CONFERENCE PROCEEDING

Sedation practices in the Neurocritical Care Unit

Abhijit Lele[1], Michael Souter[1,2]

INTRODUCTION

Neurologically injured patients often require sedation for
- Facilitating endotracheal intubation and mechanical ventilation
- Management of intracranial hypertension
- Control of pain, anxiety and distress (PAD).

The goal of sedation in these circumstances is to produce a reproducible neurological examination in a calm, cooperative patient, with maintenance of adequate cerebral perfusion pressure (CPP) while limiting intracranial pressure (ICP).

This study is written to promote understanding of sedation practices in the Neurocritical Care Unit and to provide the readers a basic knowledge of principles of sedation.

REVIEW OF BASIC CEREBRAL PHYSIOLOGY

No review of sedation practice in neurocritical care is complete without reviewing basic cerebral physiology. The brain is a highly metabolically active organ and utilises around 3–3.5 ml O_2/100 g/min, which is termed as cerebral metabolic demand for O_2 ($CMRO_2$). This takes approximately 15% of the cardiac output. Of the energy utilised by the brain, majority (60%) is used for generating electrical activity while the rest (40%) is used for cellular homeostasis. CPP measured as the difference between mean arterial pressure (MAP) and ICP, for the most part influences cerebral blood flow (CBF). In a normal brain, autoregulation of cardiac output to the brain provides a reasonably constant CBF over an MAP range of approximately 65–150 mmHg. However, in an injured brain, there may be varying degrees of regional or global compromise of cerebral autoregulation, with the worst case being where CBF varies directly as blood pressure - the 'pressure-passive' state.

These are important concepts that must be kept in mind when choosing sedation medications, all of which will have some effect on CBF, $CMRO_2$ and MAP and ICP.

GENERAL PRINCIPLES OF SEDATION

Definition of sedation

Within the context of neurocritical care, sedation is defined as incremental reduction in level of consciousness to maintain a state of amnesia, hypnosis and analgesia, from which patients can be readily recruited to participate in a comprehensive neurological examination.

There are two fundamental sedation pathways in the Intensive Care Unit (ICU):
- Use of sedative medications with primary aim to relieve pain, agitation and distress, with concomitant reduction in level of consciousness[1]
- To relieve distress refractory to standard palliative treatment.

Consideration of the second option is outside the scope of this study.

PAD are commonly observed in neurologically injured patients, just as seen in patients on general medical and surgical ICU. All patients therefore require screening for symptoms.

Various sedation strategies can be employed to reduce PAD.[2] Goal-directed sedation is a commonly practiced

Departments of [1]Anesthesiology and Pain Medicine and [2]Neurosurgery, University of Washington, Harborview Medical Center, Seattle, WA 98040, USA

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method where bedside nurses titrate sedation doses to achieve pre-determined level. Patient-targeted sedation strategy employs a structured approach to assessment of pain and distress, with provision for drug escalation and de-escalation. Intermittent sedation, a practice with long-acting sedative agents (such as lorazepam), is rarely practiced. A daily interruption of sedation strategy employs sedative and analgesic titration to desired depth, with provision to interrupt sedation daily to rouse patients to the point of awakening. Keeping in line with symptom centred sedation, while the traditional sedation regimens utilise such agents from anaesthesia practice as fentanyl, midazolam, propofol and morphine, the newer analgosedation regimens utilise synthetic opioids such as remifentanil[3] while agitation and autonomic activity may be controlled by alpha-2 agonists (e.g. dexmedetomidine) as well as psychotropic agents (e.g. haloperidol).[2]

ASSESSING PATIENTS WHILE ON SEDATION IN THE NEUROCRITICAL CARE UNIT

Neurological wake-up tests (NWTs) are commonly conducted in Neurocritical Care Units.[4] These 'neuro-checks' allows for serial neurological examinations, which serve as our gold standard for neuro-monitoring – presenting stimulus and assaying response.

