Update on Sedation in the Critical Care Unit

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Abstract: Recognition and treatment of pain, agitation and anxiety is a challenge in the care of Intensive Care Unit (ICU) patients. Management of pain, agitation and anxiety is necessary for patient comfort, and reduces long term psychological sequelae of ICU admission, time on mechanical ventilation, and length of stay in both the ICU and hospital. ICU providers must be very familiar with the pharmacologic agents available and their appropriate use. Objective, easy to use, reliable and reproducible scales to assess pain and level of sedation are necessary to provide adequate treatment and to avoid untoward effects. Lighter sedation is presently the accepted goal and newer sedatives with safer side effect profiles are being used. Neuromuscular blocking agents continue to be recommended in certain clinical situations and for as short a time period as possible. Delirium is a common problem that must be prevented with early mobilization and promotion of sleep by creating an optimal environment. The use of dexmedetomidine in at-risk mechanically ventilated patients and atypical antipsychotics may be beneficial and reduce the duration of delirium.

Keywords: Analgesia, sedation, delirium, intensive care, critical illness.

INTRODUCTION

Recognition and management of pain, agitation and anxiety is a challenge in the care of Intensive Care Unit (ICU) patients. Providing appropriate analgesia and sedation safely continues to be a topic of debate. It is important for intensive care physicians to know the pharmacologic agents available and their appropriate use in critically ill patients. In the past decade, a number of studies have added to our knowledge in this field and the Society of Critical Care Medicine (SCCM) recently published updated recommendations for the approach to pain, agitation and delirium in the ICU [1]. This discussion will include an overview of the assessment, pharmacology and strategies for analgesia, sedation, neuromuscular blockade and management of delirium in critically ill patients .

PAIN AND ANALGESIA

Incidence of Pain in Critically Ill Patients

Most critically ill patients will experience pain at some point during their ICU stay and identify it as a great source of stress [2, 3]. Pain may be defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [4]." Critically ill patients are unable to communicate or report pain due to various factors including altered level of consciousness, sedation, neuromuscular blockade, mechanical ventilation and language barriers. However, the lack of communication of pain does not negate the presence of pain and must not delay or hinder its adequate treatment.

The incidence of pain has been reported as being 50% or higher in both medical and surgical ICU patients [5, 6]. They experience pain at rest and related to surgery, trauma, burns or cancer. Patients also experience procedural pain, for example during placement of central lines and chest tubes.

In patients who are unable to communicate, the ability to acknowledge, quantify and assess a patient's pain is the foundation of its management. Clinicians must consider patients' behavioral reactions as surrogate measures of pain, such as grimacing and withdrawing to tactile stimuli [7].

The immediate physiologic and psychological effects of pain in ICU patients can have deleterious effects. Pain triggers a stress response leading to an increase in circulating catecholamines that can potentially cause vasoconstriction, impair tissue perfusion, and reduce tissue oxygen partial pressure [11]. Additionally pain contributes to hyperglycemia, lipolysis, impaired wound healing, and suppressed immune defense. It is also important to recognize that unrelieved acute pain may be the greatest risk factor for developing chronic, persistent, often neuropathic pain [12]. Moreover, adequate pain management improves clinical outcomes as pain can preclude patients from participating in their care thereby hindering weaning from mechanical ventilation and early mobilization. There is no doubt that identifying and treating pain should be a priority in ICU patients as it can have effects long term [13].

The negative physiologic and psychological consequences of unrelieved pain in ICU patients are significant and long lasting. Multiple studies have demonstrated that patients who were surveyed shortly after their ICU stay and in longer follow up reported significant pain and discomfort associated with endotracheal intubation (77%) and remembered moderate to severe pain during their ICU stay [8, 9]. In a long term follow-up study of patients

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admitted to the ICU for respiratory distress syndrome, patients who recalled pain and other traumatic situations while in the ICU had a higher incidence of chronic pain (38%), post traumatic stress disorder (PTSD) symptoms (27%), and lower health related quality of life (21%) [10].

Assessment of Pain

All patients in the ICU must be evaluated and routinely monitored for pain. Pain assessment is essential for appropriate treatment and should be part of a comprehensive pain management protocol [2].

The most reliable method to evaluate pain is the patient's ability to self-report. It is helpful to provide patients with tools to help them report the severity of pain. The Numeric Rating Scale (NRS) with visually enlarged horizontal numbers is the most valid and feasible of five pain intensity rating scales tested in over 100 ICU patients (Fig. **1**). The NRS should be used routinely and repeatedly to assess pain in patients that can self-report pain [14]. Although there are no objective pain monitors, there are several bedside assessment tools that rely on patients' behaviors as indicators of pain. For patients that are unable to self-report pain, behavioral assessments should be used routinely to assess pain.

Although there have not been sufficient studies to validate a single behavioral pain assessment tool as the gold standard, several studies have demonstrated that implementing behavioral pain assessment tools improves ICU pain management and improve clinical outcomes. The two most widely used and validated behavioral scales are the Behavioral Pain Scale (BPS) and Critical Care Pain Observation Tool (CPOT).

The BPS evaluates 3 behavioral domains: facial expression, movement of upper limbs and compliance with ventilation in response to movement and painful stimuli. Each behavioral domain is rated from 1 (no response) to 4 (full response), with a composite score ranges from 3 – 12 (Table **1**).

The CPOT is a unidimensional measure designed for use in intubated and non-intubated patients and evaluates four behavioral domains: facial expressions, movements, muscle tension and ventilator compliance. Each component is rated from 0-2 with a composite score ranging from 0 – 8 (Table **2**) [15]. Recent studies have found that a CPOT score greater than 2 had a sensitivity of 86% and a specificity of 78% for predicting significant pain in postoperative ICU adults exposed to a nociceptive procedure [16, 17].

