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.

RÉSUMÉ: Une évaluation critique de la sédation, de l'analgésie et du délire chez les patients hospitalisés à l'unité de soins intensifs neurologiques. L'administration d'analgésiques, de sédatifs et d'antipsychotiques à l'unité de soins intensifs neurologiques (USIN) demeure problématique. Nous avons révisé la littérature sur ce sujet ainsi que nos pratiques actuelles afin de mieux informer les médecins qui pratiquent à l'USIN et d'identifier les aspects qui méritent des études plus poussées. Nous avons effectué une recherche électronique des études observationnelles, d'intervention et de résultats portant sur la sédation, l'analgésie et le délire à l'USIN ainsi que de la bibliographie de ces articles. Nous avons évalué les modes de pratique dans trois USIN qui se spécialisent en soins neurologiques à Montréal. Les outils d'évaluation de la douleur au chevet du patient ont fait l'objet d'une validation psychométrique chez des patients en phase critique neurologique. Cependant les outils concernant la sédation et le délire n'ont pas été validés. L'évaluation rigoureuse de la douleur et de la sédation nous semble réalisable. Le dépistage du délire n'a pas été vérifié. Les publications portant sur les résultats et les réponses au traitement pharmacologique manquent de cohérence, de rigueur ou les deux. En pratique courante, le traitement pharmacologique varie beaucoup. Il existe peu d'information sur l'analgésie, la sédation et le délire à l'USIN. Une évaluation systématique de la douleur améliore le résultat thérapeutique. Aucune recommandation thérapeutique fondée sur des preuves ne peut être élaborée.

Pain, agitation and delirium are common in critically ill patients, and sedatives and analgesics are commonly used. The assessment and management of these three problems have been addressed in the general intensive care unit (ICU) population. We sought data to guide the Neurocritical care caregiver.

Pain is commonly reported by ICU survivors, and inadequate analgesia contributes to patient suffering[1]. Agitation contributes to adverse outcome[2] and may result in ventilator dys-synchrony, increased oxygen consumption, and accidental removal of devices such as endotracheal tubes. Because agitation and anxiety can both be due to pain, assessment and treatment of pain should be instituted prior to initiating sedation[3,4] "Self-reporting" is the most reliable and valid indicator for the presence and degree of pain. However, self reporting can be difficult in patients who are intubated, sedated or otherwise unable to communicate. Behavioural indicators can be substituted in those circumstances.

Once analgesics are administered and analgesia is provided, and if agitation and anxiety still persist, sedative administration may be indicated. Several sedation scales have now been well-validated in the general critical care literature; when these are used to guide therapy general ICU patients have better outcomes.[5]

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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 %[6]. Some authors have identified an entity called 'sub-syndromal delirium' for patients with some symptoms but not all diagnostic criteria for the delirium syndrome[7].

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[8], 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[9].

The Pain Intensity Scale compiles alterations in vital signs (blood pressure, heart rate, and respiratory frequency), facial expression (grimacing), and behaviour (agitation). The effect of implementing this scale was assessed, looking at feasibility, efficacy and patient outcome[10]. 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[11,12]. The benefit shown here may be attributable to the behavioural 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, multicentre, 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)[1]. Sedation was assessed using the Sedation Agitation Scale (SAS)[13] (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[14] 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[15]; 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[16] and the Behavioural Pain Scale[17] 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 behavioural 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[18], 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[19]. 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[20] 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[21]; 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[22]. 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[23]. The initial scale was created by Dr. Michael Ramsay in 1974[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[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[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[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[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[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 Neurocritcal 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[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. Caeiro et al assessed 68 consecutive patients with acute sub-arachnoid hemorrhage (SAH) before aneurysmal treatment and reported a delirium incidence of 16%[32]. Delirium can even be the presenting symptom in 1.4% of patients with SAH[33]. The incidence of delirium after ischemic or hemorrhagic stroke is reported as ranging between 13-48%[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[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 $PaCO_2$ 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_1) and sufentanil (1.1 ± 0.8 μg_/ kg / h). After at least 24 hours of hemodynamic and ICP stability, remifentanil was administered as a bolus followed by a continuous infusion[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[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

significant but transient increase in ICP with a return to baseline values after 15 minutes. The MAP decreased and remained significantly decreased throughout the study period in much the same fashion as described previously. Electroencephalogram tracings changed from fast to decreased activity, together with an improvement in the background activity[40].

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 O_2 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 O_2 saturation. Ketamine induced low-amplitude fast activity[41].

