A Critical Appraisal of Sedation, Analgesia and Delirium in Neurocritical Care

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ABSTRACT: Administering analgesics, sedatives and antipsychotics is challenging in the Neurological Intensive Care Unit (NICU). We reviewed this literature and our current practice to better inform the critical care practitioner and to identify gaps for future research. We electronically searched observational, intervention and outcome studies addressing sedation, analgesia and delirium in the NICU, and their bibliographies. Practice patterns were assessed in three critical care units with specialized neurological care in Montreal. Bedside pain assessment tools are psychometrically validated in the neuro-critically ill but sedation and delirium tools are not. Rigorous pain and sedation assessments appear feasible; delirium screening has not been tested. Publications addressing outcomes and responses to pharmacologic treatment lack consistency, rigor or both. In daily practice, pharmacologic management varies greatly. Clearly, little information exists on analgesia, sedation and delirium in the NICU. Systematic evaluation of pain improves outcome. No evidence-based therapeutic recommendations can be proffered.
Finally, delirium is now described in the critically ill and considered common and important, since delirious patients have worse outcomes. Most large studies describing delirium symptoms report prevalence rates between 20 and 50%. Some authors have identified an entity called 'sub-syndromal delirium' for patients with some symptoms but not all diagnostic criteria for the delirium syndrome. The neurologically ill patient presents particular challenges. Assessing the need for analgesics may be limited by neurological disease that alters consciousness, the capacity for expression, or both. Standard assessment tools may not be equally applicable to Guillain-Barré and sub-arachnoid hemorrhage patients. Intracranial pressure (ICP) is a population-specific consideration; in some cases an ICP below 20mm Hg is targeted, and this therapeutic goal will take priority over sedation titration by other criteria. Delirium symptoms may be masked by the neurologic abnormalities responsible for the patient’s admission to the Neurologic Intensive Care Unit (NICU).

Whether data from medical and surgical ICUs can be extrapolated to NICU patients is unknown. We conducted a literature search that aimed to find all published studies on the use of assessment tools for sedation, analgesia and delirium, any interventional trials for these same entities, and any articles assessing outcome measures in the neurologically critically ill. We present the results of our literature search herein, along with a survey of what is presently being practiced in three large Canadian NICU’s, and conclude with some reflections on a practical approach to assess and treat this unique group of patients.

**METHODS**

We identified observational studies of sedation, analgesia and delirium practices in the neurologically critically ill that incorporated screening tools for pain, sedation level, anxiety and delirium already validated in the ICU population. We also identified prospective, randomized studies evaluating the use of analgesics, sedatives and antipsychotics for treatment or prevention in the critically ill where a percentage of the population had severe neurological disease. To this aim, we conducted a Medline search from 1960 to June 2010 using the following keywords: analgesia, analgesics, hypnotics, pain, prevention, prophylaxis, management, treatment, AND critical care, critical care illness, intensive care, intensive care units; as well as anxiety, sedation, sedatives, hypnotics and sedatives, protocols, management, treatment AND critical care, critical care illness, intensive care, intensive care units; aripiprazole, clozapine, haloperidol, olanzapine, quetiapine, risperidone, ziprasidone, antipsychotics AND (and OR) delirium, agitation, confusion, and delirium, agitation, confusion AND critical care, critical care illness, intensive care, intensive care units. We then added ‘AND nervous system disease, nervous system neoplasms, nervous system trauma, neurological, neurointensive care patients to the previously described searches. We reviewed only those studies that included neurologically ill patients managed in an ICU setting. When evaluating treatment strategies, we only considered prospective and randomized studies. We also manually searched the bibliographies of all articles in an effort to identify additional studies meeting these criteria. All adult and pediatric studies published in English and French were included. Data from each study was independently extracted and rated by two authors (YS & JT), experienced investigators in the fields of neurology and general critical care, and by a neurocritical care trainee (OA).

Fifty-one articles met our search criteria. Of these, 18 were excluded for the following reasons: written in German language (two), a lack of extractable data (three), editorials (two), or a focus that was completely different than that of our search such as propofol infusion syndrome, refractory status epilepticus and refractory ICP management (eleven). Further analysis was conducted on the remaining thirty-three articles; all review articles that did not contain original data were excluded. After adding seven papers from our manual bibliography search, sixteen articles were reviewed and analyzed. For all studies, the following data were extracted: study type (sedation, analgesia, or delirium), study design, study objective, patient population, number of patients, type of intervention (prevention, screening, risk factor assessment, or treatment evaluation), outcome, potential bias, and the major drawbacks or weaknesses of each study. These studies and extracted data are presented in Appendix I (Identification of study settings), II (Aims and outcomes of evaluated studies) and III (Validity and Drawbacks of reviewed studies).

Because we found very few publications describing assessment and intervention, we also surveyed three intensive care environments in which neuro-critical care patients are cared for in specifically attributed specialty beds in Montreal. These include the Montreal Neurologic Institute’s Neurological ICU, the neuro and neuro-trauma critical care unit at Sacré Coeur Hospital, a regional trauma center, and the neuro-trauma beds at the Montreal General hospital, also a regional trauma center; all sites are in Montreal, Quebec, Canada. Pharmacists assigned to work in the intensive care units were interviewed to identify practice patterns (use of opiates, co-analgesics, sedatives and anti-psychotics) and requested to provide anonymous computerized drug use data when possible. Physicians were interviewed as were nurses (head nurses, and a convenience sample of two nurses per site) with the same questions. We enquired as to the presence of protocols and their application. Recommendations as to management in textbooks and reviews are currently limited to the authors’ expert opinion, and were therefore not included in this review.

**RESULTS**

Results from the systematic literature review are presented below, followed by the results of our informal current practice review. The comparison between these data, and what is published in current critical care textbooks, follows in the discussion.

