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SPECIAL ARTICLE

Role of sedation and analgesia in ICU

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ABSTRACT

Alleviation of pain is a basic human right. And patients who experience the greatest pain and suffering are the ones in the intensive care unit (ICU). Sedation allows to prevent the patients' awareness and reduction of their response to various external stimuli. However, sedation is like a double-edged sword for ICU patients. Over-sedation can cause long-term ventilatory support and increase duration of ICU stay, whereas under-sedation can cause hyper-catabolism, immunosuppression, hypercoagulability and increased sympathetic activity. Pain is widely regarded as the fifth vital sign, and it induces a myriad of deleterious physiological changes in most organ systems. Pain can cause agitation, delirium, and inadequate pain management can have psychological sequelae like post-traumatic stress disorder, depression and anxiety or it can progress to chronic pain. In this review, we will focus on the role of sedation & analgesia in ICU, current practice trends and a holistic approach for better patient care.

Key words: Sedation; Analgesia; Analgosedation; Intensive care unit; PICU; NICU

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INTRODUCTION

Alleviation or access to the treatment of pain is a basic human right. Contrary to popular perception, our principal function in patient care is not only to save lives (since this is impossible on a consistent basis), but also to relieve pain and suffering. Patients who experience greatest pain and suffering are the ones in intensive care unit (ICU).[1] Heavy sedation in adults to facilitate endotracheal tube tolerance and ventilator synchronization along with neuromuscular blocking agents, were routine practice in ICU till last decade. With the advent of modern ICU ventilators(wide range of ventilation modes and electronic flow triggering), synchronization problems have largely been reduced. The replacement of an endotracheal tube by a tracheostomy reduces the discomfort associated with an artificial airway and may often remove the need for sedation entirely.[2,3] Recent data support the role of early and regular mobilization in the management of critically ill patients which depends on the sedation-analgesia practices of the ICU.[4] The critically ill patient should be awake and alert, without pain, anxiety and delirium, as it allows the patient to actively participate in their treatment and recovery.[5] Children in neonatal or pediatric intensive care unit (NICU, PICU) are also exposed not only to painful stimuli but also have significant emotional distress and anxiety emphasizing the need for sedation in addition to analgesia.

SEDATION

It is very important to define the indication, monitoring and to determine the endpoint for sedation in ICU patients. The appropriate dose and timely use of sedatives can facilitate patient care and safety in addition to the treatment of agitation and anxiety.

Monitoring of sedation or arousal:

The use of sedation scale helps to provide adequate sedation using titrated amount of sedatives and also reduce the duration of mechanical ventilation, incidence of nosocomial infections and length of stay in ICU.

Scoring Systems:

1. **Subjective or Clinical scoring systems:**

The Richmond Agitation Sedation Scale (RASS)[6] (Table 1) and Sedation Agitation Scale (SAS)[7] are the two most validated and reliable sedation assessment tools for measuring quality and depth of sedation in adult ICU patients. However, these are subjective tools that may lead to variability in measurement and consequent clinical actions.

2. **Objective or Technological monitoring:**

Objective measures of brain function (e.g. Auditory Evoked Potentials (AEP), Bispectral Index (BIS), Narcotrend Index (NI), Patient State Index (PSI), or State Entropy (SE)) are inadequate substitutes for subjective sedation scoring systems in non-comatose, nonparalysed critically ill patients. However, they can be used as an adjunct in patients receiving neuromuscular blocking agents. A comparison of BIS with RASS for measuring the level of sedation revealed a statistically significant, positive correlation between the two systems.[8] EEG helps to monitor nonconvulsive seizure activity in ICU patients with either known or new onset seizures, or to titrate electrosuppressive medication in adult ICU patients with raised intracranial pressure.[9]

In children, sedation score is assessed by state behavioral scale, COMFORT scale and BIS. (Table 2)

Methods of sedation:

A. **Non-pharmacological methods:**

Multidisciplinary approach in addition to pharmacotherapy is essential for patient comfort. Frequent communication, physiotherapy, feeding and hydration play an important role and can be achieved through frequent assessment.[2]

B. **Pharmacological methods (Table 3):**

Historically, benzodiazepines and propofol have been commonly used to sedate critically ill patients.