Table 1.   Behavioral Pain Scale [101]

Item	Description	Score
Facial Expression	Relaxed	1
	Partially tightened	2
	Fully tightened	3
	Grimacing	4
Upper Limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with Ventilation	Tolerating movement	1
	Coughing with movement	2
	Fighting with ventilator	3
	Unable to control ventilation	4

Adapted from Payen *et al.* 2001.

There are many other behavioral scales, however further studies are required to address their validity, reliability and to confirm satisfactory psychometric support. Another advantage of the BPS and CPOT scales is that they can easily be implemented in the ICU following short, standardized training sessions [18].

Since there is inconsistent evidence for the validity of vital signs to assess pain, guidelines suggest that vital signs should be used only as a cue for further investigations regarding the presence of pain. Vital signs should not be used alone to assess pain [2].

Treatment of Pain

Opiate analgesics are the primary medications for the treatment of pain in critically ill patients. Other types of analgesics or pain modulating agents can also be used in combination with opiates to reduce the dose of opiates however, the safety profile of these medications have not been thoroughly studied.

The initial choice of medication and the dosing regimen will depend on the pharmacokinetic and pharmacodynamic property of each agent. Opioids, such as fentanyl, morphine, remifentanyl, methadone and hydromorphone are considered first line of treatment. Meperidine should be avoided because of its potential for neurologic toxicity [1]. All opioids when
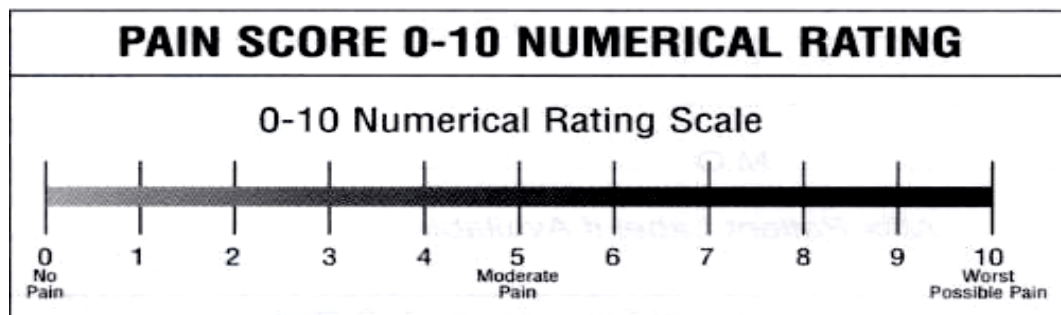

Fig. (1). Numerical Rating Scale [14].

Table 2. Critical Pain Observation Tool (CPOT) [102]

Indicator	Description	Score	
Facial Expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening and levator contractor	Tense	1
	All of the above facial movements plus eyelids tightly closed	Grimacing	2
Body Movements	Does not move at all (does not actually mean absence of pain)	Absence of movements	0
	Slow, cautious movements, touching or rubbing pain site, seeking attention through movements	Protection	1
	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
Muscle Tension (Evaluation of passive flexion and extension of upper extremities)	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2
Compliance with Ventilator (intubated patients) or Vocalization (extubated patients)	Alarms not activated, easy ventilation	Tolerating ventilator o movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2
Total Range			0 - 8

Adapted from Gélinas *et al.* 2006.

titrated are equally effective in managing and controlling pain (Tables **3** and **4**).

Since neuropathic pain is poorly treated with opiates alone, it should be treated with enterally administered gabapentin and carbamazepine in ICU patients with sufficient gastrointestinal absorption and motility [19, 20]. It is important to recognize that both these agents may have significant toxicities and drug interactions. Gabapentin is renally excreted and must be adjusted in patients with renal dysfunction. It frequently causes sedation. Abrupt discontinuation may cause withdrawal and seizures. Carbamazepine is hepatically metabolized and its dose must be adjusted in patients with liver dysfunction. It also has a number of drug interactions as it is an inducer of hepatic CYP enzyme metabolism and must be used with caution in conjunction with agents that are metabolized by this system.

Non Opiate Analgesics, such as non-steroidal anti-inflammatory drugs (NSAID) and acetaminophen provide analgesia via the nonselective, competitive inhibition of cycloxygenase, a critical enzyme in the inflammatory cascade. Administration of NSAIDs may reduce opioid requirements, but these medications have the potential to cause significant side effects, such as gastrointestinal bleeding, platelet dysfunction and renal insufficiency (Tables **5** and **6**) [14].

The decision to administer analgesic medications through enteral, intravenous or transdermal route is an individualized approach in each patient. Intravenous opioids are considered first line to treat non-neuropathic pain in critically ill patients. Enteral route should only be used in patients that have preserved gastrointestinal motility and absorption. The decision to dose analgesics through continuous infusions or intermittent intravenous administration will depend on the frequency and duration of pain as well as the patient's mental status [1]. Transdermal administration of medications is not ideal for ICU patients as absorption may be variable.

Procedure related pain is widely undertreated in critically ill patients. Preemptive analgesic therapy and/or non

Table 3.   **Pharmacology of Opiate Analgesics [1, 14]**

Medication	Equi-Analgesic Dose (mg)		Onset	Half Life	Metabolic Pathway	Active Metabolites	Side Effects and Comments
	IV	PO					
Fentanyl	0.1	n/a	1 - 2 min	2 - 4 hr	Oxidation	None	Rigidity with High Doses Accumulation with Hepatic Failure
Hydromorphone	1.5	7.5	5 - 15 min	2 - 3 hr	Glucoronidation	None	Histamine Release Accumulation with Hepatic or Renal Impairment
Morphine	10	30	5 - 10 min	3 - 4 hr	Glucoronidation	6- and 3- glucoronide metabolite	Histamine Release Accumulation with Hepatic or Renal Impairment
Remifentanyl	n/a	n/a	1 -3 min	3 - 10 min	Hydrolysis by Plasma Esterases	None	No Accumulation in Hepatic or Renal Impairment

Table 4.   **Dosage of Opiate Analgesics [1, 14]**

Medication	Intermittent Dosing	Intravenous Infusion Rate
Fentanyl	0.35 - 0.5 µg/kg IV q 0.5 - 1 hr	0.7 - 10 µg/kg/hr
Hydromorphone	0.2 - 0.6 mg IV q 1 -2 hr	0.5 - 3 mg/hr
Morphine	2 - 4 mg IV q 1 - 2 hr	2 - 30 mg/hr
Remifentanyl	n/a	Loading dose: 1.5 µg/kg IV Maintenance dose: 0.5 - 15 µg/kg/hr IV

PO: by mouth   PR: per rectum   IV: Intravenous   IM: intramuscular.

pharmacological interventions should be administered prior to invasive and potentially painful procedures [1].