Results from the systematic literature review are divided into the following categories:

- **Tools used in the assessment of pain, sedation, and delirium**
- **Risk factors for delirium,**
- **Therapeutic interventions for pain, agitation or delirium**
- **Short and long term outcome assessment after analgesic, sedative, or delirium-focused interventions.**

Articles where these topics were not the primary objective of the study were still included if assessment, therapeutic approaches or outcomes had been described.
I. Assessment

A. Pain

Four (4) articles met our criteria for pain assessment in neurologically critically ill patients. In the paper by Schnakers et al., validity and inter-rater agreement testing of the Nociception Coma scale (NCS) in patients with severe head trauma identified this scale as sensitive and easily reproducible. Nociception Coma scale total scores differed as a function of diagnosis (i.e., Vegetative state vs. Minimally Conscious) and this correlated well with the differences in cerebral activity following pain seen with functional neuro-imaging in these two groups.

The Pain Intensity Scale compiles alterations in vital signs (blood pressure, heart rate, and respiratory frequency), facial expression (grimacing), and behavior (agitation). The effect of implementing this scale was assessed, looking at feasibility, efficacy, and patient outcome. With protocolized use of this scale, the use of sedatives decreased and the use of analgesics increased, as did the proportion of patients with no reported pain. Psychometric validation of this scale was not provided in the article or in the references. Previous papers have shown that alterations in vital signs correlate poorly with pain in non-neurologic adult ICU populations. The benefit shown here may be attributable to the behavioral features of the scale, the difference in patient population, or the combination of pain and sedation features.

Karabinis and colleagues devised a randomized, open-label, observational, multicenter, parallel group study to assess the safety and efficacy of analgesia-based sedation using remifentanil in the neuro-intensive care unit. They included 161 mechanically ventilated patients from the Neurologic ICU (NICU). Sedation was assessed using the Sedation Agitation Scale (SAS) (limited to points 1, 2 and 3). Pain was self-reported if possible and, if not, hemodynamic parameters (heart rate, blood pressure) were substituted. Sedation Agitation Scale and pain control measurements achieved targeted levels 95% of the time, which suggests they were measurable in this proportion of patients. Assessing pain and sedation in NICU patients thus appears feasible. Regrettably, the drugs were administered in an open label fashion, which limits assessment as to their effectiveness.

Topolovec-Vranic et al. assessed the implementation of the Nonverbal Pain Scale (NVPS) in a trauma/neurosurgical ICU. Patient and staff satisfaction were measured in the pre and post implementation periods. Most staff (78%) found the tool easy to use and felt more confident in assessing pain in nonverbal, sedated patients. Pain assessments were more frequent, patients reported decreased levels of pain retrospectively, and there was a trend toward a decrease in the time required to receive pain medication.

No other studies describe or psychometrically validate pain measurement in the neurological ICU population. Neurological patients were part of a larger cohort of ICU patients in whom pain, sedation and delirium were systematically assessed; however, the feasibility of pain evaluation in the neurologically ill sub-population was not described. The pain level tool in this combined cohort was a numeric rating scale when patients were able to self-report and the Behavioural Pain Scale when not; both these pain scales have been validated in non-neurologically ill ICU patients.

In summary, self-reporting pain assessments with visual analog scales appear feasible and the instrument of choice in patients able to self-report. In patients unable to communicate, studies with scales that incorporate behavioral features suggest that the Nociception Scale is reliable and valid, and that application of other scales such as the Non-Verbal Pain Scale and the Pain intensity scale has benefit for patients and is feasible for caregivers.

In the general ICU population, routine pain assessments in ICU patients are associated with improved clinical outcomes, such as better odds of weaning and shorter length of stay. The current neuro-critical care evidence suggests patients should get pain evaluations routinely, given the potential benefits and very unlikely harm associated with this practice.

B. Sedation

We identified two studies relevant to sedation assessment in the neurocritically ill. In the first, 30 brain injured ICU patients were evaluated with Bispectral Index (BIS) measurements in addition to three clinical assessment scales on an hourly basis for six hours: the Richmond Agitation-Sedation Scale (RASS), the Sedation-Agitation Scale (SAS) and the Glasgow Coma Scale (GCS). A Bispectral Index (BIS) original prototype and a newer BIS XP version were described in 15 patients each.

The BIS is a statistically derived variable of the electroencephalogram (EEG), with score ranges between 0 (isoelectric) and 100 (fully awake). It reliably measures sedation in normal subjects and in the operating room setting. The RASS is a 10-point scale that permits rapid assessment by completing three clearly defined steps looking at discrete criteria for levels of sedation and agitation; it is well validated in non-neurologically ill populations. The SAS scores the patient’s level of consciousness and agitation from a seven-item list describing patient behavior; it has also been broadly validated in non-neurologic populations. The GCS was originally designed and validated to predict outcome in trauma patients; its usefulness to evaluate and follow sedation is not known.

In the 15 patients monitored with the newer BIS XP version, there was a strong correlation of BIS score with the RASS score (R2 = .810; p < .0001), SAS score (R2 = .725; p < .0001), and moderate correlation with the GCS score (R2 = .655; p < .0001). This correlation was present regardless of sedative medications. No correlation was found with the older BIS monitoring system.

These results suggest it is feasible to systematically measure RASS, SAS and GCS scores in the NICU population. Each scale correlates well or moderately well with the more sophisticated version of the BIS. The RASS appears to have the best performance if one considers the BIS as a neutral physiologic measurement. By psychometric standards, both RASS and SAS scales are sound corollaries of sedation levels, whereas the GCS is not. This study was limited by its small number of patients and the wide range of neurological disorders.