Benzodiazepines:

The four benzodiazepines, currently being used in anesthesia and critical care are classified as short-acting (midazolam), intermediate-acting (lorazepam, temazepam) and a long-acting agent (diazepam), according to their metabolism and plasma clearance.[10] They produce anxiolytic, amnestic, sedative, hypnotic, and anticonvulsant effects, by activating γ-aminobutyric acid A ($GABA_A$) neuronal receptors but have no analgesic properties. Elderly patients are significantly more sensitive to the sedative effects

Table 1: Richmond Agitation Sedation Scale

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	Anxious but movements not aggressive, vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye-contact) to voice (> =10sec)
-2	Light sedation	Briefly awakens with eye contact to voice (<10sec)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Table 2: sedation assessment in children:

Name	Features	Advantag	Limitations
State Behavioural Scale	Scores range from -3 (Unresponsive) to +2 (Agitated) depending on the child's response to voice, gentle touch or noxious stimuli.	Validated for use in critically ill infants and children to guide goal directed therapy.	There can be interobserver variation particularly for state -1 &0.
COMFORT Scale	Score based on measurement of five behavioural variables (alertness, facial tension, muscle tone, agitation and movement) and three physiologic variables (heart rate, respiration and blood pressure)	Validated for use in critically ill children.	Change in physiologic variables may be unrelated to sedation alone
Bispectral index (BIS)	Algorithm are made based on EEG findings	• Objective assessment of sedation • Particularly helpful in paralysed patients	• Validated for adults • The scoring system is based on adult EEG data which may not be applicable in children

of benzodiazepines. Benzodiazepines can cause respiratory depression and systemic hypotension, especially when administered in conjunction with other cardiopulmonary depressants, particularly opioids. Delayed emergence from sedation with benzodiazepines can result from prolonged administration (due to saturation of peripheral tissues), advanced age, hepatic dysfunction, or renal insufficiency.[11]Midazolam is the most commonly used benzodiazepine in ICU or PICU because of its very rapid onset of action and short duration of effects. But in critically ill child with potential multiorgan dysfunction, recovery from midazolam infusion may be prolonged. It has been observed that, patients on midazolam infusions take six times more time than patients on lorazepam infusion for recovery.[12] Lorazepam and diazepam both contain propylene glycol as vehicle and can cause severe metabolic acidosis in critically ill children including newborns. Remimazolam is a new benzodiazepine that has rapid onset of action, short predictable sedation and faster recovery compared to other benzodiazepines because it is hydrolyzed by nonspecific esterase.[13]

Propofol

It has sedative, hypnotic, anxiolytic, amnestic, antiemetic and anticonvulsant properties without any analgesic effects. It binds to multiple receptors in the central nervous system to interrupt neural transmission, including $GABA_A$, glycine, nicotinic, and M_1 muscarinic receptors. Cardiopulmonary instability with propofol administration is more likely to occur in patients with baseline respiratory insufficiency and/or cardiovascular instability. Because of the potential lethal syndrome known as propofol related infusion syndrome (PRIS) seen in some children, it is rarely used as prolonged infusion in PICU.[14]PRIS is characterized by metabolic acidosis, hyperlipidemia, rhabdomyolysis, hyperkalemia, renal failure, cardiac dysrhythmias and cardiac failure. Close monitoring is required when propofol is used for prolonged infusion (> 6 hours).Treatment of PRIS includes immediate cessation of infusion. Hemodialysis and plasmapheresis has been reported to have some success[15].The propofol solution is a good culture medium and can be potentially contaminated. So, unused content of an open vial should be discarded

Table 3: commonly use Sedatives:

Drug	Onset	Elimination t1/2	Dosing	Warning/Precautions
Midazolam	2 minutes	1.5-2.5 hours	Loading:0.01-0.05 mg/kg (0.5-4 mg in adults) Maintenance: 0.02-0.1mg/kg/hr. Finding the minimum effective infusion rate is important	• It can accumulate in peripheral tissues with continuous infusion • Increased chances of hypotension (especially in neonates) with increased loading dose and concomitant use of fentanyl • Dose should be decreased for elderly, in hepatic and renal impairment • Caution advised with concomitant administration of cytochrome P450-3A4 system inhibitors viz. cimetidine (not ranidtidine), erythromycin, diltiazem, verapamil, ketoconazole, itraconazole • Pediatric patients should receive slow increments of midazolam on a mg/kg basis.
Lorazepam	2-3 hours	14 hours	1-2 mg bolus 1-5 mg/hour infusion	• Not easily titratable due to its longer half-life • Prolongation of effect, with severely decreased drug requirements in the elderly • The solvents used with lorazepam (polyethylene glycol, propylene glycol) implicated in cases of reversible acute tubular necrosis, lactic acidosis, and hyperosmolar states after prolonged use.
Diazepam	1-3 minutes	60-72 hours	5-10 mg bolus	• Not suitable for infusions
Propofol	40 s	1-3 hours (Redistribution t1/2-2-8 minutes)	5-50 mcg/kg/min (not > 4 mg/kg/h)	• Abrupt discontinuation of Propofol infusion may result in rapid awakening, anxiety, agitation, and resistance to mechanical ventilation • Do not use if contamination is suspected • Pain on administration should be minimized with the use of antecubital veins, prior injection of lidocaine • Monitoring for profound hypotension and cardiovascular depression • The tubing and any unused drug should be discarded after 12 hours
Dexmedeto-midine	5 minutes	2 hours	Loading: 1 mcg/kg over 10 minutes Maintenance: 0.2-0.7 mcg/kg/h	• Dose reduction in hepatic impairment, geriatric patients • Caution to be exercised in advanced heart block, severe ventricular dysfunction, hypovolemia, diabetes mellitus, chronic hypertension • Use beyond 24 hours associated with tolerance and tachyphylaxis • Most common adverse events include bradycardia, hypotension, and dry mouth.

and infusion syringe and tubing should be changed every 6 hours.

Ketamine

It is an NMDA antagonist that produces altered state of consciousness (dissociation), amnesia and analgesia. Unlike other agents, ketamine is a bronchodilator, and has both analgesic and sedative properties making it an appealing agent in adult critically ill patients (analgosedation). The minimal respiratory depressant effects with relatively stable hemodynamics associated with its use make it a good agent for procedural sedation and analgesia in PICU also. Bolus doses (0.5 to 1 mg/kg) prior to procedures as well as short-term infusions (3-4 hours) have also been used for postoperative pain and for patients with bronchospasm.[16] It causes increased catecholamine release causing bronchodilation, increase in heart rate and blood pressure and hence useful in bronchial asthma patient and children with borderline hemodynamics. It is important to remember that ketamine is actually a negative inotrope and it is the catecholamine releasing property that helps maintain blood pressure. So, in catecholamine-depleted state e.g. prolonged shock, it can cause hypotension. Other adverse effects of ketamine are hallucination and increased salivation. To prevent these adverse effects ketamine is often administered with midazolam and atropine or glycopyrrolate. Other adverse effects include apnea in infants and myoclonic movements. Although concerns have been raised about the risk of raised ICP by ketamine; recent systematic reviewsthat ketamine does not increase ICP in ventilated sedated patients with severe traumatic brain injury.[17]

Alpha-2 agonists (Dexmedetomidine):

Dexmedetomidine is a selective α_2 receptor agonist with sedative, analgesic and sympatholytic properties, but without anticonvulsant properties. Patients sedated with dexmedetomidine are more easily arousable and interactive, with minimal respiratory depression. The most common side effects of dexmedetomidine are hypotension and bradycardia. IV loading doses can cause either transient hypertension or hypotension. Heart rate responses are not attenuated by pretreatment with glycopyrrolate but co-administration of ketamine helps to maintain the heart rate.[18] Because dexmedetomidine does not significantly affect respiratory drive, it is the only sedative approved for administration in non-intubated ICU patients, and infusions can be continued as needed following extubation.[9] A recent study suggests that ICU patients receiving dexmedetomidine may have a lower prevalence of delirium than patients sedated with midazolam.[19] Sedation from dexmedetomidine results in a patient who is tranquil but can be easily aroused. This has led to its use in patients where repeated neurological examination is required. The recommended dose is a loading dose of 1 mcg/kg over 10 minutes followed by an infusion of 0.2-0.7 mcg/kg/hr.[19] Long-term infusion (> 48 hours) can result in tolerance, withdrawal and possibly adrenal insufficiency.[20,21] Despite the apparent advantages in using either propofol or dexmedetomidine over benzodiazepines for ICU sedation, benzodiazepines remain important for managing agitation in ICU patients, especially for treating anxiety, seizures, and alcohol or benzodiazepine withdrawal. Benzodiazepines are also important when deep sedation, amnesia, or combination therapy to reduce the use of other sedative agents is required.[9]