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 algosedation (a term considered equivalent to analog-sedation, and originally coined in the German anesthesia 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 2mm 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 8mm 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.[42]

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[43].

In the general ICU population, opiates are the most commonly used analgesic[44] When opiates are compared to anti-inflammatory agents[45,46] 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. Co-analgesia, 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[5]; 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[47]. 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[48]. 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 $AVDO_2$ remain unchanged[49].

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[50,51]. 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[52].

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 remifentanyl, 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 (Nabilone) 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 (nabilone) and nozinan (methotrimeprazine). Alcohol withdrawal is treated with ethanol perfusion. There are no sedation or algosedation 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[53], 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 greater 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[15] 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[54]. 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[15]. 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 alfentanyl. Whether short acting drugs (such as remifentanil, sufentanyl or alfentanyl), 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 nozinan 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[55] 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.

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APPENDIX I

Identification of study settings

Author	Study Setting	Patient Population	Number of Patients	Sedation	Analgesia	Delirium
Assessment						
Mélanie Boly et al (ref.9)	-Prospective -Control Group	-ICU patients (presumably) -Variable etiologies -Minimally conscious or vegetative state, state with	40 patients: -5 patients with minimally conscious state -15 patients persistent vegetative state -15 control patients	No	Yes	No
Ingrid Egerod et al (ref.10)	-Prospective -Single centered -Control Group, comparing before and after implementation of the protocol	-NICU patients -Intubated for 48 hours -Continuous sedation, analgesia or both	-106 patients observational period -109 patients investigational period	Propofol and Midazolam during the observational period, with add on Fentanyl or Remifentanil to Ramsay Sedation Scale of 2-3 (5-6 in high ICP patients)	Remifentanyl infusion of <6 mic/kg/hr for use <1-2 days, Fentanyl <0.2 mic/hr for use >2 days during the investigation. Propofol/Midazolam if needed. Pain assessed by PI scale to a target of 1-2	No
Andreas Karabinis et al (ref.1)	-Randomized -Prospective -Multi centered -Blinded Open label -Control group: Analgesia based Rx + Hypnotic; and the other reversed	-NICU patients -24 hours prior to enrollment -Mechanical ventilation for 1-5 days -Daily downward titration of sedation	161 patients: -84 patients in the analgesia based -37 patients in the Fentanyl group -40 patients in morphine	Sedation	Pain Intensity score of 1-2	No
Anupa Deogaonkar et al (ref.18)	-Prospective -Single centered -Single blinded (Nurses were blinded to the BIS monitor) -Observational	-NICU patients with 4 measures assessment (RASS, SAS, GCS, BIS) -Any brain injured -Either sedated or not, who has RASS <= 0 and SAS <= 4	30 patients: -15 patients had older BIS version monitoring -15 patients had the newer version BIS XP	Sedation monitoring	No	No
Olson et al (ref.22)	-Randomized -Prospective -Single centered -Control group: Ramsay only; and Ramsay + BIS	-Adult patients -Mechanically-ventilated, continuous sedation with IV Propofol	67 patients: -35 patients in the Ramsay group -32 patients in the BIS9	Target Ramsay of 4 in the clinical group BIS 60-70 and Ramsay of 4 in the BIS group	No	No
Interventions & Outcomes						
K Engelhard et al (ref.38)	Prospective	-Patients with TBI and GCS <8 -Examined between day 2-6 after admission	20 patients	Propofol and Sufentanil were used 24 hours before investigation, then after taking baseline parameters. Remifentanil (0.5 mg/kg IV) was administered followed by a continuous infusion of Remifentanil (0.25 mg/kg/min. IV) for 20 min	Sufentanil Remifentanil	No
Jacques Albanèse et al (ref.39)	Prospective	-ICU patients -Severe head injury -Intubated, ventilated with sedation	10 patients	Continuous infusion of Propofol 3 mg/kg/hr with NMB Vecuronium 8mg/hr. Level of sedation was deepened by 6 min addition of Sufentanil (1 mic/kg loading then 0.005 mic/kg/min	Propofol + Sufentanil	No
Jacques Albanèse et al (ref.40)	-Randomized -Prospective	-ICU patients -Severe head injury / trauma -ICP monitoring	6 patients	Continuous infusion of Propofol 3 mg/kg/hr with NMB Vecuronium 8mg/hr. Level of sedation was deepened by 6 min addition of either Sufentanil (1 mg/kg), Alfentanil (100 mg/kg), or Fentanyl (10 mg/kg), followed by an infusion of 0.005 mg/kg/min, 0.75 mg/kg/min, and 0.075 mg/kg/min respectively, for 1 hour. 3 opioids were given to each patient at 24 hour intervals in a crossover fashion	Propofol + Alfentanil or Sufentanil or Fentanyl	No
Jacques Albanèse et al (ref.41)	Prospective	-Severe head injury with GCS of 8 or less -Intubated with ICP monitoring	8 patients	Continuous infusion of Propofol 3 mg/kg/hr with NMB Vecuronium 8 mg/hr. Aim is to achieve ICP of <25 mm hg for 3 hours and CPP >65 mm hg for 6 hours or more	Propofol	No
H Kolenda et al (ref.42)	-Prospective -Control Group	-NICU patients -Moderate to severe TBI -Anlgosedation of 3 or more days	24 patients: -12 patients in Ketamine -12 patients in Fentanyl group	Midazolam in both groups	Ketamine + Midazolam Vs. Fentanyl + Midazolam	No
Aurélie Bourgoin et al (ref.43)	-Randomized -Prospective	-NICU patients -Severe TBI with GCS post-resuscitation of <9 -ICP monitored	30 patients: -15 patients in the Sufentanil group -15 patients in the Ketamine group	Midazolam in both groups Follow up by BIS	Sufentanil + Midazolam Vs. Ketamine + Midazolam Efficacy was followed by behavioral pain scale	No
PA Farling et al (ref.48)		Head injury patients	10 patients	Propofol in addition to Morphine + Midazolam + Vecuronium	Morphine	No
AJ Johnston et al (ref.49)	Prospective	-Moderate to sever head injury patients -Sedation, intubation and ICP monitoring	10 patients	Propofol	No	No
Henry E Aryan et al (ref.50)		ICU Neurosurgical patients	39 patients: -12 patients with head trauma -7 patients AVM SAH in 15 -5 patients elective procedures in five, 4 of which were tumor resections and 1 of which was a complex, spinal stabilization	DEX was given according to FDA approval of loading infusion of 0.1 mcg /kg infused over 10 min followed by 0.2-0.7 mcg/kg/hr continuous infusion for 24 hours	No	No
Tina M. Grof et al (ref.51)	-Prospective -Control Group -Observational	-NICU patients -DEX infusion	6 patients	-Richmond Agitation Sedation Scale (RASS) to evaluate the response to DEX		No