A second study asked whether adding BIS measurements to a clinical assessment tool, the Ramsay scale, would alter the amount of propofol administered over a 12-hour period. Nurses assessed 35 patients with the Ramsay scale and 32 patients with both the Ramsay and a targeted BIS level. The BIS-titrated group received less drug by volume and infusion rate. However, the clinical scale comparator in this study, the Ramsay...
scale, has never been validated psychometrically in this population. Its shortcomings are described elsewhere\textsuperscript{23}. The initial scale was created by Dr. Michael Ramsay in 1974\textsuperscript{24} while comparing one sedative drug to another, and not rigorously tested otherwise despite its widespread use. These methodological differences might explain why this study did not show any benefit to adding a clinical scale when compared to the BIS alone, and why it contrasts to the one described above, where validated sedation scales were used as a comparator, but the amount of administered medication was not compared.

In the general ICU population, several assessment scales are considered psychometrically valid; the SAS and RASS scales are highly recommended. Routine sedation monitoring is recommended, as is routine medication titration to the lightest sedation level feasible within the clinical context. Whether routine sedation interruption is beneficial if sedation is titrated is unclear.

In summary, it seems to be both feasible and useful to use sedation scales in the NICU, with good correlation noted for the RASS and the SAS. Whether this will result in a direct effect on the amount of medication used and the length of stay remains to be seen and results will be confounded by the need to treat ICP with sedation in patients with intracranial hypertension. These scales will not, however, be as applicable to the severely paralyzed patient who can not communicate despite a normal level of consciousness (Guillain- Barre, locked-in syndrome).

C. Delirium

No studies were found specifically validating delirium assessments in the neurologically critically ill. Some delirium studies have included neurologic patients\textsuperscript{25,26}. However, none of these studies describe the feasibility or psychometrics of delirium measurements in the neurologically critically ill. The intensive care delirium screening checklist (ICDSC) was used in the studies retained for this review. One study described the frequency of ICDSC items in delirious and non-delirious patients and correlated these with prognosis. Neurologic patient symptom clusters were not specifically described.

II. Risk Factors and incidence of delirium

Risk factors for delirium in the neurologically critically ill are only available from a general ICU population\textsuperscript{27} where patients admitted with a neurologic diagnosis were described separately. In comparison to the general ICU population, the neurologically ill patients had a lower incidence of delirium\textsuperscript{28}. Assessment of the literature on general ICU delirium risk factors suggests that greater severity of illness, previous dementia, and hypertension are risk factors for developing delirium in the ICU. Excessive sedation also appears correlated with sub-syndromal\textsuperscript{29} or full blown delirium. Whether this association between delirium and heavy sedation is attributable to any specific drug or drug class is not known\textsuperscript{30}. In contrast to ward patients, other risk factors such as age, diagnosis and laboratory abnormalities do not appear to confer accrued risk in the general ICU patient population.

The exact incidence of delirium in Neurocritical Care patients has not been studied. In one ICU prospective study specifically addressing Guillain-Barré (GBS), 139 patients were compared to 55 patients without GBS\textsuperscript{31}. Thirty one percent (31\%) of the GBS patients had mental status changes in the form of vivid dreams, illusions, hallucinations, and delusions compared to 16\% in non GBS patients. These mental status changes occurred at a median of nine days after the onset of disease manifestation and had a median duration of eight days. All patients were interviewed and able to communicate, during the acute illness or after physical recovery.

Delirium incidence is also described in other neurological and neurosurgical diseases. Caiero et al assessed 68 consecutive patients with acute sub-arachnoid hemorrhage (SAH) before aneurysmal treatment and reported a delirium incidence of 16\%\textsuperscript{32}. Delirium can even be the presenting symptom in 1.4\% of patients with SAH\textsuperscript{33}. The incidence of delirium after ischemic or hemorrhagic stroke is reported as ranging between 13–48\%\textsuperscript{34–36}. In a cross sectional study, among 202 patients who presented with neurological illness to the emergency department, delirium occurred in 14.9\%, 22.7\% were in coma at time of presentation, and the rest had no arousal disturbances\textsuperscript{37}.

III. Therapy: pain, sedation and delirium

Therapeutic approaches can be divided into clinical effectiveness, physiological effects and other outcomes. There were no studies addressing the therapeutic effectiveness or outcomes with analgesics, sedatives, or anti-delirium medications in the neurologically critically ill.

Physiologic effects of the individual drugs are described below, in categories related to analgesia (opiates), sedation and delirium.

**Analgesia (opiates)**

**Remifentanil**

- Physiologic effects: 20 consecutive patients with traumatic brain injury (Glasgow Coma Scale <8) on ICU days 2 to 6 and with PaCO\textsubscript{2} levels maintained at 4.7—5.1 kPa were deeply sedated with a standard continuous infusion of propofol (3.1± 1.8 mg / kg / h\textsubscript{1}) and sufentanyl (1.1 ± 0.8 µg / kg / h). After at least 24 hours of hemodymanic and ICP stability, remifentanil was administered as a bolus followed by a continuous infusion\textsuperscript{38}. Neither the bolus nor the infusion had an impact on intracranial pressure, cerebral blood flow velocity or mean arterial pressure.

**Sufentanil**

- Physiologic effects: In a study of ten intubated head trauma patients, Albanese and colleagues evaluated the hemodynamic effects associated with the addition of sufentanil to an infusion of propofol. ICP increased by a max of 54\% at four minutes, and returned to baseline within 15 minutes; mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) decreased significantly in the same time frame, then began to increase but remained below baseline (23\% decrease) throughout the study period\textsuperscript{39}. Mean arterial pressure stayed above 45 mm Hg after the first five minutes, and attained such low levels in only four patients, for less than four minutes.

The effects of bolus injection and infusion of sufentanil, alfentanil, and fentanyl on cerebral hemodynamics and electroencephalogram activity in patients with increased intracranial pressure (ICP) after severe head trauma were tested in a randomized crossover study in six patients. Sufentanil, fentanyl, and alfentanil infusions were associated with a
Intravenous acetaminophen has just been approved by the Food and Drug Administration (FDA) in the United States but is not currently available in Canada. Opiate use in the general ICU population is recommended on an 'as needed' basis, and titrated in accordance with patient needs.