Inhalational sedation (AnaConDa™ and Mirus™ system):

It is an inhalational anaesthesia system designed in Sweden for use with ventilators in the ICU. It is attached to the mechanical ventilators to recycle the anaesthetic agents. Volatile anaesthetics have a rapid onset and offset of action, resulting in quicker awakening and extubation. They accumulate very little and are largely excreted by lungs, independent of liver and kidney elimination.A syringe pump delivers liquid isoflurane or sevoflurane into a porous hollow rod called "evaporator" in AnaConDa™system. Desflurane cannot be applied via syringe pump because of its low boiling point.Mirus™ system is the first to use desflurane in ICU.The problems related with the use of the device are slight hypercapnia due to the increase in the dead space, inadvertent intravenous injection; and the current standard gas monitors are not calibrated for the AnaConda device.[22]

DELIRIUM

Delirium is a syndrome characterized by the acute onset of cerebral dysfunction with a change or fluctuation in baseline mental status, inattention, and either disorganized thinking or an altered level of consciousness.[23] Delirium is associated with increased mortality, prolonged ICU stay and development of post-ICU cognitive impairment in adult patients. Routine monitoring of ICU patients for delirium is recommended. Delirium is common in both mechanically ventilated and nonmechanically ventilated ICU patients. ICU personnel often underestimate the presence of delirium because it frequently presents as hypoactive rather than hyperactive delirium.[9]

The risk factors for delirium include: preexisting dementia, history of baseline and a high severity of illness at admission. Coma is an independent risk factor. Inappropriate or inadequate sedative therapy specially benzodiazepine use may be a risk factor in the development of delirium in adult ICU patients.[9] Early mobilization of adult ICU patients whenever feasible reduces the incidence and duration of delirium. No high-quality studies with sufficient sample size or effect size demonstrate a benefit of administering prophylactic antipsychotics to the general ICU population.[9] The Confusion Assessment Method for the ICU (CAM-ICU)[24] and the Intensive Care Delirium Screening Checklist (ICDSC)[25] are the most valid and reliable delirium monitoring tools in adult ICU patients and Pediatric Confusion Assessment Method for the ICU (pCAM-ICU)[26] for pediatric patients. One of the most difficult scenarios for the pediatric intensivist is to differentiate between withdrawal and delirium as both can have similar features. A prolonged and unusually severe presentation of withdrawal, without correlated medication changes, should present a high index of suspicion of delirium.

Management of delirium consists of treatment of the underlying cause and pharmacologic therapy, if needed. Although neuroleptic agent like haloperidol or chlorpromazine are commonly used to manage but there is no published evidence that it reduces the duration of delirium in ICU patients. Atypical antipsychotics may reduce the duration of delirium in adult ICU patients. However, antipsychotics should be avoided in patients at significant risk for torsades de pointes (i.e., patients with baseline prolongation of QT interval, patients receiving concomitant medications known to prolong the QT interval, or patients with a history of this arrhythmia).[9] In adult ICU patients with delirium unrelated to alcohol and benzodiazepine withdrawal, continuous IV infusions of dexmedetomidine rather than benzodiazepine infusions should be administered for sedation in order to reduce the duration of delirium in these patients.[19]

ANALGESIA

Recognition and management of pain in ICU patients is another important aspect for better outcome. Pain can be related to various etiopathology, like procedural pain (drawing blood sample, catheterization, laryngoscopy etc.), acute disease pathologies (myocardial infarction, trauma etc.) and chronic disease conditions (cancer, neuropathies etc.) Inadequate pain relief in ICU patients can result in increased stress response, sleep deprivation, disorientation, anxiety, delayed recovery, delirium, post traumatic stress disorder and may be a risk factor for development of chronic pain.

