertension, hypothermia and decompressive craniectomy (DC), have become obsolete or at least controversial in view of the results of recent RCT's. Indeed, trials on prophylactic [63] as well as second tier hypothermia [64] have demonstrated harm, rather than benefit. Early decompressive craniectomy (DC) results in worse clinical outcomes [65] while secondary DC [66] will result in a higher proportion of patients who will remain in a vegetative state, and only a small proportion of patients with good clinical outcomes at 1 year. Therefore, barbiturates are now the first rescue therapy to control elevated ICP refractory to

maximum standard medical and surgical treatment, as recommended by the current guidelines [19] Thiopental (loading dose 2-5mg/kg, maintenance dose 3mg/kg/h) has demonstrated a higher effectiveness than pentobarbital (loading dose 10 mg/kg, followed by maintenance dosage of 1 mg/kg/h) in a RCT[67].,

However, no RCTs exist comparing barbiturates to other sedatives as last resort therapy for both desperate situations, leading to only weak or no evidence [68, 69]. However, since there is no other agent with a similar powerful effect, it is very likely that they will remain to be used in these settings.

General conclusion:

Specific indications for sedation in the NCCU exist, outside the indications of general ICU patients. It is important to target sedatives to a specific therapeutic goal, and to monitor for effect and side-effects. The physiological effects of the most frequently used sedatives are well-known, unfortunately the evidence upon which their use in brain-injured patients is based is weak. Often multiple agents will be necessary to maximize desirable effects and minimize adverse effects.

Key Points:

1. Daily interruption or reduction of sedation is recommended in mechanically ventilated patients to enhance neurological evaluations and to improve short- and long-term outcomes. Specific indications exist for sedation in NCCU: ICP control, seizure control, reduction in $CMRO_2$, PSH, and to allow for brain-protective therapy.

2. Future studies on the use of sedatives for neuroprotection in patients with severe acute acquired brain injury, should focus on relevant outcomes, while at the same time monitoring the important pathophysiological mechanisms involved in secondary brain damage, such as detection of cortical spreading depression, of neuro-inflammation and energy dysfunction.

3. Individualized sedation in neuro-critical care patients, should consider all known effects, potential advantages and side effects, possible drug interactions, to determine the optimal sedative regimen adapted to a particular clinical scenario.

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Conflicts of interest

There are no conflicts of interest.

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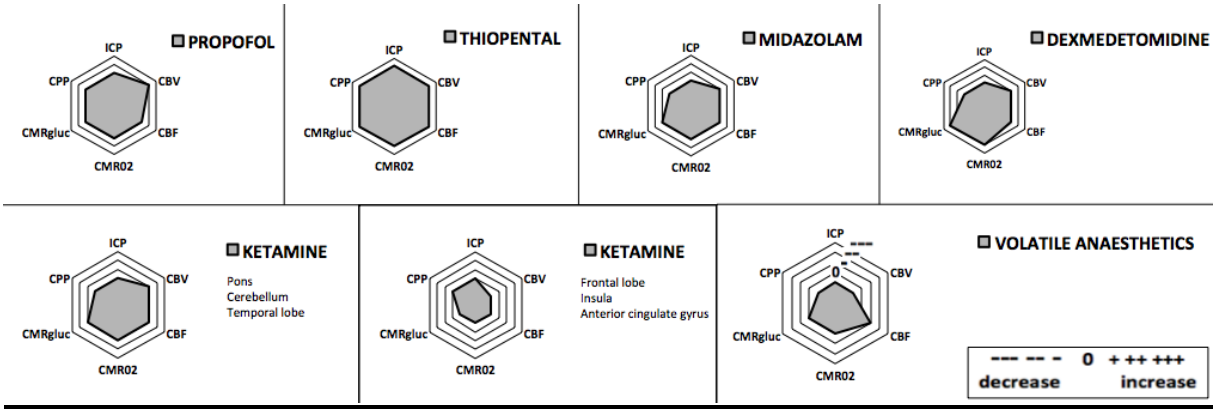
Figures and Tables:

Table 1: Comparison of the advantages and disadvantages of sedative agents in the ICU

	Indications in the neuro-ICU	Advantages	Disadvantages
Propofol	• First-line sedative to treat intracranial hypertension • First choice sedative for status epilepticus unresponsive to anti-epileptic drugs • Post-cardiac arrest, when rapid awakening is important	• Pharmacokinetic profile. • Anticonvulsive • Dose-dependent reduction of ICP, $CMRO_2$, CMR_{gluc}, and CBF.	• Hemodynamic instability (MAP↓ CPP↓) • Risk of Propofol Infusion Syndrome • Lack of analgesic effect • Hypertriglyceridemia
Midazolam	• Second line sedative, to be added when other sedatives are insufficient or at their maximum dose • Sedation of hemodynamically unstable patients	• Anticonvulsive • Amnesic effect • More hemodynamically stable compared to propofol	• Risk of accumulation • Increased ICU length of stay • Increased duration of MV • Increased risk of delirium and PTSD • No analgesic effect
Barbiturates	• Rescue therapy for intracranial hypertension and refractory or superrefractory status epilepticus	• Strong effect on ICP reduction, $CMRO_2$, CMR_{gluc}, and CBF. • Burst suppression of EEG	• Hypotension (MAP↓↓ CPP ↓↓) • Adrenal dysfunction • Immunosuppression • Nefro- and hepatotoxicity • Long context-sensitive half-life
Opioids	• Analgesia • Tolerance of mechanical ventilation	• Only mild CPP and ICP effect	• No ICP- lowering effect • Risk of accumulation (except for remifentanil) • Remifentanil: hyperalgesia • Dependence

Figure 1: Comparison of the effect of sedative agents on neurophysiology (CPP, ICP, CBV, CBF, $CMRO_2$, CMR_{gluc})



Comparison of the neurophyisiological effect of sedative agents: propofol, midazolam, dexmedetomidine, ketamine, volatile agents and thiopental. The differential regional effects on CBF/$CMRO_2$ of ketamine are shown: frontal regions, the insula, and the anterior cingulate gyrus show an increase, while a decrease is observed in pons, cerebellum, and temporal lobe.