Sedation in neurological intensive care unit

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Abstract

Analgesia and sedation has been widely used in intensive care units where iatrogenic discomfort often complicates patient management. In neurological patients maximal comfort without diminishing patient responsiveness is desirable. In these patients successful management of sedation and analgesia incorporates a patient based approach that includes detection and management of predisposing and causative factors, including delirium, monitoring using sedation scales, proper medication selection, emphasis on analgesia based drugs and incorporation of protocols or algorithms. So, to optimize care clinician should be familiar with the pharmacokinetic and pharmacodynamic variables that can affect the safety and efficacy of analgesics and sedatives.

Key Words

Analgesia, neurocritical care, sedation

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Introduction

All clinicians who provide care to critically-ill patients face daily management issues, including ensuring patient comfort and pain relief and at the same time avoiding complications of therapy. Critical illness can be a frightening experience for a variety of reasons. Pain is the root cause of distress experienced by many intensive care unit (ICU) patients but anxiety, dyspnea, delirium, sleep deprivation and other factors may contribute and may be additive or synergistic. For the tolerance of the endotracheal tube and ventilation heavy sedation was required in the past but this clinical practice has now largely changed with the availability of modern ventilators with wide range of modes and additional advantage of electronic flow triggering. Thus, recent revolution of critical care management has emphasized the need to minimize continuous deep sedation and paralysis. This recommendation is especially important in patients with neurological dysfunction owing to the need to serially monitor their neurological status. This revolution of encouraging maximal patient cognition has required a change on the part of the intensivists in their approach to sedation, and also forced a reappraisal of the medications selected, dosing algorithms, routes and modes of administration.[1] This

review focuses on the recent developments in the assessment and delivery of sedation strategies especially in neurological patients.

Indications and goals for sedation

Triggers for initiating sedation may be many. In general medical or surgical ICU's, sedation may be required for cardiopulmonary stabilization and decrease catecholamine activity, performance of endotracheal intubation, placement of intra-vascular catheters, to reduce oxygen demand in patients with critical hypoxemia, to decrease the dyspnea secondary to pulmonary processes or metabolic acidosis. Although these indications may coexist in neurological patients, a significant number have isolated intra-cranial pathology. Indication unique to neuro ICU[2] may be

- To control intracranial pressure (ICP) and cerebral perfusion pressure and decrease the cerebral rate of oxygen utilization.
- Blunt central hyperventilation.
- Refractory status epilepsy (added to a regimen of anti-seizure medications).
- Patients with traumatic brain injury (TBI) may be physically aggressive or may manifest inappropriate verbal behavior.
- To control agitation in intoxicated patients or withdrawl from drug or alcohol use because this may compromise the ability of the staff to provide adequate patient care.

Pain

The ICU environment along with numerous medical/neurological conditions is very discomforting for the patient. But prior to initiation of sedation it is imperative to treat pain as a cause of anxiety, agitation and sympathetic over-activity. Common clinical conditions requiring pain relief

in neurological patients include:
- Post-operative wound and incision discomfort
- Sub-arachnoid hemorrhage
- Raised intra-cranial pressure
- Guillain–Barre syndrome with radicular pains
- Endotracheal tube irritation
- Invasive line and other procedure placement
- Cranial nerve dysfunction
- Meningitis, meningo-encephalitis

Anxiety

Anxiety and agitation are known to occur at least once in about 70% patients in ICUs.[3] Conditions are too numerous to enumerate but the very common ones include hypoxia, hypercarbia, metabolic disturbances, hepatic or renal insufficiency, disturbed sleep-wake cycles and traumatic head injury.[4] Patients with brain disease will have a variable degree of insight and may need significant anxiolysis because of fear of death or long-term health effects.

Delirium

Delirium is characterized by an acutely fluctuating mental status, inattention, disorganized thinking, and an altered level of consciousness that may or may not be accompanied by agitation. Delirium affects 60-80% of mechanically ventilated patients and is under-recognized 75% of the time in the absence of a validated instrument.[5] Delirium is an independent predictor of increased cost, hospital length of stay (LOS), long-term cognitive impairment and death. Each additional ICU day spent in delirium was associated with a 10% increased risk of death.[6] Pre-disposing factors in the neurological ICU include an underlying diagnosis of inta cranial hemorrhage, Subarachnoid hemorrhage or stroke.