Assessment of Pain:

A. Pain scales for patients able to communicate:

i. Visual analogue scale (VAS): Patients mark their pain on a 100 mm line, with verbal descriptors at each end (0: no pain; 100: very severe pain). The score is obtained by measuring the distance in millimeters from the left end of the line.

ii. Numerical Rating Scale (NRS): Patients rate pain on an 11-point scale (0: no pain; 10: severe pain).

iii. Verbal Rating Scale (VRS): 4-point scale, in which the pain can be rated as 1: absent, 2: mild, 3: moderate, and 4: severe.

B. Pain scales for patients not able to communicate:

i. Behavioral Pain Scale (BPS): this scale uses clinical observations of facial expression, upper limb movements, and synchrony with mechanical ventilation. BPS ranges from3 to 12, scores > 6 require pain management.[27]

ii. Critical Care Pain Observation Tool (CPOT): the scale uses a four-component clinical observation of: facial expression, body movements, muscle tension, and compliance with the ventilator for intubated patients or vocalization for extubated patients. Each component has a score of 0-2, and total score ranges from 0 to 8. A score of > 2 has a high sensitivity and specificity for predicting significant pain in postoperative ICU patients exposed to a painful procedure.[28]

Pain scales used for pediatric patients are summarized in Table 4.

Methods of Analgesia for ICU patients:

It can be divided in non-pharmacological and pharmacological methods (Table 5).

a. **Opioid analgesics (Table 6):**

The opioids have analgesic and sedative property but no amnestic and anxiolytic property. They are considered to be the mainstay for treatment of acute pain in critically ill patients. Opioids act by stimulating μ, κ, and δ-opioid receptors, which are widely distributed within the CNS and throughout the peripheral tissues. Management of background pain is best achieved by an initial bolus followed by a continuous infusion. The dose of morphine should

Table 4: Pain assessment in children

Name	Features	Age range	Advantages	Limitations
Faces scale (Wong-baker FACES scale or six faces pain rating scale)	Children rate their level of pain by identifying pictures of faces from no pain to severe pain	4 year and older	Can be used in younger ages than Visual analog scale and Numerical Rating Scale	Choice of 'no pain' affects response (whether neutral or smiling)
Visual Analog Scale	Children or teenagers are asked to move an indicator along a mechanical slide to depict the level of pain; the clinician reads a number along a 10 cm indicator on the back to determine the numeric score.	8 years and older	• Good psychometric properties • Validated for research purposes	• Can't be used in younger children or in those with cognitive limitations • Requires language skills and numerical processing • Most pain requires an experiential reference point which is lacking in most children
Numeric Rating scale	Older Children are asked to rate their pain on a scale of '0' (no pain) to '10' (worst pain)	8 years and older	Same as Visual Analog Scale	Same as Visual Analog Scale
Individualised Numeric Rating Scale (INRS)	Similar to Numeric rating scale but here the ratings are mostly done by the parents by comparing to previous painful experiences in their child (developmentally delayed and cognitively impaired)	3 years and older	Useful in developmentally delayed and cognitively impaired child	Nonspecific
FLACC (Face, legs, activity, cry and consolability) Scale	Scoring of observed behaviours	Newborns to 7 years of age	Useful in infants and nonverbal children	• Nonspecific • Overrates pain in infants and toddlers • Underrates persistent pain
Neonatal Pain and sedation scale (N-PASS)	Assesses both pain and sedation numerically using indicators: crying/irritability, behaviour/state, facial expression, extremities/tone, and vital signs	Newborns	Useful in newborns	• Nonspecific • Vital signs can change without pain also
Change in physi-ologic parameters (heart rate, blood pressure, adrenal stress hormones)	Pain assessment in children who are paralysed or in neonates can be done by assessing changes in behavioural status from baseline	Any children who are paralysed	Can be used in children who are paralysed	• Vital signs can change without pain also

be reduced by 50 % when used in infants younger than 3 months of age as the active metabolite Morphine-6-glucuronide accumulates because of renal immaturity.[29]Fentanyl has rapid onset of action and short duration of action, but the context sensitive half-life increases when given by continuous infusion.[30] The new synthetic opioid remifentanil is gaining popularity because of its rapid onset of action and short context sensitive half-life (3-5 minutes) even after prolonged infusion, which is attributable to its hydrolysis by nonspecific tissue and plasma esterase.[31] The prolonged use of opioids has been associated with high incidence of side effects like tolerance and withdrawal. The adverse effects