**Ketamine**

- Physiologic effects: In eight trauma patients, three doses of ketamine (1.5, 3, and 5 mg/kg) were tested for effect on ICP, perfusion pressure, jugular O₂ saturation, middle cerebral artery velocity, and electrographic activities of the brain. Intracranial pressure decreased without change in cerebral perfusion, middle cerebral artery (MCA) velocity, or jugular O₂ saturation. Ketamine induced low-amplitude fast activity.

Thirty five (35) patients suffering from moderate to severe head injury were allocated to receive either ketamine or fentanyl as a supplement to their baseline perfusion of midazolam. Doses of all medications were titrated to achieve successful algesedation (a term considered equivalent to analges-sedation, and originally coined in the German anesthesiology literature to describe drugs with both analgesic and sedating effects). The ICP in the Ketamine group (median of all values 14.6 mm Hg) was slightly higher than that of the control group by approximately 2 mm Hg. This difference was significant on Days 8 and 10 only (p<0.05) and did not affect CPP. Indeed, the very significant rise in MAP resulted in an 8 mm rise of CPP despite the small increase in ICP. In the fentanyl group, ICP was stable, but MAP and CPP required more dopamine than the ketamine group to insure a CPP above or equal to 75 mm Hg.

In another similar study, the continuous infusion of ketamine-midazolam was compared to sufentanil-midazolam infusion in 25 head injury patients. Intracranial pressure and cerebral perfusion pressure were similar in both groups, as were neuromuscular blocking agents, propofol, and thiopental requirements. Heart rate values were significantly higher in the ketamine group. More fluids were required and there was a trend toward greater use of vasopressors in the sufentanil group. In a later study by the same authors, doubling the doses of either ketamine or sufentanil was tested for 15 minute periods. Intracranial pressure, cerebral perfusion pressure, and mean velocity of middle cerebral artery in both the ketamine and the sufentanil groups were similar.

In the general ICU population, opiates are the most commonly used analgesic. When opiates are compared to anti-inflamatory agents, the evidence favors better pain control when an anti-inflammatory is administered; however, there are only two studies and they include small numbers of patients. Cocaine, with acetaminophen or anti-inflammatory agents, appears to reduce opiate requirements in the ICU; however, acetaminophen has not been prospectively evaluated. Intravenous acetaminophen has just been approved by the Food and Drug Administration (FDA) in the United States but is not currently available in Canada. Opiate use in the general ICU population is recommended on an ‘as needed’ basis, and titrated in accordance with patient needs; however up to 45% of patients never require them for analgesia.

**Sedation**

No data were available for the use of benzodiazepines for sedation in the neurologically critically ill.

- Propofol: Propofol has also been utilized for sedation, electroconvulsive therapy, cardioversion, tracheal intubation, mechanical ventilation, status epilepticus, tetanus, and as an antiemetic and antipruritic. Its effectiveness as a sedative is well established in current practice in the ICU and Neuro-ICU population.

**Physiologic studies**

Propofol reduces ICP without deleterious effect on early heart rate or mean arterial pressure measurements in head injury patients. Step increases in propofol doses lead to a large increase in EEG burst-suppression ratio in patients with moderate to severe head injury; tissue gas levels, tissue chemistry, and AVDO₂ remain unchanged.

**Dexmedetomidine**

Dexmedetomidine use in the neurologically critically ill is described, but the quality of the studies does not allow any conclusions to be drawn from their observations. One small study addressing cognitive function in awake, brain injured patients receiving sedatives suggest that cognition may be better preserved with dexmedetomidine than with propofol.

**Current Practice in North-American NICUs and in the Neurological population of general ICUs**

Critical care caregiver surveys have indirectly evaluated the current perceptions, practices, and caregiver behaviors with regard to the use of analgesics and sedatives. Published surveys only address the general ICU population. The purpose of this review was to describe published data. Given its absence, we surveyed three Neurocritical care units in Montreal, as described in the methods section.

The Pharmacy data bases only allowed us to document which analgesic and sedative drugs were prescribed the most. No database contained individual patient information. Assessment scale use in these neurologic ICUs (if any) was assessed by caregiver interviews. Traumatic brain injury patients were medicated differently than patients with other acute severe neurological illness; they are thus described separately. Each unit is presented separately.

Hospital #1, trauma unit: the Ramsay sedation scale is routinely performed by the bedside nurse in all patients. Pain and delirium are not evaluated systematically with a scale. Analgesia and sedation are combined in the majority of patients using a combination of midazolam and fentanyl (70%). These two drugs are administered in continuous infusion, with additional boluses as needed, and the administration is titrated to the Ramsay scale. Lorazepam is also administered for sedation in intermittent doses as needed, again titrated to the Ramsay scale. Other choices for analgesia include remifentanil, as an adjunct to the basic perfusion, and anti-inflammatory agents either alone or as adjunctive therapy. Ketamine is very rarely used. Dexmedetomidine use was stopped because clinicians were not satisfied that it achieved desired sedation or analgesia goals. The doses required were large (up to 2.4 +/- 0.5 mcg/kg/h), and often remained insufficient to achieve the therapeutic goal (RASS).
and because of side-effects (hypotension and bradycardia). Delirium is treated with intravenous (IV) haloperidol. Delirium is reported as rare in the intubated and severely brain injured patient; however, the incidence of delirium in this traumatically brain injured population is estimated as 40–50% of patients upon discharge from ICU. Looking at the pharmacy records, delirium in the head trauma patient discharged to the ward was treated mainly with risperidone and quetiapine.

Hospital #1 Non-trauma NICU unit: Over 90% of patients are sedated with propofol. The analgo-sedation regimen consists of propofol and fentanyl. The RAMSAY Sedation Scale is the only scale used. Neuropathic pain is treated with NSAIDS, Cesamet (Nabilestone) and Lyrica (Pregabalin). Delirium is treated with Haloperidol. Daily interruption of continuous infusions of sedatives or analgesics is routinely performed for all patients unless intracranial hypertension precludes it.