Monitoring of sedation

Neurologically ill patients in ICUs present particularly complex sedation issues, owing to the need to serially monitor their neurological status. An optimum state of analgesia, sedation, and delirium management results in reduced pain, decreased anxiety, managed delirium, amnesia and recovery [Figure 1].[7] Sedation is not always a threat in neurological examination; rather a calm, non-anxious, un-agitated patient will allow a better examination. Hemodynamic response as a measure of sedation is unreliable therefore many sedation scales have been studied and validated like Ramsay Sedation Scale, Motor Activity
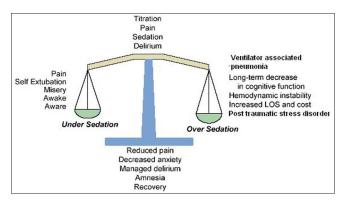
Assessment Scale, Richmond Agitation–Sedation Scale (RASS) and Adaptation to intensive care environment.[8] [Figure 2a-c] illustrates the specific sedation scales.

Concerns with clinical scoring systems include interpreter variability and lack of discrimination between deeper levels of sedation. To avoid this variability investigators have turned to the potential utility of neurological monitors, specifically the electroencephalogram (EEG). Bispectral index technique is mostly used to monitor depth of surgical anesthesia in the operating theatre; has a controversial role in the ICU[9] because of erroneous high values due to motor artifacts in non-paralyzed patients. Its values may also be affected by hypothermia, shock, drugs and metabolic disturbances.

Sedative agents

Opioids

In the ICU, opioids are mainly used to provide analgesia but they also serve as sedative/hypnotics in low doses. All opioids act by binding to opioid receptors in the central and peripheral nervous systems as agonists, partial agonists, or agonist–antagonists to produce the pharmacological effects like analgesia, decreased level of consciousness, respiratory depression, miosis, gastrointestinal hypo-motility and vasodilatation. Fentanyl, remifentanil and morphine are µ-receptor agonists commonly used in the ICU.[10]

Rationale for use and adverse reactions

Advantages of opioids in the neuro ICU includes easy titrability, provision of patient comfort and reversibility. Caution should be used in administrating morphine to TBI patients as it increases ICP and cerebral blood flow (CBF).[10] Other opioids in general have no consistent effect on ICP or CBF but hypercarbia due to the potential to cause respiratory depression may lead to cerebral vasodilatation and raised ICP. Hence, patients receiving narcotic sedation must have continuous monitoring of oxygen saturation and respiratory rate.

Additionally, frequent hemodynamic monitoring in patients on narcotic agonists is required due to the potential for hypotension and bradycardia. Morphine may induce

Figure 1: Balancing pain and anxiety treatment

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s), aggressive	
+2	Agitated	Frequent non-purposeful movement, fights ventilator	
+1	Restless vigorous	Anxious but movements not aggressive	
0	Alert and calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)	Verbal stimulation
-2	Light sedation	Briefly awakens with eye contact to voice (< 10 seconds)	
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)	
-4	Deep sedation	Noresponse to voice, but movement or eye opening to physical stimulation	Physical stimulation
-5	Unarousable	No response to voice physical stimulation	

Figure 2a: The Richmond Agitation–Sedation Scale. *Adapted from Sessler CN, Gosnell MS, Grap MJ, *et al.* The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166:1338-1344

Consciousness domain		Tolerance domain		
Awakeness (graded 0 to 5)	Comprehension (sum of the 1-point responses)	Calmness (graded 0 to 3)	Ventilator synchrony (sum of the 1-points elements)	Face relaxation (graded 0 to 3)
Eyes closed, no mimic — 0	"Open (close) your eyes" — 1	Life-threatening agitation — 0	No blockade of the inspiratory phase of ventilation — 1	Permanent grimacing — 0
Eyes closed, only face mimic after strong painful stimulation — 1	"Open your mouth" — 1	Agitation, does not respond to verbal order — 1	No respiratory rate > 30 — 1	Severe provoked grimacing — 1
Eyes opening after strong painful stimulation — 2	"Look at me" — 1	Agitation, not respond to verbal order — 2	No cough — 1	Moderate provoked grimming — 2
Eyes opening after light painful stimulation — 3	"Nod yes with your head" — 1			
Eyes opening after verbal order — 4	"Close your eyes and open your mouth" — 1	Calm — 3	No use of accessory respiratory muscles — 1	Relaxed face — 3
Eyes opening spontaneously — 5				