Table 5: Analgesia Methods in the ICU

Non-Pharmacological Methods	Remarks
1. Hypnosis 2. Massage therapy 3. Removal of noxious stimulus 4. Music therapy 5. Repositioning of the patient 6. Stabilization/ immobilization of injured part in trauma patients 7. Application of heat and cold 8. Transcutaneous Electrical Nerve Stimulation 9. Auriculotherapy 10.Acupuncture	• Devoid of side effects • Repeatable • Limited and unpredictable efficacy
Pharmacological Methods	**Remarks**
1. Opioid Analgesics 2. Non-opioid analgesics 3. Analgesic adjuncts: neuropathic drugs	Can be administered via several routes: • Enteral/oral • Parenteral (intramuscular or intravenous) • Transdermal/transmucous • Neuraxial (Intrathecal/Epidural)

Table 6: opioid Analgesics:

Drug	Onset	Elimination $t_{1/2}$	Dosing	Warnings/Precautions
Morphine	5-10 min	3-4 hours	Bolus: 0.1-0.2 mg/kg Infusion: 0.05-0.1 mg/kg/h PCA: 0.01-0.03 mg/kg bolus Lockout: 5-10 min 4 h limit: 30-70 mg	• Renal metabolism play significant role • No decrease in systemic clearance in patients with hepatic cirrhosis or during the anhepatic phase of orthotopic liver transplantation • Avoided in cases of severe asthma (causes histamine release and depresses respiratory mucous transport)
Fentanyl	1-2 min	2-4 hours	Bolus: 1-2 μg/kg Infusion: 1-10 μg/kg/h PCA: 0.5-1 μg/kg bolus lockout: 5-10 min 4 h limit: 400-800 μg Patches: 25-100 μg/h	• Caution to be exercised with concomitant administration of CYP3A4 inhibitors such as Macrolide antibiotics, azole antifungal agents, and protease inhibitors • Dose reduction in elderly, neonates (Immature cytochrome P450 system) hepatic impairment • Risk of Skeletal Muscle Rigidity with higher doses and rapid injection • Precipitation of serotonin syndrome with concomitant use of Serotonergic drugs • Causes spasm of Sphincter of Oddi, Increases in Serum amylase • Renal failure- no gross alteration in pharmacokinetics
Alfentanil	1-2 min	1.4-1.5 h	Bolus: 10-30 μg/kg Infusion: 20-60 μg/kg/h PCA: 0.1-0.2 mg bolus. Lockout-5-8 min	• Seizure like activity on rapid IV administration • Caution advised in elderly and Parkinsonism • Clearance affected in hepatic impairment but not in renal impairment
Remifentanil	1-3 min	17-33 min	Bolus: 1 μg/kg Infusion: 0.05-2 μg/kg/min	• Short recovery period warrants careful titration of infusion avoiding abrupt cessation • Associated with acute opioid tolerance

of opioids include hypotension, bradycardia, ileus, nausea, vomiting, urinary retention, constipation, delirium, hallucinations, and hyperalgesia. Rare side effects include immunosuppression, seizures and muscle rigidity.[32] Low dose naloxone infusion (0.25 mcg/kg/hr) can significantly reduce opioid induced side effects without interfering opioid induced analgesia.[33]

b. **Non-opioid analgesics:**

Analgesics like paracetamol and NSAIDs are effective for treating mild nociceptive pain.