Hospital #2, trauma unit: traumatic brain injury patients are all prescribed a sedation protocol. All patients requiring sedation first receive fentanyl IV by bolus followed by continuous infusion. If agitation persists, patients are sedated with propofol. The RAMSAY is the only scale in use.

Hospital #3, Non-trauma NICU: Over 90% of patients are sedated with propofol. Analgo-sedation consists of propofol and fentanyl (50%) or morphine (50%). In patients who do not require sedation, pain is treated with morphine IV much more often than fentanyl. Dilaudid and anti-inflammatory agents are used in post-operative patients. Pain with agitation in the conscious patient is treated with the addition of cesamet (nabilestone) and noziban (methotrimepazine). Alcohol withdrawal is treated with ethanol perfusion. There are no sedation or algesis protocols in place and sedation, pain and delirium scales are not used.}

**DISCUSSION**

Intensive care unit survivors describe traumatic memories of insufficient analgesia from their critical care stay. Routine pain assessments in ICU patients are associated with improved clinical outcomes, better odds of weaning and lower length of stay.

Pain should be addressed with validated tools, and managed with appropriately selected drugs. Self-reporting of pain, by writing, speaking or by the use of an enlarged numeric scale is the gold standard in general ICU populations. In patients who are more heavily sedated or otherwise unable to express pain, careful observation of behavioral changes such as facial expression, posturing, and respiratory synchrony has been validated. The BPS (behavioural pain scale) and the CCPOT (clinical critical pain observation tool) are useful in the general ICU population. These scales have been validated in both English and French. Neuromuscular blocking agents preclude pain assessment, and hemodynamic variables are not reliable to assess pain in the general critical care setting.

The feasibility of self-reporting of pain has been assessed in only one study in the neurologically critically ill. Two studies using scales that consist of, or include, behavioural items describe improved outcomes with their use. These limited data suggest that pain assessments are feasible and should probably be routinely performed in all Neurologic ICU patients, despite the need for more data on psychometric validation of specific tools.

Sedation assessments help objectively quantify agitation and anxiety, but should be preceded by pain assessments in order to avoid sedating without analgesia. In general ICU patients, maintaining lighter levels of sedation is associated with a shorter duration of mechanical ventilation and shorter length of stay (LOS). Maintaining lighter levels of sedation in ICU patients is also associated with a higher physiologic stress response, but is not associated with a higher incidence of myocardial ischemia. The relationship between depth of sedation and psychological stress in patients is unclear, as both insufficient and deep sedation appear to have negative consequences. How and whether these findings apply to the neurologically critically ill with and without intracranial hypertension or seizures is unclear. Many sedative scales have been validated in the ICU setting (RASS, MASS, SAS, and others). Based on the limited data from our current review, it would appear that sedation assessment is feasible in the NICU, and that RASS and SAS assessments are helpful in assessing sedation level. Whether the psychometric values of these scales can be upheld in the context of neurologically ill patients with important potential confounders remains to be addressed. The psychometrics of such scales would probably also differ for traumatic brain injury patients, sub-arachnoid hemorrhage patients, neurosurgical patients, and patients whose primary reason for admission to the NICU is a neuro-muscular disease.

Two delirium scales are well validated (ICDSC, CAM-ICU) and attain excellent psychometric standards in non-neurological mechanically ventilated ICU patients. Whether delirium can be diagnosed and differentiated from confounders in this very special population with a scale or with a clinical assessment in the NICU is not clear. Since the ICDSC contains explicit individual clinical features which are associated with outcome in general ICU patient populations correlating specific symptoms to outcome rather than trying to make a delirium diagnosis in all NICU patients may be more feasible. The absence of studies specifically addressing diagnostic criteria, risk factors or assessment scales for delirium in the neurocritical care population is unsurprising. The traditional diagnostic criteria in this population, and clinical scales would have to be altered to take into account the symptomatology of the critically ill neurological patient, including alterations in level of consciousness attributable to other causes than delirium, aphasia, seizures and temporal lobe dysfunction among others.

No delirium treatment approach has been shown to reduce the severity or the duration of delirium symptoms in the general ICU, with the exception of incremental quetiapine doses in one pilot study. There is no benefit to prophylactic or pre-emptive treatment.

Few studies address the effectiveness of pharmacologic interventions for treating pain, sedating patients or addressing delirium. What appears clear in the general ICU population is that a multidisciplinary approach paired with routine pain, sedation and delirium assessments and drug administration driven by patient symptoms improves outcome. Many of the studies we reviewed considered NICU-specific variables such as ICP or CPP but did not address pain, sedation or delirium management effectiveness. We were unable to find descriptors of
drug use on a large scale. From our simple and single city survey it appears clear that there is variability in practice, and that some drugs are used more frequently in the neurological ICU than in general ICUs, such as Ketamine and Cesamet (nabilone).

Indications and goals for the provision of sedation in the neurologic ICU often differ from those in the general ICU. Depending on clinical circumstances, the indications for sedation differ between the neurologically critically ill and their general ICU counterparts.

Despite all these caveats, a few recommendations can cautiously be made:

• Pain and sedation should be routinely gauged with validated scales in neuro-ICU patients. The Nociception Coma scale (NCS) appears useful and feasible in patients with severe head trauma. Use of the Pain Intensity Scale in neurologically critically ill patients is feasible and associated with improved outcomes. Pain scales with better psychometric validation such as the BPS or the CCPOT for patients unable to communicate, and a self-report numeric scale if contact is possible, remain to be validated in this population.

• Sedation should be assessed with scales such as the SAS or RASS, but not with the Ramsay or the Glasgow coma scales. Recommendations as to choice of sedatives cannot be made for lack of comparative studies.

• Analgesia and sedation should be distinguished, and ‘analgo-sedation’ regimens re-assessed to better target specific patient symptoms.