Figure 2b: The Adaptation to the intensive care environment (ATICE) scale. ATICE. This scale contains two domains: (a) Consciousness (two questions) (b) tolerance (three questions). The total score is a sum of two domains, ranging from 0 (extremely poor adaptation) to 20 (very good adaptation). *Adapted from De Jonghe BD, Cook D, Griffith L, *et al.* Adaptation to the intensive care environment (ATICE): Development and validation of a new sedation assessment instrument. Crit Care Med 2003;31:2344-2354

hypotension even at low therapeutic doses, but fentanyl and remifentanil have little effect on blood pressure at usual sedative doses. The maximum dose of an opioid that should be used in the ICU is limited by the occurrence of adverse effects.

Remifentanyl, a new ultra-short acting opioid, is a potent pure µ-agonist and is metabolized by non-specific blood and tissue esterase. Hence, elimination is not dependent on hepatic and renal function. It has a stable context sensitive half-life of 3-10 min.[11] Thus, when used as a sedative it allows rapid awakening and helps to differentiate between over-sedation and neurological dysfunction.

Benzodiazepines

Benzodiazepines (diazepam, midazoloam, lorazepam) are the most commonly administered class of drugs in the ICU. They bind to gamma aminobutyric acid A (GABA A) ligand gated chloride ion channels and modulate the effects of gamma amino butyric acid. Subsequent clinical effect depends on the degree to which they bind to these receptors; anxiolysis (20% receptor blockade), sedation (30-50%), anterograde amnesia and hypnosis (60% receptor blockade), muscle relaxation, respiratory depression and anticonvulsant activity occur with increasing degree of blockade in that order.[12]

Rationale for use and adverse reactions

Because of effective anxiolysis and anterograde amnesia, their use is favored in the neuro ICU; however analgesia should be supplemented. They have opioid sparing effect by the ability to modulate anticipatory pain response.

Benzodiazepines do not cause significant alteration in either blood pressure or heart rate, and respiratory drive is well preserved unless high doses are used but synergistic effects with other medication may alter level of consciousness, suppress respiratory drive, or decrease systemic blood pressure. Thus it is important that careful hemodynamic monitoring is maintained for those on continuous infusions, and those who are not mechanically ventilated. Alone, benzodiazepines have little or no effect on ICP.[13] However, reduction in mean arterial pressure associated with midazolam administration may impair cerebral perfusion.

The anticonvulsant effect of benzodiazepines confers additional advantage of their use in neuro ICU. Lorazepam and midazolam have been used in primary therapy for convulsive status epilepticus. However, continuous use may lead to development of tolerance and diminished efficacy with time.

Another unintended consequence of benzodiazepine

Feature 1: Acute Onset of Fluctuating Course	Score	Check here if present
Is the pt different than his/her baseline mental status? OR Has the patient has any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (i.e. RASS). GCS, or previous delirium assessment?	Either question Yes →	☐
Feature 2: Inattention		
<u>Letters Attention Test</u> (See training manual for alternate Pictures) <u>Directions</u>: Say to the patient, *"I am going to read you a series of 10 letters. Whenever you hear the letter "A," indicate by squeezing my hand.* Read letters from the following letter list in a notmal tone 3 seconds apart. S A V E A H A A R T Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."	Number of Errors > 2 →	☐
Feature 3: Altered Level of Consciousness		
Present if the Actual RASS score is anything other than alert and calm (zero)	RASS anything other than zero →	☐
Feature 4: Disorganized Thinking		
<u>Yes/No Questions</u> (See training manual for alternate set of questions) 1. Will a stone float on water? 2. Are ther fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? Errors are counted when the patient incorrectly answers a question. <u>Command</u> Say to patient: 'Hold up this many fingers' (Hold 2 fingers in front of patient) 'Now do the same thing with the other hand' (Do not repeat number of fingers) *if pt is unable to move both arms for 2nd part of command ask patient to 'Add one more finer.' An error is counted if patient is unablde to complete the entire command.'	Combined number of errors >1 →	☐

| **Overall CAM-ICU** Feature 1 <u>plus</u> 2 <u>and</u> either 3 <u>or</u> 4 present = CAM-ICU positive | Criteria Met → Criteria Not Met → | ☐ CAM-ICU Positive (Dellrium Preaent) ☐ CAM-ICU Negative (No Dellrium) |