Paracetamol:

It has a central analgesic effect that is mediated through activation of descending serotonergic pathways, and a debatable inhibitory effect on prostaglandin synthesis. Acetaminophen is one of the most commonly used nonopioid analgesic used in PICU. Regardless of route of delivery the maximum daily dose of acetaminophen in preterm, term and older child is 60, 80 and 90 mg/kg respectively.[34]

Non-steroidal anti-inflammatory drugs:

NSAIDs work by inhibition of the cyclooxygenase (COX) enzymes COX-1 and COX-2. They regulate the production of prostaglandins and thromboxane from arachidonic acid with varying ratio of COX-1 *vs* COX-2 inhibition. NSAIDs have analgesic, antipyretic, and anti-inflammatory properties. NSAIDs can be used in selected critically ill patients but should be used judiciously because of the potential for toxic adverse events, particularly renal toxicity in hypovolemic patients. The lowest effective dose of the NSAID should be used for the shortest duration indicated. Appropriate clinical and laboratory follow-up is necessary.[35] Administration of ketorolac early after injury significantly decreases the risk of pneumonia among patients with rib fractures. It also appeared to reduce time on the ventilator and in the intensive care unit without any prominent increase in acute kidney injury, myocardial infarction, stroke, gastrointestinal hemorrhage, or fracture non-union.[36] Aspirin has largely been abandoned in pediatric practice because of its possible role in Reye syndrome, platelet dysfunction and gastric irritant properties.

c. **Analgesic adjuncts:**

Pre-existing adjuvant drugs like gabapentinoids and tricyclic antidepressants (TCAs) should be continued in ICU as cessation can precipitate withdrawal states. Neuropathic pain, poorly treated with opioids alone, can be treated with enterally administered gabapentin and carbamazepine in ICU patients with sufficient gastrointestinal absorption and motility.[9] Gabapentin and pregabalin work by binding to the

Table 7: ABCDEF Bundle management strategy

A	Assess, prevent and manage pain	• Emphasis on adequate analgesia before sedation (Analgo-sedation) • Routine assessment of pain • Self-report preferred over use of pain scales • BPS and CPOT are the most valid and reliable behavioural pain scales • Opioids are first line of treatment of non-neuropathic pain • Non-opioid analgesics to reduce opioid requirements • Gabapentinoids for non-neuropathic pain • Use of regional anaesthesia
B	Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT)	• Performing the trials during day shifts • Link SATs and SBTs • SAT safety screen: 1. No active seizures 2. No alcohol withdrawal 3. No agitation 4. No paralytics 5. No myocardial ischaemia 6. Normal intracranial pressure • SAT Failure: 1. Anxiety, agitation or pain 2. Respiratory rate > 35/min 3. Oxygen saturation <88% 4. Respiratory distress 5. Acute cardiac arrhythmia • If SAT is passed, proceed to SBT. SBT safety screen 1. No agitation 2. Oxygen saturation ≥88% 3. FiO2 ≤ 50% 4. PEEP ≤ 7.5 cm H2O 5. No myocardial ischaemia 6. No vasopressor use 7. Inspiratory efforts • SBT Failure 1. Respiratory rate > 35/min 2. Respiratory rate < 8/min 3. Oxygen saturation < 88% 4. Respiratory distress 5. Mental status change 6. Acute cardiac arrhythmia • If both trials passed, consider extubation • If the trials fail, start sedation and continue ventilatory support
C	Choice of Sedation	• Depth and quality of sedation should be routinely assessed in ICU • The RASS and SAS are the most valid and reliable scales for assessment • Objective measures of brain function as adjuncts to monitor sedation in patients receiving neuromuscular blocking agents • Target the lightest possible level of sedation and/or use daily sedative interruption • Non-benzodiazepines (either propofol or dexmedetomidine) preferred over benzodiazepines (either midazolam or lorazepam)
D	Delirium monitoring and management	• Identify delirium risk factors • Delirium assessment should be routinely done • The CAM-ICU and ICDSC delirium monitoring tools are the most valid and reliable scales to assess delirium • Early mobilization whenever feasible • Promote sleep by controlling light and noise, clustering patient care activities, and decreasing stimuli at night • When sedation is required in delirious patients, non-benzodiazepines preferred over benzodiazepines unless delirium is related to either alcohol or benzodiazepine withdrawal
E	Early mobility and exercise	• Physical and occupational therapy assessment • Coordinate activity with SAT • Progress through 1. Passive transfer in chair 2. Active transfer in chair 3. Cycle ergometer in bed 4. Standing 5. Assisted walk
F	Family engagement and empowerment	• Reorientation, provision of emotional and verbal support • Cognitive stimulation • Participation in mobilization