While sedation in neurologically impaired patients may seem counterintuitive, it is necessary to produce ethical, humanistic goals of permitting patient comfort, by the alleviation of pain and distress, while also avoiding the deleterious pathophysiological changes associated with excesses of pain and agitation. There are also pathophysiological consequences of over sedation.

Thus, a balance must be achieved to reduce PAD as well as preserving neurological examination.

Studies focusing on outcomes in patients requiring sedation infusion have demonstrated that while sedation may be indicated for reasons mentioned above, they are associated with worse outcomes if infusions are continued incessantly without interruption to assess readiness for extubation.[5] This introduced the concept of daily awakening trials and a need for sedation interruption.

While sedation interruption is a familiar practice in the daily care of neurocritical care patients, it required testing in general medical and surgical ICUs.

Subsequent studies on daily sedation interruption have shown that it does not significantly increase the risk of self-extubation but also provides additional benefit of early liberation from mechanical ventilation and reduction in length of stay in the ICU[5] although this latter reason still requires further confirmatory research.[6]

Sedation interruption is however not completely without risk. In the Neurocritical Care Unit, arousing patients may be disinhibited, with exaggerated motor responsiveness, gross head and body movements – which do pose some risk for self-extubation if left unobserved.

Over-sedation confounds neuro assessment, necessitating need for frequent neuroimaging studies to assess impaired conscious state, contribute to delayed emergence and disuse atrophy of muscles, in addition to causing respiratory depression, hypotension, venous stasis and set up for venous thrombosis, hampers progressive upright mobility, increases time on ventilator, ICU length of stay and costs. On the other hand, under sedation can lead to agitation and anxiety, pain, distress, elevated ICP, tachycardia, hypertension, predispose to arrhythmias and myocardial ischaemia, promote ventilator dyssynchrony, ineffective ventilation, wound disruption, increased oxygen consumption, pose fall risk and accidental removal of tubes, catheters, lines and drains.

In patients with traumatic brain injury, it has been demonstrated that while these NWTs may result in transiently increased levels of ICP and CPP,[7] they do not impair neurochemistry or cerebral oxygenation.[8] The merits of these NWTs must be weighed with the side effects, and it still remains to be proven whether any of these ICP and CPP changes influence patient outcome.

Some unique situations in neurocritical care where NWTs reconsidered are patients with recently occluded arteriovenous malformation with risk for normal perfusion pressure breakthrough and in patients with significant intracranial hypertension undergoing burst suppression with barbiturates, where the longer half-life of barbiturates used to achieve desired effect essentially render serial NWTs impossible.

USE OF SEDATION SCALES

There are a number of validated clinical sedation assessment scales in ICU practice - essentially nursing driven tools to record the patient's condition, which in turn is used to monitor and adjust sedation to the desired goal.

Commonly described scales over the years include:

- Ramsay scale (1974)[9]
- Observer's assessment of alertness/sedation scale (1990)[10]
- Riker sedation-agitation scale (1999)[11]

- Motor activity assessment scale (1999)[12]
- Minnesota sedation assessment tool (2000)[13]
- Vancouver interaction and calmness scale (2000)[14]
- AVRIPAS (agitation, alertness, heart rate and respiration) (2001)[15]
- Richmond agitation sedation scale (RASS) (2002)[16]
- ATICE (consciousness domain and tolerance domain) (2003)[17]
- The nursing instrument for the communication of sedation scale (2010).[18]

As per the Society of Critical Care Medicine's (SCCM) 2013 clinical practice guidelines for management of pain, agitation and delirium in adult patients in the ICU,[19] the most commonly used sedation assessment tools for measuring quality and depth of sedation in adult ICU patients are RASS. The target sedation scores on individual scales vary per patients and clinical scenarios.

Contrary to some opinions, processed electroencephalogram (EEG) is not universally accepted as a monitoring tool to assess depth of sedation as studies using such techniques have often found these to be unreliable[20,21] and subject to myogenic artefacts.[22-24] Since healthy human volunteers were used to primarily obtain and validate processed EEG numerical, it is generally unknown if any severity of underlying brain injury would impact such readings in the presence of sedation.[25] In fact, the SCCM guidelines recommend against routine use of processed EEG in non-comatose, non-paralysed patients.