Figure 2c: The confusion assessment method for the intensive care unit (CAM-ICU) scale. *Adapted from Ely EW, Margolin R, Francis J, *et al*., evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001;29 (7):1370-1379

administration is inducing frank delirium. Other side effects of these agents include headache, nausea or vomiting, vertigo, confusion, somnolence, obtundation, hypotonia/loss of reflexes, or muscular weakness.[12]

Intravenous anesthetic agents

Propofol

It is an ultra-short acting general anesthetic agent that is extensively used in the ICU. It exhibits sedative and hypnotic activities at even low doses and has amnestic properties similar to benzodiazepines. Although structurally different, its clinical actions and effects on cerebral activity and intracranial dynamics are very similar to short acting barbiturates (e.g., thiopentone).

Rationale for use and adverse reactions

The rapid onset and offset of action makes it the preferred drug in neuro ICU, provided close monitoring of respiration and hemodynamic is available. Propofol reduces ICP after TBI more effectively than morphine or fentanyl and also decreases CBF and cerebral metabolism. There have been recent reports of fatal metabolic acidosis and myocardial depression, known as "Propofol infusion syndrome" following prolonged infusion (>48 h) of high doses (>80 µg/kg/min), especially in patients of refractory status epilepticus.[14]

Propofol has a high clearance rate, thus significant accumulation does not occur after bolus or continuous infusion. Propofol is a lipid emulsion so the calorie content (900 cal/Lt) must be considered whenever it is administered along with parenteral nutrition. It is by no means an ideal drug in the ICU because it lacks analgesic effects and adverse effects like significant hypotension and myocardial depression (especially in volume depleted patients), pain on injection and rarely potential anaphylactoid reaction. Dose dependent respiratory depression is predictable, so propofol should be used in the setting of a controlled airway.

Propofol, administered by conventional rate-controlled infusion, is an effective sedative in critically ill patients but "Target Controlled Infusion" systems have also been successfully used in anaesthesia and during post-operative period. Using these systems, propofol is administered via an infusion pump which incorporates a pharmacokinetic model. The clinician enters the patient's body weight and the concentration of propofol required in the patient's blood, instead of setting the dose rate. The required concentration, expressed in ug/ml, is known as the target concentration setting.[15] The target blood propofol can be adjusted to achieve the sedation depth desired in an individual patient and the blood propofol concentration settings required to achieve an optimum depth of sedation are generally within the range of 0.2-2.0 ug/ml. This is based on computer simulation of the concentrations achieved with current doses of propofol recommended for sedation (0.3-4.0 mg/kg/h).

Thiopentone

Barbiturates are centrally acting agents that have a dose-dependent sedative, hypnotic, or anesthetic action; along with anticonvulsant and cerebro-protective properties. The commonly used barbiturates in the neuro ICU setting are phenobarbital, pentobarbital, and sodium thiopental. They produce central nervous system depression by facilitation of chloride conductance at inhibitory GABAA ion channels.

Rationale for use and adverse reactions

Currently, the only indications of continuous infusion of thiopentone are in the management of refractory status epilepticus and reduction of refractory intra cranial hypertension. It decreases ICP by reducing CBF and cerebral metabolic rate of oxygen utilization by 25-30% within seconds of bolus injection.[16] In low doses, it has little effect on blood pressure and heart rate but higher doses producing EEG burst suppression may lead to severe hypotension requiring inotropic support. It has a low clearance rate and when given as an infusion, its metabolism may become linear (zero order) due to saturation of hepatic enzymes; thus, accumulation may lead to myocardial depression and immunosupression. Potential adverse effects are bronchospasm, angiodema, cough, laryngospasm, loss of airway reflexes and respiratory depression.

α2-agonists

The two agents of this group are clonidine and dexmedetomidine (DEX). They have commonly been used as efficacious anaesthetic adjuncts, markedly decreasing the requirement of general anesthesia.