All analgesics should be titrated to achieve pain control, while avoiding negative side effects and excessive or inadequate dosing. Combining opioid sparing medications and non-pharmacologic therapies can help decrease the dosage of opiates and the side effects of excessive opioid therapy. Music therapy and relaxation techniques are non-pharmacologic interventions for pain management. These alternate therapies can be opiate sparing and analgesia enhancing. They are low cost, safe and easy to access and should be encouraged as part of a multimodal approach for pain management in the ICU [21].

Neuroaxial or regional analgesic delivery over systemic analgesia has limited indications in the ICU due to lack of evidence in critically ill patients. Postoperative thoracic epidural analgesia/anesthesia is only recommended in patients undergoing abdominal aortic surgery and in those that have traumatic rib fractures [8].

It is important to remember that adequate pain management can be facilitated by identifying and treating pain earlier rather than waiting until pain is more pronounced [2]. Frequent assessments of pain and adequate

and careful titration of analgesia can achieve pain control and improve patient mobilization and experience in the ICU.

SEDATION IN THE INTENSIVE CARE UNIT

Indications for Sedation

Patients in the intensive care unit are in a distressed state secondary to their underlying illness, the invasive interventions they undergo and the stressful environment of the ICU. This often contributes to anxiety and agitation, which may become harmful for the patient. For example it can lead to unplanned extubations or removal of other life-sustaining equipment and can contribute to psychological and cognitive disturbances after the critical illness has resolved.

The first step is identifying whether the agitation is due to a dangerous or life-threatening cause, such as hypoxemia, hypoglycemia, electrolyte abnormalities, hypotension, sepsis or withdrawal from drugs or alcohol [22]. Once these etiologies are corrected, pain and anxiety must be addressed [23]. It is has been shown that with initial appropriate analgesia, often there may be less or no need for sedation [24]. In these cases opiates are generally utilized.

Table 5.   Pharmacokinetics of Non Opiate Analgesics [1, 14]

Medications	Onset	Half-Life	Metabolic Pathway	Active Metabolites	Side Effects and Comments
Acetaminophen (PO) Acetaminophen (PR)	30 - 60 min Variable	2 - 4 hr	Glucoronidation Sulfonation	None	Contraindicated in patients with significant hepatic dysfunction
Acetaminophen (IV)	5 - 10 min	2 hr	Glucoronidation Sulfonation	None	Contraindicated in patients with significant hepatic dysfunction
Ketorolac (IM and IV)	10 min	2.4 -8.6 hr	Hydroxylation Conjugation Renal Excretion	None	Contraindicated in pain management in patients after CABG Avoid in renal dysfunction, bleeding, platelet dysfunction, congestive heart failure, cirrhosis
Ibuprofen (IV)	n/a	2.2 - 2.4 hr	Oxidation	None	Contraindicated in pain management in patients after CABG Avoid in renal dysfunction, gastrointestinal bleed, platelet dysfunction, congestive heart failure, cirrhosis
Ibuprofen (PO)	25 min	1.8 - 2.5 hr	Oxidation	None	Contraindicated in pain management in patients after CABG Avoid in renal dysfunction, gastrointestinal bleed, platelet dysfunction, congestive heart failure, cirrhosis
Gabapentin (PO)	n/a	5 - 7 hr	Renal Excretion	None	Side effects: Sedation, Confusion, Dizziness, Ataxia Adjust dose in renal failure Abrupt discontinuation may be associated with withdrawal seizures
Carbamazepine (PO)	4 - 5 hrs	First 25 - 65 hrs then 12 – 17 hrs	Oxidation	None	Side effects: nystagmus, dizziness, diplopia, lightheadedness lethargy, aplastic anemia, agranulocytosis, Steven Johnson Syndrome (rare) Multiple drug interactions due to hepatic enzyme induction

PO: by mouth   **PR:** per rectum   **IV:** Intravenous   **IM:** intramuscular.

Proper sedation has been shown to help decrease overall oxygen consumption of critically ill mechanically ventilated patients [25]. In mechanically ventilated patients, one analgesic (usually an opiate) and/or one sedative medication is the usual approach. A nonpharmacologic approach can also be used to reduce agitation with frequent reorientation and optimization of sleep cycle before sedatives.