However, one of the potential uses of processed EEG is in management of patients with status epilepticus, wherein anaesthetic medications are used to achieve burst suppression.

PHARMACOLOGY OF SEDATIVE AGENTS

Consideration of goals of sedation, as well as the associated detrimental side effects, allows characterisation of the ideal sedative agent. It may possess one or several of the following properties:

- Readily available and inexpensive
- Favourable context-sensitive half-life for NWTs
- Reduce $CMRO_2$
- Reduce ICP
- Anti-convulsant
- Anxiolytic
- Analgesic
- Independent of hepatic metabolism and renal excretion
- Lack of active metabolites
- Cardiovascular stability (preserve MAP)
- Preserve spontaneous respiration
- Ability to produce burst suppression
- Demonstrate reduction in times to extubation
- Demonstrate reduction in ICU length of stay
- Demonstrate reduction in mortality.

Various drugs are available and are extensively used for sedation in an intensive care environment. Commonly used agents include propofol, dexmedetomidine, benzodiazepines, opioids and barbiturates.

While not one of these agents fulfils all of the above criteria for an ideal agent, a drug, or combination thereof of couple or more drugs when appropriately chosen for a particular patient and given in a particular clinical scenario may achieve the desired effect.

CLINICAL SCENARIO

Traumatic brain injury

A 25-year-old man who was crossing a street involved in a hit and ran with a high-speed motor vehicle is admitted to the neurocritical unit with severe traumatic brain injury. The patient is agitated and requires multiple health care providers at bedside from causing self-harm. Admission computed tomography scan performed with much difficulty reveals bi-frontal contusions with a subdural hematoma. His admission Glasgow Coma Scale is 9, and he continues to remain extremely agitated trashing all four extremities, has tachycardia and hypertension and hyperventilation. Nursing and physician providers have difficulty in even completing a thorough neurological assessment.

It is important to note that agitation in the setting of traumatic brain injury is multifactorial. Agitation could be due to pain, which in this case may be caused to trauma and associated bony fractures or soft-tissue injuries. It may be a manifestation of ICP elevations, hypoxia or a concomitant surgical abdomen. It can also be a manifestation of hypercarbia, hypoglycaemia or a symptom of drug or alcohol withdrawal. Thus, correct diagnosis of underlying mechanisms causing agitation is an important determining factor in which sedation regimen perhaps, may work best.

Symptomatic treatment of agitation may be begun with small doses of antipsychotic agents such as haloperidol (1–5 mg intravenously). It has been demonstrated that short-term use of haloperidol is well tolerated[26] in patients with acute agitation and results in quantifiable reduction in agitation for general medical/surgical populations[27] and especially in the subset of patients with traumatic brain injury. However, chronic use of haloperidol should probably be avoided as it has been associated with delayed behavioural recovery in animal models.[28,29]

If the agitation is related to hypoxia and or elevated ICP, it is prudent to secure the airway and provide

mechanical ventilation and aggressively treat intracranial hypertension with medical and or surgical interventions.

One possible approach is to use propofol. Propofol's context-sensitive half-life makes it conducive to faster, more predictable awakenings, facilitating NWTs and earlier extubation. It offers advantageous cerebral haemodynamics, which if systemic arterial pressure is maintained, make it a very attractive agent in neurocritical care.[30] Propofol decreased $CMRO_2$ and CBF and is a useful adjunct to reduce ICP. In fact, propofol may provide the most rapid means to diminish ICP since the onset begins within one arm-brain circulation time.

It may be used as an anaesthetic agent during endotracheal intubation and subsequently continued for sedation thereafter when the patient is placed on mechanical ventilation. According to the 2007 Brain Trauma Foundation Guidelines, propofol is recommended for the control of ICP, but its use does not result in improvement in 6-month mortality.[31]

We recommend initiating propofol with a test dose of 0.5 mg/kg followed by continuous infusion of 25–75 mcg/kg/min (dose not to exceed 5 mg/kg/h)[31] titrating to maintain RASS between 0 (patient alert and calm) and −2 (light sedation, patient awakens with eye contact to voice).