Dexmedetomidine

It is an imidazole compound and pharmacologically active dextroisomer of medetomidine. It is eight times more specific and selective than clonidine for these receptors (ratios of α2:α1 activity, 1620:1 for DEX, 220:1 for clonidine). The pre-synaptic activation of the α2-adrenoceptor inhibits the release of norepinephrine, terminating the propagation of pain signals. Post-synaptic activation of α2-adrenoceptors in the central nervous system inhibits sympathetic activity and thus can decrease blood pressure and heart rate. These effects in combination produce analgesia, sedation, and anxiolysis, thus avoiding multiple therapies.[17]

The onset of action is within 15 min after intravenous bolus and peak concentrations are achieved after 1 h with continuous infusion. It has a half-life of 6 min and a terminal elimination half-life of 2-2.5 h. There are no known active or toxic metabolites.

The administration of a bolus of 1 µg/kg, initially results in a transient increase of the blood pressure and a reflex decrease in heart rate[18] lasting for 5-10 min. This is followed by a decrease in blood pressure and a stabilization of the heart rate, both of which are due to the central sympathetic outflow inhibition. Higher doses produce bradycardia in about 40% of healthy surgical patients.[19] These temporary effects are successfully treated with atropine or ephedrine and volume infusions.

Rationale for use and adverse reactions

The mechanism of action is unique and differs from the currently used sedative agents. DEX produces dose-dependent decrease in vigilance and increase in sedation that correlates well with EEG-based spectral entropy monitoring. Arousability is maintained at deeper levels of sedation, with good correlation between sedation (RASS score) and Bispectral EEG. Upon arousal, patients perform well on the tests of vigilance. This state of "cooperative sedation" is useful during sophisticated neurological testing during craniotomies for tumor dissection or stereotactic implantations. It facilitates arousal and rapid orientation of a sedated patient.

Sedation induced by DEX has respiratory pattern and EEG

stages that resemble the natural sleep cycle. Functional MRI confirms that DEX preserves CBF similar to natural sleep.

At clinically effective doses, DEX causes much less respiratory depression and even at very high plasma levels (>8 ng/ml) there is marked cathecholamine suppression and deepening sedation but no clinically significant respiratory depression. All effects of DEX could be antagonized easily by administering the α2-adrenoceptor antagonist, atipamezole.[20]

The FDA approves infusion of DEX for a maximum of 24 h as evidence of long-term safety are lacking and there are concerns about rebound hypertension and tachycardia on discontinuation. However, several clinical studies have demonstrated safe use for a week and longer in mechanically ventilated critically ill patients. Unlike clonidine, cessation of infusion is not associated with rebound hypertension or agitation.

Tables 1 and 2 illustrate the general properties and doses of the commonly used ICU sedative agents.

Comparative trials
Many agents have been used for sedation and anxiolysis in the ICU but no one agent has been identified as the ideal agent. Therefore, several trials have compared the common agents. The Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction[21] trial compared lorazepam and DEX for the effect of sedative agents on delirium-free and coma-free days. The use of DEX was associated with a greater number of delirium-free and coma-free days; however, there was no difference in outcomes, including duration of mechanical ventilation, ICU LOS, or 28-day mortality. One major limitation of the trial was the depth of sedation, which was chosen to be −3 and −4 RASS scores for the DEX and lorazepam groups respectively. Had lighter sedation goals been achieved (RASS scores closer 0 to −1), the incidence of drug-induced coma would likely have been less (particularly with lorazepam), and results may have differed. Another double-blind trial, the Safety and Efficacy of DEX Compared with Midazolam[22] trial, compared midazolam to DEX requiring daily awakening trials

and targeted a RASS score of −2-1. The primary outcome was percentage of time within RASS goal (−2 ± 1) and secondary outcomes included assessment of delirium, duration of mechanical ventilation and ICU/LOS. There was no difference in the primary outcome; however, patients in the DEX group had a lower prevalence of delirium and a larger number of delirium-free days.

The recently concluded acute neurological ICU sedation trial[23] compared intellectual capacity, measured with the adapted cognitive examination (ACE), in neurological ICU patients sedated with propofol or DEX. Following treatment with propofol, patients had lower mean ACE scores (−12.4, $P < 0.001$; wherein higher score indicates better cognitive function), whereas after treatment with DEX mean ACE scores improved (+6.8, $P < 0.018$). This improvement was particularly marked in patients with baseline cognitive dysfunction. These data are intriguing, but further studies are required to determine the true magnitude of effect of these sedatives on cognition.