APPENDIX II

Aims and outcomes of evaluated studies

Author	Aims	Medication used/ Intervention	Outcome/ p value/ Confidence interval	Why the study is important
Assessment				
Mélanie Boly et al (9)	To prove that patients minimally conscious do perceive pain at a central level, despite lack of response externally	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 ^{15}O-radiolabelled water PET	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 patients in MCS than in those in PVS	Patients with these conditions have pain perception. Authors advocate for use of analgesics particularly in MCS patients
Ingrid Egerod et al (10)	Feasibility of shift from sedation-based to analgesia based sedation		Use of sedatives dropped and analgesics increased. Increased number of pain free patients, and patients with sedation interruption woke up faster	Implement protocols to standardize use of analgesics and sedatives carefully. Analgesia-based protocol may have better pain control, similar sedation efficacy and faster wake up time
Andreas Karabinis et al (1)	Safety and efficacy of analgesia-based sedation with Remifentanil	Group1: Remifentanil (initial dose of 9 mic/kg/hr) was titrated before the addition of propofol (0.5 mg/kg/hr) in the first 1-3 days then shift to Midazolam (0.03 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 extubated faster than morphine but no difference between Remifentanil and Fentanyl	Analgesia with Fentanyl, Remifentanil and morphine appear equally efficient. Analgesia based sedation with Remifentanil offered significantly faster and more predictable time to assessment of neurological function than hypnotics
Anupa Deogaonkar et al (18)	Correlation between Bispectral Index and the clinical sedation scales (RASS, SAS, GCS)	None specifically for the study	Positive correlation BIS XP version correlated reasonably with RASS (R2= 0.810, $P<0.0001$), SAS (R2=0.725, $P<0.0001$), GCS (R2=0.655, $P<0.0001$). The old BIS correlated poorly with RASS (R2= 0.30, $P<0.008$), SAS (R2=0.376, $P<0.0001$), GCS (R2=0.274, $P<0.015$	RASS, SAS and GCS all feasible to measure in the neurological ICU population
Olson 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 got less Propofol by volume and had lower infusion rates. The BIS-augmentation group woke up more quickly than those in the Ramsay-alone group (1.2 vs. 7.5 min; $P<0.0001$)	-BIS use decreases the use of sedatives used without increasing under sedation incidence -BIS use allows quicker awakening when sedatives are withdrawn
Interventions & Outcomes				
K Engelhard et al (38)	The effect of opiates (Remifentanil) on systemic and cerebral hemodynamic	Propofol and Sufentanil were used 24 hours before investigation, then after taking baseline parameters. Remifentanil (0.5 mg/kg IV) was administered followed by a continuous infusion of Remifentanil (0.25 mg/kg/min. IV) for 20 min	Administration and withdrawal of Remifentanil does not affect MAP, ICP, and CBFV in head-injured patients at the intensive care unit	Safety of Sufentanil use and lack of hemodynamic side effects
Jacques Albanèse et al (39)	Effect on ICP (mainly)	6 min addition of Sufentanil (1mic/kg loading then 0005 mic/kg/min then measurements of ICP, CPP, HR, MAP, SPO_2, $ETCO_2$	Sufentanil increased ICP by 53% ($P<0.05$) There was 24% decrease in MAP ($P<0.05$), and 38% decrease in CPP ($P<0.05$) 15% reduction in HR ($P<0.05$). No change in SPO_2, $ETCO_2$, arterial gas	Potential side effects of Sufentanil