Important considerations while using propofol

Principal disadvantages of using propofol include its respiratory and cardiovascular depressant effects. Consequently, its use should be limited to patients who are already endotracheally intubated or where the ability to rapidly secure, the airway is immediately available.

It is associated vasodilation with reduced venous return requires more use of intravenous fluids and vasopressors than benzodiazepines.

When used for long-term (>72 h) in doses exceeding 80 mcg/kg/min, patients are at risk for hypertriglyceridemia, lactic acidosis, rhabdomyolysis and renal failure, which encompass the development of propofol-infusion-syndrome, most commonly seen in the paediatric population.

Risk factors for severe propofol sedation induced hypotension, (defined by MAP < 60 mmHg) in the Neurocritical Care Unit, include renal replacement therapy MAP 60–70 mmHg immediately preceding infusion initiation, changes in propofol infusion rate and concomitant use of clonidine.[32] Hypotension related to propofol is also seen in the elderly and in patients with hypovolemia. Importantly, hypotension resulting from propofol, if unopposed, can contribute to secondary increases in ICP as a result of reflex cerebral vasodilation.

Propofol may also be used for bedside procedural sedation such as bronchoscopy, percutaneous tracheostomy and placement of gastrostomy feeding tubes and in of gastrointestinal procedures such as endoscopies.

Need for additional drugs

Propofol does not possess significant analgesic properties, thus additional medications such as opioids will be required to treat pain.

Analgesia may be required to allow patient tolerance of many various ICU bedside procedures such as intubation, mechanical ventilation, placement of arterial and central venous catheters, placement of ICP and other multi-modality monitoring devices. It is also required in specific neurological situations such as Guillain–Barre syndrome as well as emergent medical or surgical conditions such as acute myocardial infarction and surgical abdomen. It is suggested that any analgesic regimen be used to reduce pain to <3 on a 0–10 scale.[33]

While no one particular sedative agent has been shown to be more efficacious than others in patients with traumatic brain injury, high-bolus doses of opioids have (via vasodilation and hypotension) potentially deleterious effects on ICP and CPP.[34]

It is preferable to use short-acting opioids such as remifentanil or intermediate-acting agents such as fentanyl in an infusion form, due to favourable context-sensitive half-life. In fact, remifentanil being 250 times as potent as morphine, with its fast onset of action (1–3 min), short elimination half-life by plasma esterases (3–10 min) and with its extremely favourable context-sensitive half-life (3–4 min), is a very attractive option in this clinical scenario. One of the shortcomings of remifentanil preventing its widespread use is that it is cost prohibitive for short- or long-term sedation regimens. Exclusive use of remifentanil has been described in the concept of analgosedation.[3] Remifentanil[35-37] has been safely used in patients without deleterious effects on ICP, whose airway is secured with an endotracheal tube, thus preventing effects of hypoventilation and hypercarbia on ICP, which are potential problems in using these drugs in non-intubated patients. Caution must be exercised while using remifentanil as reduction in heart rate and blood pressure has been reported in patients exposed to remifentanil compared to controls.[38] It may not reliably blunt ICP response in patients receiving tracheobronchial suctioning[39] although instillation of endotracheal lidocaine may be beneficial in preventing ICP elevation and thus preserving CPP,[40] it can contribute to the development in chest wall rigidity via an effect of gamma efferent innervation. There is a theoretical concern for hyperalgesia with use of remifentanil, but a recent systematic review failed to find

support or refute the existence of remifentanil-induced hyperalgesia.[41]

Fentanyl may be a suitable agent for immediate duration sedation regimen due to its rapid onset (1–2 min). However, a longer elimination half-life (2–4 h) and longer context-sensitive half-life (200 min for 6 h infusion and 300 min for 12 h infusion)[19] may be a major shortcoming in long-term sedation as it does not favour rapid NWTs. Fentanyl used as bolus or infusion have again been associated with increased ICP,[42-44] and thus it is recommended to be used in patients with stable haemodynamic profile and as stable infusions without significant changes in dosing.[45] Suggested fentanyl doses in patients with traumatic brain injury are 2 mcg/kg test dose followed by 2–5 mcg/kg/h continuous infusion.[31] Morphine may be used in dose of 4 mg/h with titration as needed, but with risks of histamine release, longer half-life and a higher risk/benefit profile.