Accumulation of sedatives and sedation protocols
Sedation needs in ICU patients vary frequently due to unpredictable drug effects because of renal and hepatic dysfunction, drug-drug interactions, shock and hypoproteinemia. Accumulation of the sedative drug or its active metabolites occurs in tissue stores and this leads to over-sedation, greater hemodynamic instability, prolonged duration of intubation and ICU stay. Accumulation and over-sedation may be reduced or even avoided by the use of two well-known strategies
- Use of patient-targeted sedation protocol based on *Analgo-sedation*: This implies
- A structured approach to the assessment of patient's pain and distress
- Coupled with an algorithm that directs drug escalation and de-escalation based on the assessment

Brook and co-workers[24] first compared the practice of protocol-directed sedation during mechanical ventilation implemented by nurses versus traditional non-protocol-directed administration of sedation. This application of protocol resulted in

Table 1: Pharmacokinetics and dosing parameters of common intensive care unit sedatives

Drug	Half life	Starting dose	Infusion dose
Morphine	1.5-4.5 h IV, IM, SQ	5-20 mg IM q 4 h 2-10 mg IV q 4 h	Caution: Active metabolite (morphine-3-glucoronide) may accumulate
Fentanyl	30-60 min after single IV dose	12.5-50 μg IV q 20-30 min	Infusion 0.01-0.03 μg/kg/min and titrate q 15-30 min, up to 50-100 μg/h
Remifentanyl	3-10 min after single dose	0.5-1.0 μg/kg IV bolus	Infusion 0.05-0.2 μg/kg/min
Diazepam	30-60 h	2 mg IV q 30-60 min	
Lorazepam	10-20 h	0.25-0.5 mg IV q 1-2 h	
Midazolam	1-2.5 h	0.5-1 mg IV q 5-30 min	Infusion 0.25-1.0 μg/kg/min
Propofol	4-10 min	1.0-2.5 mg/kg IV (anesthesia induction) 5 μg/kg/min for 5 min IV (sedation)	Increase infusion by 5-10 μg/kg/min q 5-10 min to maintenance 25-100 μg/kg/min (maximum: 100-300 μg/kg/min)
Thiopentone	8-12 h	1-5 mg/kg IV	
Clonidine	12-16 h	0.1 mg PO q 8-24 h. Increase 0.1 mg/d q 1-2 d up to 0.6 mg/d	
Dexmedetomidine	2 h	1 μg/kg IV over 10 min	Infusion 0.2-0.7 μg/kg/h

ICP=Intracranial pressure, IV=Intravenous, IM=Intramuscular, SQ=Subcutaneous

a significantly shorter duration of mechanical ventilation (median duration 55.9 h vs. 117.0 h). Since then many trials have demonstrated the success of protocols in decreasing the duration of mechanical ventilation and its complications like ventilator associated pneumonias, length of ICU and hospital stay.

The second approach comprises of *Wake-up call* or daily interruption of continuous sedative infusions till the patient awakens and restarting infusion at half the previous dose if the patient exhibits distress. A landmark trial of 128 mechanically ventilated medical ICU patients randomized to daily sedation interruption versus interruption at the discrepancy of the treating physician, resulted in 2.4 fewer days on the ventilator and a significantly shorter LOS (6.4 vs. 9.9 days).[25]

Despite the success of sedation protocols outlined above, there is still surprisingly low implementation of sedation scoring systems and protocols. Worldwide surveys documented a 50% use of sedation scoring systems with sedation protocols being utilized in only 33%.[26] Some factors for the reluctance to adopt these may stem from the absence of large-scale, multicenter, randomized trials, institutional and individual bias regarding agents employed, fear of extubation, decannulation, worsening cardiac ischemia and precipitation of psychological distress. But the need of the hour is to target sedation according to the patient and re-evaluate on a daily basis. This allows therapy to be titrated appropriately, to achieve the desired response, and therefore prevent over and under-sedation as the clinical needs of the patient change.