Jacques Albanèse et al (40)	Effect of these opiates when injected by boluses and infusion on cerebral hemodynamic and EEG activity	HR, MAP, CPP (MAP - ICP), SpO_2, jugular bulb oxygen saturation ($SvjO_2$), and $PetCO_2$ were continuously measured and recorded at 1-min intervals throughout the 1-hr study period Arterial and jugular vein bulb blood samples were obtained at baseline and 10, 30, and 60 min after opioid administration EEG was continuously monitored as well	Sufentanil, Fentanyl, and Alfentanil infusions associated with significant but transient increase in ICP. The increase in ICP peaked at 5, 6, and 3 min, respectively, then decreased to baseline values at 15 min a significant decrease in MAP and, thus, in CPP	Transient effects of opiates on cerebral hemodynamic
Jacques Albanèse et al (41)	Effect of Ketamine on cerebral hemodynamic	3 doses of Ketamine (1.5/3/5mg) were given at 6 hour intervals to deepen sedation ICP, CPP, MAP, HR, O_2sat, $ETCO_2$ recorded at 1 min interval for 30 min	Ketamine (1.5/3/5mg/kg) associated with decrease in ICP among study patients regardless of the dose. No difference in CPP, jugular O_2 sat, MCA velocity Ketamine induced burst suppression in EEG	Favorable effect of Ketamine on cerebral hemodynamic
H Kolenda et al (42)	Effect on hemodynamic and ICP, CPP	An initial dosage of 6.5 mg/kg/day midazolam, 65 mg/kg/day Ketamine or 65 btg/kg/day. Fentanyl that was later adjusted according to clinical requirements. Prn medications allowed	There was a lower requirement of Catecholamine (significant on first day, $P<0.05$), an on average 8 mm Hg higher cerebral perfusion pressure and a 2 mm Hg higher intracranial pressure in the Fentanyl group	Use of Ketamine up to 14 days does not affect hemodynamic significantly
Aurélie Bourgoin et al (43)	Effect of this target controlled infusion on cerebral hemodynamic	2 medications administered with TCI - 24 hour later study drugs doubled for 15 min MAP, ICP, CPP, BIS are recorded, plasma levels drawn	No change in ICP, CPP, or mean velocity of MCA BIS was not different in both groups	BPS (pain scale validated in other populations) recorded in the study but NOT reported in the results. Reliability and feasibility, or comparison to BIS or drug levels impossible to deduce
PA Farling et al (48)	Hemodynamic effects of propofol infusion	Propofol infusion	No change in BP, HR, ICP, CPP, quality of sedation was recorded as good in 90%	One of the early studies to prove efficacy of propofol
AJ Johnston et al (49)	Is the step increase in Propofol dose impair flow-metabolism coupling specially in the ischemic brain areas. Flow is determined by $AVDO_2$ and local PBO_2. Metabolism is measured by local lactate, glucose, pyruvate, glycerol	Propofol was kept at 2 mic/ml in infusion of 3-4 mg/kg/hr for 4 hours before 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±1.1) to 46.1% (range 0±61.7), $P<0.05$); no change in tissue gas levels, tissue chemistry, or $AVDO_2$	No significant changes in cerebral physiology with increased metabolic suppression and indicate that low-metabolism coupling is intact
Henry E Aryan et al (ref.50)	To gather information on the dosage, sedative effects and adverse effects of dexmedetomidine in neurosurgical patients specially on ICP, CPP and MAP	DEX infusion as per protocol to check for MAP, SBP, DBP, HR, ICP, CPP 24 hour prior to DEX initiation, then hourly while on infusion, lastly 2-5 hours after D/C of DEX	Mean CPP increased and mean ICP decreased; Non relevant clinically 10 patients experienced hypotension specially in those who received loading dose. There was central tendency for MAP was to increase slightly, central tendency for HR was to decrease slightly	Safety of DEX use in neurosurgical patients with variant diagnoses
Tina M Grof et al (ref.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