α2δ subunits of voltage dependent calcium ion channels. They reduce the development of hyperalgesia and central sensitization and are useful adjuncts in the treatment of neuropathic pain.[37] Gabapentinoids are only available in the enteral formulation. Bioavailability of gabapentin is inversely related to the dose. Gabapentin is absorbed in a relatively small part of the duodenum and has a lower bioavailability compared with pregabalin, which is absorbed throughout the small intestine. Hence, gabapentin will be ineffective in patients on jejunal feeding. Side-effects of gabapentinoids include somnolence, dizziness, confusion, convulsions, and ataxia.[3]

A. **Regional Analgesia:**

Regional analgesia techniques (central neuraxial and peripheral nerve blocks),are underused in the management of pain, in critically ill patients. They allow a decrease in the overall use of opioid analgesics and sedatives and reduce the possibility of developing potentially dangerous side effects, associated with the use of these medications. It can play a significant role

in multimodal pain management in ICU patients. A correct indication as well as an appropriate timing for their use is required in order to increase their beneficial effects. With the advent of ultrasound, the quality and safety of the neuraxial, truncal blocks, upper, and lower extremity peripheral nerve blocks even in heavily sedated ICU patients have improved.[38] It can be used for procedural analgesia, post-operative analgesia or analgesia in trauma patients. The readers can find the detailed description of regional anaesthesia or analgesia techniques for ICU patients in another special article in current issue of the journal.

Patient Controlled Analgesia (PCA):

When compared with traditional PRN (prore nata) analgesic regimens, intravenous PCA provides superior postoperative analgesia and improves patient satisfaction. However, the incidence of opioid-related adverse events from intravenous PCA is not different from that of PRN opioids administered intravenously, intramuscularly, or subcutaneously.[39]

The ABCDEF bundle in Critical Care (Table 7):

The ABCDEF bundle represents an evidence-based guide for clinicians to optimize recovery and outcomes in ICU patient.[40] It acts as a checklist of symptoms like pain, agitation and delirium (PAD) in ICU patients. The **ABCDEF** bundle includes:

Assess, Prevent, and Manage Pain,

Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT),

Choice of analgesia and sedation**,**

Delirium: Assess, Prevent and Manage,

Early mobility and Exercise, and

Family engagement and empowerment.

Strategies to improve clinical outcomes:

Daily sedation interruption is associated with clinical benefit in medical ICU patients, but the benefits remain uncertain in those who are alcohol-dependent or not admitted to a medical ICU service. Studies investigating the efficacy and safety of this strategy in surgical, trauma, neurologic, and neurosurgical patients are needed. Protocolized management strategies (e.g., hourly titration) to avoid deep sedation are also associated with clinical benefit, but it remains unclear whether combining sedation protocolization with daily sedative interruption would lead to additional benefits.[41]

Providing analgesia-first sedation for many ICU patients is supported by the high frequency of pain and discomfort as primary causes of agitation and by reports implicating standard hypnotic-based sedative regimens as having negative clinical and quality-of-life outcomes.[9] Promoting sleep in adult ICU patients by optimizing patients' environments, using strategies to control light and noise, clustering patient care activities, and decreasing stimuli at night to protect patients' sleep cycles is recommended. Sleep deprivation impairs tissue repair and cellular immune function and may affect the healing response. In critically ill patients, sleep deprivation may contribute to the development of delirium and increased levels of physiologic stress.[9]

Using an interdisciplinary ICU team approach that includes provider education, preprinted and/or computerized protocols and order forms, and quality ICU rounds checklists to facilitate the use of PAD management guidelines or protocols in ICUs are recommended.[9]

CONCLUSION

Sedation and analgesia play an important role in the management of critically ill patients. Even though, there are currently a wide variety of pharmacological agents available, not a single one can be termed as an ideal drug. Hence, the treatment should be tailored to meet individualized goals to assure better outcome. The ABCDEF bundle helps to guide well-rounded patient care and optimal resource utilization; resulting in more interactive ICU patients with better controlled pain, who can safely participate in higher-order physical and cognitive activities at the earliest point in their critical illness.

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