• Delirium symptom screening remains to be validated in this population

• Titrating analgesia and sedation to patient-specific goals is desirable. These goals can be adapted as needed to a clinical scale or to ICP values.

• Anti-inflammatories and Tylenol are associated with an opiate sparing effect and sometimes better analgesia in general ICU patients. It is reasonable to believe the effect would be no different in the neuro-ICU population. Side effects such as gastric irritation and worsening of renal dysfunction must, however, be weighed against clinical benefit. Ketamine is associated with greater hemodynamic stability than opiates but the side effects of the drug and its effectiveness have not been sufficiently assessed.

• Short-acting opiate analgesics such as remifentanil appear to have less hemodynamic effect than longer acting opiates in the NICU. There is conflicting data as to possible benefits of remifentanil over sufentanyl or alfentanil. Whether short acting drugs (such as remifentanil, sufentanyl or alfentanil), in comparison to fentanyl or morphine, would confer any benefit if all opiates where titrated to symptoms is not clear.

• Propofol is safe and reduces ICP. Benzodiazepine use has not been prospectively assessed in the NICU population or compared to other sedatives such as propofol or dexmedetomidine.

• There is no evidence for the use of haloperidol or nozam despite their widespread use in agitation. The only anti-psychotic that has any potential benefit at the time of this writing is Quetiapine.

• For the paralyzed patient unable to communicate and often with autonomic abnormalities, none of the scales will apply. Continuous EEG and or newer versions of the BIS may allow lower and more targeted sedative administration.

**Conclusion**

Much work remains to be done in the neuro ICU population. Validated scales and close observation of patient response should be encouraged, and further studies to better validate therapeutic approaches for efficacy and outcomes are urgently needed.

**References**


**Patient population**

- ICU patients (presumably)
- Patients with minimally conscious state
- Patients with persistent vegetative state
- 15 patients with a complex spinal stabilization
- 40 patients
- Patients with minimally conscious state
- Patients with persistent vegetative state
- 15 patients with a complex spinal stabilization
- 40 patients

**Sedation**

- Propofol + Midazolam during the investigational period
- Continuous infusion of Fentanyl + Midazolam during the investigational period
- Remifentanil + Midazolam during the investigational period

**Analgesia**

- Remifentanil infusion of 0.75 mg/kg/hr for use <12 days
- Fentanyl +0.2 mg/kg/hr for use >2 days during the investigational period
- Pain assessed by P1 scale to a target of 1-2

**Delirium**

- No
- No
- No

**Interventions & Outcomes**

- K Engelhard et al (ref.43)
  - Prospective
  - Patients with TBI and GCS <8
  - Examined before day 2-6 after admission
  - Propofol and Remifentanil were used 24 hours before investigation, then after taking baseline parameters. Remifentanil 0.5 mg/kg/hr was administered followed by a continuous infusion of Remifentanil 0.25 mg/kg/hr, IV for 20 min
  - Propofol + Remifentanil
  - No

- Jacques Allain et al (ref.49)
  - Prospective
  - ICU patients
  - Severe head injury/trauma
  - Ketamine and Midazolam were used 24 hours before investigation, then after taking baseline parameters. Ketamine 0.5 mg/kg/hr was administered followed by a continuous infusion of Ketamine 0.25 mg/kg/hr, IV for 20 min
  - Ketamine + Midazolam
  - No

- Jacques Allain et al (ref.40)
  - Randomized
  - ICU patients
  - Severe head injury/trauma
  - Ketamine and Midazolam were used 24 hours before investigation, then after taking baseline parameters. Ketamine 0.5 mg/kg/hr was administered followed by a continuous infusion of Ketamine 0.25 mg/kg/hr, IV for 20 min
  - Ketamine + Midazolam
  - No

- Jacques Allain et al (ref.41)
  - Prospective
  - Severe head injury with GCS of 8 or less
  - Ketamine and Midazolam were used 24 hours before investigation, then after taking baseline parameters. Ketamine 0.5 mg/kg/hr was administered followed by a continuous infusion of Ketamine 0.25 mg/kg/hr, IV for 20 min
  - Ketamine + Midazolam
  - No
### ANMELIA BOLLY ET AL (9)

**Aims**

To prove that patients minimally conscious do perceive pain at a central level, despite lack of response externally.

**Medication/Intervention**

Bilateral electric stimulation of the median nerve increased until all components of the somatosensory evoked potentials showed maximum amplitude. The stimulation intensity was kept constant throughout the experiment. Changes in regional cerebral blood flow were measured with 15O-labeled bolus PET.

**Outcome/Value Conference Interval**

No area was less activated in the patients in MCS than in the controls. All areas of the cortical pain matrix showed greater activation in a patient in MCS than in those in PVS.

**Why the Study is Important**

Patients with these conditions have pain perception. Authors advocate for use of analgesics particularly in MCS patients.

### INGRID EGER et al (10)

**Feasibility of shift from sedation-based to analgesia-based sedation**

Group 1: Remifentanil (initial dose of 9 mg/kg/hr) was titrated before the addition of propofol (0.5 mg/kg/hr) in the first 1-3 days then shifted to Midazolam (0.05 mg/kg/hr) in day 4-5. Group 2: Hypnotics first then either Fentanyl or morphine.

**Use of sedatives dropped and analgesics increased.**

**Increased number of pain free patients, and patients with sedation interruption woke up faster.**

### ANDRE-CHARLES KARABIMBI et al (11)

**Safety and efficacy of analgesia-based sedation with Remifentanil**

Group 1: Remifentanil (dose of 0.5 mg/kg/hr) was titrated before the addition of propofol (0.5 mg/kg/hr) in the first 1-3 days then shifted to Midazolam (0.05 mg/kg/hr) in day 4-5. Group 2: Hypnotics first then either Fentanyl or morphine.