APPENDIX **III**

Validity and drawbacks of reviewed studies

AUTHOR	CONTENT VALIDITY	FACE VALIDITY	POTENTIAL BIAS OR CONFLICT OF INTEREST	DRAWBACKS
			Assessment	
Mélanie Boly et al (9)	Objective use of PET to evaluate response to pain	Patients were assessed four times by trained and experienced assessors: 1 week and 1 day before scanning, the day of the scan, and 1 week after the scan. An anesthetist or an ICU physician monitored the patients during procedure.	The number of patients is not unified across groups. Variability of pain perception is different among people	No MRI correlates in the PVS Only MRI in the MCS
Ingrid Egerod et al (10)	Ramsay Sedation Scale Pain Intensity GCS	Nurses performed one assessment of pain and sedation per shift (morning, afternoon, and evening)	Daily awakening was left to the discretion of the physician	Single centered Non randomized Small sample of patients
Andreas Karabinis et al (1)	SAS PI	SAS and PI was assessed by the study nurse or investigator	1.Downtitration or discontinuation of drugs for neurological assessments was left to the discretion of the investigator. 2. open label	Poorly designed study- no validated scales, 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 remifentanil group 25% vs. 8% and 10% in other groups
Anupa Deogaonkar et al (18)	Richmond Agitation Sedation Scale (RASS) Sedation Agitation Scale (SAS) Glasgow Coma Scale (GCS)	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 was collected and averaged as single reading	The authors did not declare a conflict of interest but it is not clear how the study was funded (potential COI)	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. Medications unknown. No TBI
M. Olson et al (22)	Ramsay Sedation Scale	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	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	Hawthorne effect Variability among nurse assessments No data on concurrent medications used The use of Ramsay tool which is not validated in NICU
			Interventions & Outcomes	
K Engelhard et al (38)	TCD was used for CBFV (velocity) 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), 5 min (T2), and 20 min (T4) after drug administration and 20 min after cessation of Remifentanil (T5)	No mention of parameters used to lower ICP. No surgical interventions were conducted	Remifentanil is used on the background of adequate sedation with propofol and Sufentanil. The use of vasopressors may also confound the results
Jacques Albanèse et al (39)	None	Investigators	Short duration of Sufentanil administration	Small sample of patients. No control group. Other injuries on top of head trauma that may affect parameters. How clinically important are these changes?
Jacques Albanèse et al (40)	None for sedation EEG was used to	Investigators	EEG interpretation is not well characterized	Small sample of patients. No control group. No outcome data
Jacques Albanèse et al (41)	None	Investigators collected data		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
H Kolenda et al (42)	Motor response of the GCS during the anlgosedation	Physicians independent from the investigators	We do not know how much, how often and what type of Pm medication was given	Small sample of patients. Limited population High number of withdrawals
Aurélie Bourgoin et al (43)	Behavioral Pain Scale for effective Sedation	Investigators		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?
PA Farling et al (48)	None	Investigators		Small sample of patients No control group Patients usually paralyzed Sedation titrated to ICP only Non randomized
AJ Johnston et al (49)	ICP monitored by intraparenchymal catheters. Metabolic products were taken from microdialysis catheter. EEG was monitored.	Investigators	The duration of propofol infusion is not enough to show changes in metabolism (4 hours to attain sedation and then metabolites were taken 20 min after a step increase)	Small sample of patients No control group No sedation protocol
Henry E Aryan et al (50)	UCSD Agitation scale	Not specified	Other sedatives not specified. The exact protocol of DEX use was not mentioned	Small sample of patients. Retrospective. Statistical analysis not known. Confusing results. 10 patients had hypotension, but vasopressors . Unknown if other measure were used for ICP
Tina M. Grof et al (51)	RASS	Not specified	Variability of the adjunctive sedatives/analgesics 2. population or disease process are not defined	Small sample of patients. No control group. Feasibility and reliability of RASS not well described. Unknown diagnosis of patients