Clinical Pharmacology

Physicians must have a proper knowledge of the pharmacokinetic and pharmacodynamic properties of the various sedative agents available. The two most important pharmacokinetic factors are the volume of distribution (Vd) and clearance [26]. Clearance is often an issue in critically ill patients, as a majority will have renal and/or hepatic

Table 6.   Dosage of Non Opiate Analgesics [1, 14]

Medications	Dosing	Maximal Dosing
Acetaminophen (PO and PR)	325 - 1000 mg every 4 - 6 hours	< 4 g in 24 hours
Acetaminophen (IV)	650 mg IV every 4 hours 1000 mg IV every 6 hours	< 4 g in 24 hours
Ketorolac (IM and IV)	30 mg IV/IM then 15 - 30 mg IV/IM every 6 hours	120 mg/day for 5 days
Ibuprofen (IV)	400 -800 mg every 6 hours Infused over 30 min	3.2 g in 24 hours
Ibuprofen (PO)	400 mg PO every 4 hours	2.4 g in 24 hours
Gabapentin (PO)	Starting Dose: 100 mg PO three times a day Maintenance Dose: 900 - 3600 mg/day in 3 divided doses	
Carbamazepine (PO)	Starting Dose: 100 mg PO three times a day Maintenance Dose: 100 -200 mg every 4 - 6 hours	1200 mg in 24 hours

dysfunction and low flow shock states. Sedatives and analgesics must be adjusted accordingly so as to be safely administered and some agents should be completely avoided. In patients with a history of dependence on alcohol or other drugs, certain agents should be considered to help prevent withdrawal symptoms (Table **7**).

Benzodiazepines are a class of sedative agents that are frequently used in the ICU. They include lorazepam, midazolam and diazepam, in order of decreasing potency.

Their mechanism of action is activation of the gama-aminobutyric acid A (GABA) receptors in the brain with resultant anxiolytic, amnesic, sedative, hypnotic and anticonvulsant effects. They are also often used to treat patients with alcohol or benzodiazepine withdrawal. They do not provide analgesia. All benzodiazepines are metabolized by the liver and excreted in the urine. Therefore they must be utilized with caution in patients with either hepatic or renal dysfunction. Side effects of these agents include respiratory

Table 7.   Clinical Pharmacology of Sedative Medications [1]

Medication	Onset After IV Loading Dose	Half Life	Active Metabolites	Loading Dose (IV)	Maintenance Dose (IV)	Side Effects and Comments
Midazolam	2 - 5 min	3 - 11 hr	Yes	0.01-0.05 mg/kg	0.002-0.1 mg/kg/hr	Respiratory depression, hypotension
						Accumulation of metabolites with renal failure can prolong sedation
Lorazepam	15 - 20 min	8 - 15 hr	None	0.02-0.04 mg/kg	0.01-0.1 mg/kg/hr	Respiratory depression, hypotension
						Propylene glycol toxicity, Nephrotoxicity
Diazepam	2- 5 min	20-120 hr	Yes	5-10 mg	0.03-0.1 mg/kg	Respiratory depression, hypotension, phlebitis
						Accumulation of metabolites with renal failure can prolong sedation
Propofol	1 -2 min	Short-term use= 3-12 hr	None	5 µg/kg/min over 5 min	5-50 µg/kg/min	Pain on injection, hypotension, respiratory depression, hypertriglyceridemia, pancreatitis
		Long-term use= 50 hr				Propofol-related infusion syndrome; deep sedation associated with significantly longer emergence times
Dexmedetomidine	5-10 min	1.8-3.1 hr	None	1 µg/kg over 10 min	0.2-0.7 µg/kg/hr	Bradycardia, hypotension or hypertension with loading dose; Loss of oropharyngeal reflexes

depression and hypotension, especially when used in conjunction with opioids. Elderly patients are more prone to the side effects of benzodiazepines and delirium [27].

Midazolam is short acting with a half-life of 1.5 to 3 hours [28] and water soluble, metabolized in the liver by the CYP450 enzyme system into water soluble renally excreted hydroxylated metabolites [29]. A primary metabolite, 1-hydroxymidazolam glucuronide, has central nervous system depressant effects and in patients with renal failure, may accumulate and cause significant prolonged sedation. It has greater lipid solubility than lorazepam and crosses the blood brain barrier more rapidly. This contributes to its faster onset of action making it useful for rapid infusion, though it has a prolonged effect when administered for longer periods of time. These prolonged effects are especially seen in obese patients and in those with reduced serum albumin levels [29].

Lorazepam has a longer time to onset of action of approximately 5-20 minutes and half-life of 10-20 hours [29]. It is metabolized by hepatic glucoronidation into inactive metabolites that are excreted through the urine. Lorazepam has greater potency and slower clearance than Midazolam, therefore is expected to cause prolonged sedation. However comparative studies of long-term sedation have found minimal difference in time to awakening between the two agents [30, 31]. This may be secondary to the complexity of midazolam's hepatic metabolism and sensitivity to liver dysfunction which is common in critically ill patients and contributes to its increased time to clearance. Though rare, there is a safety concern of propylene glycol toxicity in patients receiving intravenous lorazepam [32, 33]. Propylene glycol is a diluent that increases the solubility of lorazepam and when the agent is infused at higher doses (> 0.1 mg/kg/hour), for prolonged periods of time (>72 hours) especially in patients with renal impairment, the metabolites of propylene glycol can have toxic effects. Lactic acidosis, with a high osmolar state and acute tubular necrosis have been reported. Serum osmolarity should be monitored and discontinuing lorazepam should be considered once the osmolar gap has become greater than 10-15, as this may be indicative of propylene glycol toxicity [34]. If there is suspicion of toxicity, stopping the agent may reverse it, although hemodialysis may be indicated with significant hyperosmolar state.

Propofol is an anesthetic that has been utilized in the ICU for more than two decades. It has an unclear mechanism of action, though it has been theorized that it acts through modulation of neurotransmitter release such as GABA [35]. It is highly lipid soluble and rapidly crosses the blood-brain barrier which results in quick onset and offset of action. It also rapidly distributes to the peripheral tissues with a large volume of distribution. It allows for an easily titratable affect and is often preferred by critical care physicians for patients in whom rapid awakening is important [14]. It has sedative, hypnotic, and amnestic properties. It also reduces intracranial pressure after traumatic brain injury and does so more effectively than opiates [36]. It functions as an anticonvulsant, especially in cases of severe refractory status epilepticus [37]. Adverse effects include hypotension at the time of infusion (especially with large bolus doses) and respiratory depression, which makes it challenging to use in

hypovolemic, critically ill patients. Propofol is stored in a 10% fat emulsion and must be considered as part of caloric intake. It can cause hypertriglyceridemia and pancreatitis, therefore it is recommended that serum lipid panel be monitored every 72 hours. There is also a potential for sepsis as the lipid medium creates a nidus for microorganisms to proliferate. Intravenous infusion sets and the medication bottles should be disposed of every 12 hours [29].