The concept of 'bundling' therapies to ensure that patients receive evidence-based care treatments has been applied to early management of sepsis and prevention of ventilator-associated pneumonia with improved outcome. Recent evidence supports that combining evidence-based interventions into an "*ABCDE bundle*"[27] when applied to critically ill patients who need sedation can make life saving interventions tolerable and can reduce the complications of sedation such as prolonged mechanical ventilation, delirium, and ICU acquired weakness. The bundle consists of [Box 1].

A-Spontaneous awakening trial
B-Spontaneous breathing trial
C-Choice of sedation
D-Delirium monitoring
E-Early mobility and exercise

Box 1

Table 2: General characteristics of common intensive care unit sedatives

Drug	Sedation	Analgesia	Advantage	ICP effects	Seizure threshold	Adverse effects
Opioids						
Morphine	+	+++	Reversible	Elevates ICP	Myoclonus no seizures	Respiratory depression, gastric dysmotility, hypotension, hallucinations
Fentanyl	+	+++	Reversible, rapid onset, short duration	Indirect elevation (hypercarbia)	Myoclonus no seizures	Respiratory depression, chest wall rigdity, gastric dysmotility, hypotension
Remifentanyl	+	+++	Reversible, rapid onset, short duration	Indirect elevation (hypercarbia)	Myoclonus no seizures	Respiratory depression, chest wall rigdity, gastric dysmotility, hypotension
Benzodiazepines						
Diazepam	+++	+	Reversible	Indirect elevation-hypercarbia	Treat seizures	Respiratory depression, hypotension, confusion
Lorazepam	+++	–	Reversible	Indirect elevation-hypercarbia	Treat seizures	Respiratory depression, hypotension, confusion
Midazolam	+++	–	Reversible, short duration, titratable	No direct effect. Indirect elevation-hypercarbia hypotension	Treat seizures	Respiratory depression, hypotension, confusion
i.v. anesthetic agents						
Propofol	+++	–	Very short duration, easy titratable	Lowers ICP	conflicting results but likely to decrease ICP	Hypotension, respiratory depression, metabolic acidosis, rhabdomyolysis, anaphylaxis, sepsis, pain at venous site
Thiopentone	+++	–	–	ICP reduction	Treat seizures	Respiratory depression, hypotension, gastric dysmotility, bronchospasm, angioedema
α2 agonists						
Clonidine	++	++	Useful in setting of alcohol or drug withdrawal	No effect	Little data: Increases epileptiform activity in known focal seizures?	Dry mouth, bradycardia, hypotension, rebound hypertension
Dexmedetomidine	++	++	Useful in setting of alcohol or drug withdrawal	No effect	No human studies	Dry mouth, bradycardia, hypotension, adrenal suppression, atrial fibrillation

ICP=Intracranial pressure

Sedation regimes for specific situations

Patients with elevated ICP: Agitated patients with increased ICP should be sedated to the point where they are quiet and motionless (Ramsey level 5 or 6). A combination of a sedative-hypnotic and analgesic agent is usually most effective. The preferred regimen is the combination of fentanyl (1-3 μg/kg/h) or sufentanil (0.1-0.6 μg/kg/h), to provide analgesia and propofol (0.3-3 mg/kg/h) for sedation. These drugs are short acting, such that the agent may be stopped for frequent neurologic assessments throughout the day. Table 3 shows the selected short acting sedative-analgesics for raised ICP management.

Patients receiving ventilator therapy: There is little logic in using very short-acting substances in patients receiving ventilator therapy. On the other hand use of longer-acting drugs can delay the weaning process. Use of sedation protocols and daily awakening trials have been shown to reduce the duration of mechanical ventilation and the use of scoring systems for analgesia even reduces the incidence of nosocomial infections.[28] Some of the important clinical practice guidelines that help in managing patient on long-term mechanical ventilation are shown in Figure 3 and Table 4.

Patients with myasthenia gravis: Propofol has the theoretic advantages of short duration of action without effect on neuromuscular transmission. Benzodiadepines and opioid analgesics in therapeutic concentrations do not appear to depress neuromuscular transmission in myasthenic muscle. However, central respiratory depression may be a problem with these drugs. The use of short-acting opioids like remifentanil is more titratable in the myasthenic. The myasthenic patient is typically sensitive to nondepolarizing neuromuscular blockers and these agents should be used with careful monitoring of neuromuscular transmission, preferably with electromyogram or mechanomyogram, which measure the evoked electrical or mechanical responses following electrical stimulation of a peripheral motor nerve.