**Between-patient variability in neurologic assessment smaller when using Remifentanil.**

**Mean neurological assessment times shorter with Remifentanil.**

**Remifentanil 0.41 hour vs. Fentanyl 0.71 hour (P < 0.001) vs. morphine 0.82 hour (P < 0.001).**

**Remifentanil-based were evaluated faster than morphine but no difference between Remifentanil and Fentanyl.**

### AMANDEEP DINGAMKAR et al (18)

**Correlation between Bispectral Index and the clinical sedation scales (RASS, SAS, GCS).**

**Note:** specifically for the study.

**Positive correlation:** BIS vs. propofol, RASS vs. propofol, SAS vs. propofol, GCS vs. propofol, REMF vs. propofol, SAS vs. GCS (R2 = 0.67, P < 0.001).

**RASS, SAS and GCS all feasible to measure in the neurological ICU population.**

### OLSEN et al (22)

**Use of BIS in addition to clinical evaluation decrease the total amount of sedation in a 12 hour period.**

**Propofol infusion.**

**BIS group less Propofol by volume and had lower infusion rates.**

**The BIS-BSA group was awake more quickly than those in the Ramsay scale group.**

**12 vs. 7.5 min; (P < 0.001).**

### K, ENGELHARD at al (38)

**Effect of epidural (Remifentanil) on systemic and cerebral hemodynamic effects of sedation.**

**Remifentanil and Sufentanil were used 24 hours before and after administration.**

**RASS, SAS, GCS were all feasible to measure.**

### JACQUES ALBANÈSE et al (39)

**Effect of ICP on hemodynamic and EEG activity.**

**6 mm addition of Subarachnoid (1 mg/kg loading then 0.05 mg/kg/min) measurements of ICP, CPP, HR, MAP, SPO2, EEG.**

**Tetrapar A, B, C, D epilepsy, increased blood samples were obtained at baseline and 10, 30, and 60 minutes after administration.**

**EEG was continuously monitored as well.**

### JACQUES ALBANÈSE et al (40)

**Effect of Ketamine on cerebral hemodynamic and EEG activity.**

**3 doses of Ketamine (1.5, 3/5mg/kg) were given at 6 hour intervals to a total of 6 patients.**

**Ketamine (1.5, 3/5mg/kg) associated with decrease in ICP among study patients regardless of the dose.**

**No difference in CPP, the mean arterial pressure was on average 8 mm Hg higher cerebral perfusion pressure and a 2 mm Hg higher intracranial pressure in the Ketamine group.**

### H KOLENDA et al (42)

**Effect of hemodynamic and ICP, CPP.**

**A total of 20 patients aged 6.5 mg/kg/day midazolam, 0.5 mg/kg/day ketamine or 65 mg/kg/day sufentanil.**

**Fentanyl was later adjusted according to clinical requirements.**

**Positive changes in ICP, CPP, or mean velocity of MCA.**

**BPS (pain scale validated in other populations) was recorded in the study but not reported in the results.**

**Safety of Sufentanil use and lack of hemodynamic side effects.**

### AURÈLE BOUGRAIN et al (43)

**Effect of the target controlled infusion on cerebral hemodynamic responses.**

**Propofol infusion.**

**No change in BP, HR, ICP, CPP, quality of sedation was recorded as good in 90%.**

### P, FARLING et al (44)

**Hemodynamic effects of propofol infusion.**

**Propofol infusion.**

**No change in BP, HR, ICP, CPP, quality of sedation was recorded as good in 90%.**

### A) JOHNSTON et al (49)

**Is the step increase in Propofol dose impair flow-metabolism coupling?**

**Propofol was kept at 2 mg/kg/min in the dose of 3 mg/kg/hr for 4 hours by day study. Then the dose was doubled for parameters to be taken.**

**The step increase in propofol led to a large increase in EEG burst-suppression ratio (0% range 0.0-1.1 to 46% range 0.6-17, P < 0.05); no change in tissue gas levels, tissue chemistry, or AVDO2.**

**No significant change in cerebral physiology with increased metabolic suppression and indicate that low-metabolism coupling is intact.**

### HENRY F. ALY et al (50)

**To gather information on the dosages, sedative effects and adverse effects of DEX, PBO metabolism in neurosurgical patients.**

**DEX infusion as per protocol to check for MAP, SBP, DBP, HR, ICP, CPP 24 hour prior to DEX initiation.**

**Mean CPP increased and ICP decreased.**

**Safety of DEX use in neurological patients with variant diagnoses.**

### TINA GROF et al (51)

**DEX dose, application in NICU and effect on hemodynamic.**

**DEX infusion for >6 hours.**

**DEX in NICU may require higher doses than other ICU settings.**

**May affect hemodynamic that is irrelevant clinically.**

**Potential hemodynamic effects of DEX and the prolonged time interval to achieve proper sedation.**

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**Aims and outcomes of neurologic sciences**

**Interventions & Outcomes**

**Administration and withdrawal of Propofol was fast and intravenous.**

**Safety of Sedation use and lack of hemodynamic side effects.**

**Potential side effects of Sufentanil.**

**To gather information on the dosages, sedative effects and adverse effects of DEX, PBO metabolism in neurosurgical patients.**

**MAP, CPP, MAP, HR, SPO2, EEG, PET.**

**Use of Ketamine up to 14 days does not affect hemodynamic significantly.**

**One of the early studies to prove efficacy of propofol.**

**No significant change in cerebral physiology with increased metabolic suppression and indicate that low-metabolism coupling is intact.**