Propofol related infusion syndrome (PRIS) was initially described in 1992 in a case series of pediatric patients who developed metabolic acidosis and progressive myocardial failure and death while receiving high doses of propofol [38]. Depending on the case series and definition, PRIS has a mortality of greater than 80% [39]. Manifestations include rhabdomyolysis, myocardial infarction, bradyarrhythmias, acute renal failure, severe metabolic acidosis, hypotension and cardiac arrest [39-41]. Risk factors include high doses of infusion (>80 mcg/kg/min), prolonged infusion (>48 hours), and concomitant use of vasopressors or glucocorticoids [43, 44]. Recommendations are to maintain infusions at less than 4-5 mg/kg/hr.

Dexmedetomidine was approved in 1999 by the Food and Drug Administration (FDA) as a sedative-hypnotic [42]. It is a centrally acting α_2-agonist that inhibits norepinephrine release. It is a sedative and opioid sparing analgesic but does not have antiepileptic effect and differs from most other sedatives in that it does not cause respiratory depression. Overall, patients are more easily arousable while on this medication as compared to other sedatives. It is the only sedative in the US approved for sedation in non-intubated patients. Onset of sedation occurs within 15 minutes peaks at 1 hour, and is widely distributed throughout the peripheral tissues [43]. It is metabolized by the liver and in patients with normal liver function has a half –life of 3 hours [44]. Side effects include hypotension or hypertension and bradycardia with rapid infusions. Although it does not cause respiratory depression, it can cause loss of oropharyngeal muscle tone which may cause airway obstruction in non-intubated patients [1]. Dexmedetomidine is currently approved for short term sedation of <24 hours at a maximal dose of 0.7 mcg/kg/hr, however a number of recent studies have demonstrated safe administration for more the 24 hours and at higher doses of up to 1.5 mcg/kg/hr [45-47]. Additional studies of safety are needed and comparison to other agents that are used for prolonged sedation are discussed below.

Choosing a Sedative agent

There has been debate over which agents to use as first line. The recommendations by the SCCM have changed in the past decade with a shift from benzodiazepines towards utilizing non-benzodiazepines, such as propofol or dexmedetomidine, initially. The exception to this is an indication for benzodiazepines, such as alcohol or benzodiazepine withdrawal. Multiple studies have been conducted on prolonged benzodiazepine use and clinical outcomes. Many have shown adverse outcomes with this approach such as prolonged time on mechanical ventilator, difficulty weaning, increased rates of delirium and increased ICU length of stay [48-50]. The results of other studies have been mixed [51, 52]. A meta-analysis by the SCCM of six

trials showed that benzodiazepines may increase ICU LOS by about 0.5 days, with a trend towards longer time spent on mechanical ventilation. However, no difference in mortality was demonstrated [1].

There have been few studies comparing propofol versus dexmedetomidine [53-55]. Small trials found no difference in length of mechanical ventilation, ICU length of stay or mortality. Further studies in a larger, multicenter setting should be conducted. Current clinical practice is to utilize the agents interchangeably, though cost is an issue that must be considered. For example, a 50 mL vial of Propofol at a concentration of 10 mg/mL costs $3.70 while a 2 mL vial of Precedex at a concentration of 100 mcg/mL costs $73.22. Approximate drug costs at equivalent therapeutic doses per 24 hours for a 70 kg person would be as follows: Versed at a concentration of 1 mg/ml, average dose of 4 mg/hr would amount to a total of 96 mg/day and cost $32. For Propofol if the assumed average dose is 20mcg/kg/min then a 500 mg bag will provide 20 hours and need two 500 mg bags a day and the cost will be $7.42 while Precedex, if it is assumed that the average dose is 0.5 mcg/kg/hr then approximately 840 mcg/day will be used. As one bag of Precedex contains 200 mcg, about 4 bags will be needed per day and the cost will be $307.50.

Presently dexmedetomidine is only approved for short term sedation of <24 hours with a maximal dose of 0.7 mcg/kg/hr. There have been additional studies showing safety for longer periods of time and at higher doses. Dexmedetomidine has also been compared to other agents. In a recently published noninferiority trial by Jakob and colleagues [55], dexmedetomidine was compared separately to midazolam and propofol in ICU patients receiving prolonged mechanical ventilation. Dexmedetomidine was found not to be inferior in maintaining appropriate levels of sedation. It also was shown to decrease the amount of time spent on the ventilator as compared to midazolam and allowed the patients to better communicate when compared to both propofol and midazolam. There were however, more adverse events with dexmedetomidine including hypotension and bradycardia, and mixed results for rates of delirium. Overall ICU and hospital length of stay were similar.

The choice of sedative should be based on clinical scenario, indication for sedation, the pharmacology of the drug, its potential side effects and cost [1].

Strategies for Sedation

A number of studies have shown that lighter sedation has many benefits in both intubated and non-intubated patients. Lighter levels of sedation have been associated with improved clinical outcomes: decreased time of mechanical ventilation with faster weaning, decreased incidence of delirium and long-term cognitive dysfunction, decreased sequelae of mechanical ventilation such as ventilator associated pneumonia, and shorter length of ICU and hospital stay [56-58].

A recent large multicenter study by Shehabi and colleagues examined the effect of the depth of early sedation within the first few to 48 hours of mechanically ventilated patients on mortality and time to extubation [59]. More than 50% of patients were deeply sedated (as documented by

Richmond Agitation and Sedation Score) in the first hours after intubation and had resultant increased time to extubation, increased short term (within 30 days) and long term (6 months) mortality as well as rates of delirium. This study highlights the importance of lighter sedation from the onset of treatment and its affect on outcome. It calls for the early use of protocols and close monitoring in all patients being sedated.