Non-ventilated patients: Pain should be titrated with opioids to the desired level. Cooperative patients may benefit from patient-controlled analgesia. The patient-controlled narcotic delivery systems use either intravenous opioids or epidural infusions of local anesthetics or opioids. In some centres a newer technique of sedation is employed- patient-controlled sedation-[29] using increments of propofol, as opposed to patient-controlled analgesia. This is a very effective technique in the awake, orientated patient but the neurosurgical patient presents a dilemma in the decision-making process. Careful attention must be given to the baseline pre-operative function in regard to the ability to understand the use of a patient controlled analgesia system and to the expected post-operative cognitive function and the ability to utilize the system.
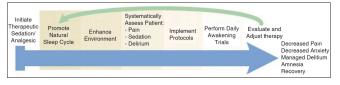

Figure 3: Roadmap for sedation care process in intensive care unit

Table 3: Selected short acting intravenous sedatives for intracranial pressure management

Agent	Pharmacology	Dosage range
Sedative-analgesic agents		
Morphine sulfate	Opioid (sedative-hypnotic with analgesic properties)	2-5 mg IVP every 1-4 h
Fentanyl	Opioid (short acting, 100 times more potent than morphine)	0.5-3.0 μg/kg/h
Sufentanil	Opioid (ultrashort acting)	0.1-0.6 μg/kg/h
Sedative-hypnotic agents		
Propofol	Alkylphenol (ultrashort acting)	0.6-6 mg/kg/h
Midazolam	Benzodiazepine (short acting)	0.05-0.1 mg/kg/h

Dosages are approximate and should be titrated to the patient's level of agitation and ICP. A combination of a sedative-analgesic and sedative-hypnotic agent may be more effective than the use of a single agent

Table 4: Practice points for patients on mechanical ventilation

1. Presence of pain/discomfort is a primary source of agitation in a ventilated patient

2. Assessment of pain and response to therapy should be performed regularly by using a validated scale

3. Sedation of agitated critically ill patients should be started only
   • After providing adequate analgesia and
   • Treating reversible physiological causes

4. Level of sedation be measured regularly. It is more important that the level of sedation be measured regularly and reproducibly than the way it is measured.

5. Choice of drugs depends on-
   Fentanyl - Rapid onset of analgesia (preferred for patients with haemodynamic instability or renal insufficiency)
   Remifentanyl - Differentiates b/w over-sedation & neurological dysfunction
   Midazolam - Used for rapid sedation of acutely agitated patients.
       - Recommended for short-term use only, as it produces unpredictable awakening and time to extubation when infusions continue longer than 48–72 hours

6. Titrate sedative dose to a defined endpoint with systematic tapering of the dose or daily interruption to minimize prolonged sedative effects.

7. Neuromuscular blocking agents should be used in the following conditions only when all other means to maximally sedate the patient have been tried without success
   • Manage ventilation
   • Manage increased ICP
   • Treat muscle spasms
   • Decrease oxygen consumption

8. Monitor all patients for delirium with monitoring tools like the CAM-ICU, even those who are calm and not agitated.
   BDZ - Increased duration of delirium
   Propofol - Although not associated with delirium, does affect cognition
   Dexmedetomidine - Superior to the present alternatives for preservation of cognition and avoidance of delirium

Post-operative patients: Many options are available for the treatment of post-operative pain, including systemic (i.e., opioid and nonopioid) and regional (i.e., neuraxial and peripheral) analgesic techniques. Multimodal analgesia is achieved by combining different analgesics that act by different mechanisms and at different sites in the nervous system, resulting in additive or synergistic analgesia with lowered adverse effects than when individual analgesics are administered as sole agents.[30]

Conclusions

Patients who are critically ill experience numerous physiological derangements and commonly require long duration of analgesic and sedative therapy. The ideal sedative or analgesic agent should have a rapid onset of activity, rapid recovery after drug discontinuation, predictable dose response, lack of drug accumulation and toxicity. Sedative regimens in the neuro ICU are complex owing to the need to monitor these patient's serial neurological examinations. So, to optimize care clinician should be familiar with the pharmacokinetic and pharmacodynamic variables that can affect the safety and efficacy of analgesics and sedatives.

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