While prophylactic administration of barbiturates to produce burst suppression EEG is not recommended, high-dose barbiturate administration is used for control of elevated ICP refractory to maximal medical and surgical treatment, and caution must be exercised to maintain haemodynamic stability.[31]

NOVEL THERAPIES

Use of inhalational agents for sedation in the Intensive Care Unit

Inhalational agents such as isoflurane, sevoflurane and desflurane have been extensively tested in neurosurgical patients as part of their anaesthetic regimen. Inhalational anaesthetics not only increase CBF by being cerebral vasodilators but also reduce $CMRO_2$, thus producing what is known as a favourable uncoupling of blood flow and oxygenation consumption, when correctly titrated. Isoflurane has been demonstrated to decrease cortical spreading depolarisations, which have been implicated in delayed brain injury in stroke and brain trauma.[46]

Isoflurane (2 times minimal alveolar concentration [MAC]) and sevoflurane (4 times MAC) can induce burst suppression and thus are potential therapeutic options in patients with refractory status epilepticus.

Some of the barriers to using them at the bedside in neurocritical care have been logistical challenges of equipment, personnel and cost.

Inhalational conserving systems such as AnaConDa® have been used for sedation in the Neurocritical Care Unit.[46-49] While targeted sedation levels were reached with isoflurane and sevoflurane, there was no significant increase in ICP in patients with baseline low or normal ICP.[50] However, increase in ICP reduction in MAP and CPP can be expected in certain patients, related to rebreathing of CO_2 within the conserving system, and thus baseline PCO_2 levels are elevated during its use. Currently, this system is not available in the USA.

Use of ketamine in analgosedation regimens: Return of a black-boxed agent

Ketamine, a non-competitive N-methyl-D-aspartate receptor antagonist, has traditionally not been favourably looked on for routine use in neurocritical patients due to historic data demonstrating its negative effects on $CMRO_2$, CBF and ICP.[50,51]

However, recent animal and human studies suggest that ketamine does not alter cerebral autoregulation[52,53] nor does it increase ICP.[54-56] When compared to opioids such as sufentanil, ketamine has not demonstrated elevation in ICP.[57] There is level 2b evidence in adult patients that ketamine does not increase ICP in patients with non-traumatic[58] and traumatic brain injury when patients are sedated and mechanically ventilated.[59,60] In fact, ketamine (dose range of 1.5–3 mg/kg) in combination with propofol has been shown to reduce ICP in patients with traumatic brain injury with no significant differences in CPP, jugular oxygen saturation and middle cerebral artery blood flow, with induction of a low-amplitude fast activity EEG, with marked depression, such as burst suppression.[61]

Ketamine has also been used to facilitate routine bedside procedures such as endotracheal suctioning. In a study by Caricato *et al*., racemic ketamine (100 γ/kg/min for 10 min) used before endotracheal suctioning was not associated with significant variation in CPP, and SJO_2 although ketamine was not completely effective in controlling ICP elevations during this time period.[62]

It must be remembered that ketamine is often used in conjunction with a benzodiazepine such as midazolam or propofol,[63] and the concurrent use of ketamine results in less requirements for vasopressors,[60,64] maintenance of MAP and CPP[65] and carries a risk profile similar to propofol and benzodiazepines.[66]

Overall, ketamine has not shown to adversely affect patient outcomes.[67]

Ketamine is also well suited for patients requiring analgosedation after major spine surgeries, with the added advantage of having an opioid-sparing effect.

SUMMARY

Thorough understanding of available drugs, underlying pathophysiology and goals of sedation, with targeted sedation regimens to achieve reliable neurological

wake up while maintaining physiological parameters can provide a good framework for optimal sedation in neurocritical care patients.

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Conflicts of interest

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