After critical illness with respiratory failure, it has also been shown that patients are at increased risk for Post Traumatic Stress disorder (PTSD) and this may be related to sedation use [60]. Studies comparing the effects of lighter versus deeper sedation on psychological outcomes have had mixed results. Treggiari and colleagues showed that there was low incidence of adverse psychological outcomes with light sedation [61] and Kress with colleagues [62] showed that daily sedation interruption had similar results. However a study by Samuelson and colleagues [63] reported that periods of wakefulness were associated with recall of stressful ICU memories. Lighter levels of sedation have also been associated with an increase in physiologic stress response yet the significance of this is unclear, as there is no clear association with clinical outcomes such as myocardial infarction [64, 65].

The SCCM consensus is that the overall benefits of lighter sedation outweigh the risk. This approach is recommended in the majority of ICU patients, with the exception of difficult to ventilate patients with ARDS and severe asthma in which deeper sedation is necessitated for ventilator synchrony. Lighter sedation can be incorporated into daily practice with protocol driven sedation and daily interruption of sedation administration in mechanically ventilated patients [60].

Both protocol driven sedation and daily interruption of sedation have been associated with decreased number of mechanical ventilator days and decreased ICU and hospital length of stay. A study of nurse-directed drug titration algorithms versus traditional non-protocolized sedation concluded that sedation protocols can reduce the duration of mechanical ventilation, intensive care unit and hospital lengths of stay, and significantly decreased tracheostomy rates for patients with acute respiratory failure [60].

In a landmark trial by Kress and colleagues, daily interruptions of sedation infusions decreased the total amount of benzodiazepine infused, number of days of mechanical ventilation, ICU length of stay and allowed for better assessment of neurologic status [57]. Although there were criticisms to this single-centered trial, it nevertheless began the trend towards protocolized sedation with daily interruptions of sedation. Girard and colleagues compared protocolized sedation paired with spontaneous awakening trials (SATs) (daily interruption of sedatives) with spontaneous breathing trials (SBTS) versus protocolized sedation combined with SBTs [56]. This group found that patients with interrupted sedation and SBT allowed for better evaluation of neurologic status, had more ventilator free days, and decreased ICU and hospital length of stay. Multiple studies followed with mixed results [66-68] however its use in ICUs has shown to be inconsistent [69].

A large multicenter, international study by Mehta and colleagues examined patients who received protocolized sedation titration that targeted light sedation and compared those who received daily sedation interruptions with those who did not [70]. This study did not show improvement in clinical outcomes with daily sedation interruptions and those patients actually required increased amounts of opioids and benzodiazepines. Nursing workload was self-perceived as increased as well. This study was the first to be conducted in both medical and surgical ICU patients and was more representative of daily realities of ICU physicians, rather than research personnel, managing patients according to the study protocol in this large trial that included 16 ICUs in both the US and Canada. The results of this study emphasize that light sedation and sedation protocols should be part of daily ICU care, however the utility of daily spontaneous breathing trials remains unclear.

Monitoring Sedation: Utilizing Sedation Scales

Sedation scales and protocols have been designed to minimize sedative use and have been shown to improve clinical outcomes. The scales should be easy to use, can be applied on a daily basis and use an interdisciplinary approach [58].

Multiple sedation scales have been studied, though they vary in their degree of validity and the psychometric properties they test. The SCCM in its current recommendations compares ten different scales and comments on their usefulness and validity. The Ramsay Sedation Scale (RSS) has been widely used to monitor sedation [71] however does not account for different levels of agitation. The Riker Sedation-Agitation Scale (SAS) was built on RSS and better delineates levels of agitation (Table **8**) [72]. The two most commonly utilized tools are the Richmond Agitation-Sedation Scale (RASS) and SAS. The RASS combines levels of sedation or agitation with cognition and length of response (Table **9**) [73, 74]. Scores range from +4 which is combative to -5 which correlates to unarousable to voice or physical stimulation. In uncomplicated critically ill patients, sedation should not be less than -2. Patients with severe illness who required deeper sedation should target -3 to -4 [26]. RASS and SAS have been shown to have the highest degree of inter-rater reliability and were able to discriminate sedation levels in different clinical situations [75, 76]. Both RASS and SAS also have a high correlation of sedation scores when comparing these scales with results of electroencephalogram (EEG) or bispectral index (BSI) [77]. Thus either RASS or SAS are recommended sedation scales for daily use in the ICU.

Other scales such as the Adaptation to the Intensive Care Environment (ATICE), Minnesota Sedation Assessment Tool (MSAT), and Vancouver Interaction and Calmness Scale (VICS) are considered to be moderately valid and reliable and the SCCM suggests that these scales need further testing to better elucidate their use.

Table 8. **Riker Sedation Agitation Scale [72]**

Term	Description	Score
Dangerous agitation	Pulling at ET tube, trying to remove catheters, climbing over bed rail, striking at the staff, thrashing from side to side	7
Very agitated	Does not calm, despite frequent verbal reminding of limits; required physical restraints, biting ET tube	6
Agitated	Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions	5
Calm and cooperative	Calm, awakes easily, follows commands	4
Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands	3
Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously	2
Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands	1

Adapted from Riker, Pichard, Fraser 1999.

Table 9. **The Richmond Agitation-Sedation Scale [73]**

Term	Description	Score
Combative	Overtly combative or violent; imminent danger to self	+4
Very agitated	Pulls on or removes tubes or catheters or has aggressive behavior toward staff	+3
Agitated	Frequent nonpurposeful movement or patient-ventilator dyssynchrony	+2
Restless	Anxious or apprehensive but movements not aggressive or vigorous	+1
Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice	-1
Light sedation	Briefly (<10 seconds) awakens with eye contact to voice	-2
Moderate sedation	Any movement (but no eye contact) to voice	-3
Deep sedation	No response to voice, but any movement to physical stimulation	-4
Unarousable	No response to voice or physical stimulation	-5

Adapted from Sessler, Gosnell, Grap, *et al*. 2002.