**Safety of DEX use in neurological patients with variant diagnoses.**
<table>
<thead>
<tr>
<th>Author</th>
<th>Content Validity</th>
<th>Face Validity</th>
<th>Potential Bias or Conflict of Interest</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mélanie Boly et al</td>
<td>Objective use of PET to evaluate response to pain</td>
<td>Patients were assessed four times by trained and experienced assessors: 1 week and 1 day before, the day of the scan, and 1 week after the scan. An anesthetist or an ICU physician monitored the patient during the procedure.</td>
<td>The number of patients is not satisfied across groups. Variability of pain perception is different among people</td>
<td>No MRI correlates in the PVS Only MRI in the MCS</td>
</tr>
<tr>
<td>Ingrid Egerod et al</td>
<td>Ramsay Sedation Scale Pain Intensity</td>
<td>Nurses performed one assessment of pain and sedation per shift (morning, afternoon, and evening)</td>
<td>Daily awakening was late to the discretion of the physician</td>
<td>Single centered Non randomized Small sample of patients</td>
</tr>
<tr>
<td>Andreas Karabulut et al</td>
<td>SAS PI</td>
<td>SAS and PI were assessed by the study nurse or investigator</td>
<td>1. Downregulation or discontinuation of drugs for neurological assessment was left to the discretion of the investigator. 2. Open label</td>
<td>Poorly designed study: no validated scale, no feasibility data (how often could each of these assessments be made?). Reduction in sedation or awakening was left up to the physician. More adverse events in the nonremifentanil group 2.5% vs. 8% and 10% in other groups</td>
</tr>
<tr>
<td>Anupa Desmukh et al</td>
<td>Richmond Agitation Sedation Scale (RASS) Sedation Agitation Scale (SAS) Glasgow Coma Scale (GCS)</td>
<td>RASS, SAS, and GCS are assessed hourly by the nurses, BIS is recorded for 6 hours only, 3 min before and 3 min after the nurse assessment, the BIS score is collected and averaged as single reading</td>
<td>The authors did not declare a conflict of interest but it is not clear how the study was funded (potential COI)</td>
<td>Small sample of patients. Glasgow scale originally intended to predict trauma. The RASS and SAS never validated in NICU patients Number of sedated patients unknown. Only correlation between BIS and scales. Medical was unknown. No TBI</td>
</tr>
<tr>
<td>M. Olson et al</td>
<td>Ramsay Sedation Scale</td>
<td>Assessment conducted by the nurse for both Ramsay scores and BIS reading. The wakefulness was assessed by an independent nurse, not involved with the study</td>
<td>Under sedation was defined only as either removal of medical support systems as IV lines or ET, or ventilator asynchrony. Assessment time and frequency was not specified and not sedation algorithm was followed</td>
<td>Hawthorne effect Variability among nurse assessments No data on concurrent medications used The use of Ramsay tool which is not validated in NICU</td>
</tr>
<tr>
<td>K. Engelhard et al</td>
<td>TCD was used for CBFV (velocity)</td>
<td>No sedation protocol was used. No mention of who did the assessment. MAP, ICP, CPP and CBFV were monitored at baseline (T1), 1 min (T2), 3 min (T2), and 20 min (T4) after drug administration and 20 min after cessation of Remifentanil (T5)</td>
<td>No mention of parameters used to low or ICP. No surgical interventions were conducted</td>
<td>Remifentanil is used on the background of adequate sedation with propofol and Srikantil. The use of vasopressors may also confound the results</td>
</tr>
<tr>
<td>Jacques Albanié et al</td>
<td>None</td>
<td>Short duration of Sedation Administration</td>
<td>Small sample of patients. No control group. Other injuries on top of head trauma that may affect parameters. How clinically important are these changes?</td>
<td></td>
</tr>
<tr>
<td>Jacques Albanié et al</td>
<td>None for sedation E/EG was used to</td>
<td>Investigators</td>
<td>EEG interpretation is not well characterized</td>
<td>Small sample of patients. No control group. No outcome data</td>
</tr>
<tr>
<td>Jacques Albanié et al</td>
<td>None</td>
<td>Investigators collected data</td>
<td>Small sample of patients. No control group Not clear which patient received which dose and if there was incremental doses of Ketamine given in a single patient</td>
<td></td>
</tr>
<tr>
<td>H. Ebelinga et al</td>
<td>Motor response of the GCS during the anesthetic</td>
<td>Physicians independent from the investigators</td>
<td>We do not know how much, how often and what type of Prn modification was given</td>
<td>Small sample of patients. Limited population. High number of withdrawals</td>
</tr>
<tr>
<td>Aurélie Bourgoi et al</td>
<td>Effective Sedation</td>
<td>Investigators</td>
<td>Behavioral pain scale used instead of a sedation scale, and labeled as a sedation scale Did not provide p values or CI for the change in MAP, ICP, or CPP Applicability to less severe TBI patients or other?</td>
<td></td>
</tr>
<tr>
<td>PA Farling et al</td>
<td>None</td>
<td>Investigators</td>
<td>Small sample of patients. No control group Patients usually paralyzed Sedation titrated to ICP only Non randomized</td>
<td></td>
</tr>
<tr>
<td>A. Johnston et al</td>
<td>ICP monitored by intracranial catheters</td>
<td>Investigators</td>
<td>The duration of propofol infusion is not enough to show changes in metabolism (4 hours to attain sedation and then metabolites were taken 30 min after a step increase)</td>
<td>Small sample of patients. No control group No sedation protocol</td>
</tr>
<tr>
<td>Henry E. Aryan et al</td>
<td>UCSD Agitation scale</td>
<td>Not specified</td>
<td>Other sedatives not specified. The exact protocol of DEX use was not mentioned</td>
<td>Small sample of patients. Retrospective. Statistical analysis not known. Confounding factors. Only 10 patients had hypotension, but vasopressors. Unknown if other measures were used for ICP</td>
</tr>
<tr>
<td>Tina M. Grad et al</td>
<td>RASS</td>
<td>Not specified</td>
<td>Variability of the adjunctive sedatives/analgoses 2 population or disease process are not defined</td>
<td>Small sample of patients. No control group. Feasibility and reliability of RASS not well described. Unknown diagnosis of patients</td>
</tr>
</tbody>
</table>