A number of objective neurologic measures have been investigated for use in monitoring sedation. The results comparing objective and subjective scales are conflicting, with some studies concluding that objective measures be used in conjunction with subjective sedation scales [78-80]. Other studies conclude that objective scores only distinguish between light and deep sedation but do not correlate with sedation scores [81, 82]. In patients who are paralyzed with neuromuscular blockers or with neurologic impairment in which subjective measures are unobtainable, objective measures should be used with RASS and SAS. Such methods include Bispectral index (BSI) and Patient State Index (PSI) which analyze EEG data to estimate depth of sedation [78], as well as Auditory evoked potentials (AEPs), Narcotrend Index (NI) or state entropy (SE).

The SCCM does not recommend that objective measures of brain function be used in noncomatose patients as the primary method of monitoring depth of sedation. In these patients, subjective sedation scores such as RASS or SAS should be used. EEG can be used to monitor patients for potential nonconvulsive seizure activity.

NEUROMUSCULAR BLOCKADE

Indications

Neuromuscular blocking agents (NMBA) paralyze muscles by blocking the transmission of nerve impulses at the myoneural junction. Other than for induction at the time of endotracheal intubation extended use of NMBA is usually a choice of last resort in most ICUs because of concern of long term muscle weakness with prolonged use of NMBAs. NMBA are helpful in managing ventilation by preventing respiratory dyssynchrony. It is thought that stopping spontaneous ventilatory efforts and muscle movement improves gas exchange and decreases oxygen consumption [83]. They are also useful in managing increased intracranial pressure in patients that are coughing or require frequent tracheal suctioning while intubated [84]. NMBAs have also been used to treat muscle spasm in tetanus, drug overdose, neuroleptic malignant syndrome and seizures [85].

In a study published in 2010 Papazian *et al.* showed that early administration of a particular NMBA (cisatracurium) in patients with severe acute respiratory distress syndrome (ARDS) increased time off the ventilator and decreased incidence of barotrauma without increasing muscle weakness [86]. They also showed that in patients with PaO_2/FiO_2 ratio of 120 or less the 90 day survival was improved. It is not known if these benefits are secondary only to cisatracurium or can be extended across the whole class of drugs. It is thought that by paralyzing the respiratory muscles, NMBA reduce the risk of ventilator induced lung injury. Systemically the use of NMBA decreases oxygen consumption by paralyzing muscles thereby reducing cardiac output and increasing the partial pressure of oxygen. In addition there is some evidence that changes in respiratory mechanics can reduce the release of cytokines minimizing further organ damage [87].

There is insufficient evidence to establish if patients with severe ARDS are actually managed better by using NMBAs, however data from case reports and small clinical trials suggest that there may be a benefit of using NMBAs in these

situations when all other resorts have been exhausted [88]. It must be kept in mind however, prior to their initiation, all patients must be adequately sedated and their pain must be controlled.

Pharmacologic Agents

There are depolarizing and non-depolarizing NMBAs. Depolarizing NMBAs resemble acetylcholine and bind and activate acetylcholine receptors. Non-depolarizing NMBAs also bind to acetylcholine receptors but don't activate them and therefore function as competitive antagonists. Succinylcholine is the only depolarizing NMBA and it is not used for long term blockade.

There are several amino steroidal and benzylisoquolinium compounds available to provide adequate neuromuscular blockade (Table **10**) [86]. Most patients can be managed effectively with pancuronium, unless they have a contraindication for vagolysis, since pancuronium is known to cause vagolysis and increase heart rate. Additionally, cisatracurium or atracurium is recommended in patients with significant hepatic and renal disease because of their unique metabolism [88].

Monitoring Neuromuscular Blockade

It is recommended that all patients receiving NMBAs should be assessed clinically and by Train of Four (TOF) monitoring. TOF measures the degree of neuromuscular blockade using a peripheral nerve stimulator, with a goal of adjusting the degree of neuromuscular blockade to achieve one or two twitches [88].

Complications of Neuromuscular Blockade

One of the most common complications of neuromuscular blockade is skeletal muscle weakness. Clinically it manifests as prolonged recovery from NMBAs and as acute quadriplegic myopathy syndrome. As interactions with other drugs such as corticosteroids can potentiate the depth of motor blockade, NMBAs should be discontinued as soon as possible.

Myositis ossificans, corneal ulcers and deep venous thrombosis can also develop in patients that are treated with NMBAs for prolonged periods of time. Latest guidelines recommend prophylactic eye care, early physical therapy and DVT prophylaxis in all patients receiving NMBAs [88].

Tachyphylaxis to NMBAs will develop within a few days due to changes in the acetylcholine receptors. Therefore if there is continual indication for NMDA, it is recommended to change the agent being used and this often results in adequate neuromuscular blockade [88].

DELIRIUM

Incidence and Impact

Delirium is an acute confusional state, defined by fluctuating mental status, inattention and disorganized thinking with altered level of consciousness and cognition. Patients with delirium can have fluctuating levels of mental status; they can alternate between calm, lethargic or agitated [89]. Presence of delirium has been associated with increased mortality, increased length of hospitalization, increased cost

Table 10.   Pharmacology of Neuromuscular Receptor Blockers [86]

Medication	Duration of Action	Bolus Dose	Maintenance Dose	
			Intermittent Injection	Continuous Infusion
Aminoesteroidal Compounds				
Vecuronium	Intermediate	0.08 - 0.1 mg/kg	0.1 - 0.2 mg/kg	0.8 - 1.2 µg/kg/min
Rocuronium	Intermediate	0.6 - 1 mg/kg	0.1 - 0.2 mg/kg	8 - 12 µg/kg/min
Pancuronium	Long	0.05 - 0.1 mg/kg	0.05 - 0.1 mg/kg	1 - 2 µg/kg/min
Pipercuronium	Long	0.085 - 0.1 mg/kg	0.01 - 0.015 mg/kg	0.5 - 2 µg/kg/min
Benzylisoquinolinium Compounds				
Mivacurium	Short	0.15 - 0.25 mg/kg	0.15 - 0.25 mg/kg	9 - 10 µg/kg/min
Atracururium	Intermediate	0.4 - 0.5 mg/kg	0.08 - 0.1 mg/kg	4 - 12 µg/kg/min
Cisatracurium	Intermediate	0.1 - 0.2 mg/kg	0.03 mg/kg	1 - 3 µg/kg/min
D-tubocuranine	Long	0.1 - 0.2 mg/kg	0.04 - 0.06 mg/kg	2 - 3 µg/kg/min
Doxacurium	Long	0.05 - 0.1 mg/kg	n/a	0.3 - 0.5 µg/kg/min

Adapted from Murray M, Cowan J, Block H, *et al.* 2002.

of care and development of post-ICU cognitive impairment [90-93].

There is a high incidence of delirium in the intensive care unit and it is common in both mechanically ventilated and non-ventilated patients. In a study of older patients being admitted to the ICU, 30% presented with delirium, with 80% developing delirium during their overall hospital and ICU stay [94].

Monitoring for delirium in the ICU is feasible and should be routinely done. The Confusion Assessment Method for the ICU (CAM-ICU) [95] (Table **11**) and the Intensive Care Delirium Screening Checklist (ICDSC) [96] are the most studied and reliable tools in adult patients to monitor for delirium [1].

Risk Factors

Patients with preexisting dementia, hypertension, alcoholism and high severity of illness on admission are at increased risk for developing delirium. In a study by Ouimet

and colleagues, it was found that sedative induced coma and multifactorial coma (coma secondary to both underlying medical illness and sedation) are significantly associated with the development of delirium, but medical coma (coma solely from medical illness such as anoxic brain injury or stroke) is not [97]. There is insufficient evidence to correlate the use of opiates and propofol with the development of delirium however benzodiazepine use has been associated may be a risk factor for developing delirium in the ICU [1].

Prevention and Treatment of Delirium

The approach to prevention and treatment of delirium is multifaceted and may utilize a combination of nonpharmacologic and pharmacologic methods. Risk-factor reduction is an important initial step. This includes decreasing iatrogenic factors, such as avoidance of excessive sedative and opiate medications as well as physical restraints. Early mobilization and frequent orientation can be therapeutic. Modification of the ICU environment by

Table 11.   CAM-ICU Assessment [93]

Feature	Assessment
1. Acute onset and fluctuating course	A. Is there evidence of an acute change in mental status from the baseline? B. Or, did the (abnormal) behavior fluctuate during the past 24 hours, tending to come and go or increase and decrease in severity as evidence by fluctuations on the Richmond Agitation Sedation Scale (RASS) or the Glasgow Coma Scale?
2. Inattention	Did the patient have difficulty focusing attention as evidenced by a score of less than 8 correct answers on either the visual or auditory components of the Attention Screening Examination (ASE)?
3. Disorganized thinking	Is there evidence of disorganized or incoherent thinking as evidence by incorrect answers to 3 or more of the 4 questions and inability to follow the commands?
4. Altered level of consciousness	Is the patient's level of consciousness anything other than alert, such as being vigilant or lethargic or in a stupor of coma?
Overall CAM-ICU assessment: the diagnosis of delirium requires the presence of features 1 and 2 and either features 3 or 4)	

Adapted from Ely, EW, Inouye SK, Bernard GR 2001.

minimizing the amount of noise and light exposure can help maintain normal circadian rhythm and allow for restorative sleep [1]. A number of studies have been conducted in non-ICU patients with this approach, there have not been large studies in ICU patients.

Once delirium has occurred, it is often treated with a number of antipsychotics. There has not been, however, a large, well powered, randomized, placebo controlled trial that establishes the safest and most efficacious agent to use. However, multiple critical care societies support the use of antipsychotics in the treatment of delirium. The most commonly used agents include haloperidol or atypical antipsychotics, such as olanzapine, quetiapine and ziprasidone. While atypical antipsychotics may reduce the duration of delirium, haloperidol has not been proven to do the same [98]. Antipsychotics should be used with caution in patients with significant risk for torsades de pointes, prolonged QT interval or history of arrhythmias due to increased risk for arrhythmias [99].

ICU patients at risk for delirium may benefit from sedation with dexmedetomidine as it reduces the incidence and duration of delirium in this group of patients [46, 100]. This however does not apply to delirium that is associated with ethanol or benzodiazepine withdrawal.

CONCLUSION

Management of pain, agitation and anxiety is important not only for patient comfort but also to reduce long term psychological sequelae of ICU admission, time on mechanical ventilation, and both ICU and hospital length of stay. Critical care physicians have changed their management of analgesia and sedation over the years to an interdisciplinary approach, with the goal of providing pain, agitation and anxiety relief in the safest and most effective manner possible. Objective, easy to use, reliable and reproducible scales to assess pain and level of sedation are necessary to provide adequate treatment and to avoid the untoward effects. Overall lighter sedation should be the goal and newer sedative medications with safer side effect profiles are being used. Neuromuscular blockading agents should only be used in certain clinical situations and for as short a time period as possible. Delirium is a common problem encountered in the ICU and it is key to try and prevent delirium with early mobilization and promotion of sleep by creating an optimal environment. The use of dexmedetomidine in at-risk mechanically ventilated patients and atypical antipsychotics may be beneficial and reduce the duration of delirium.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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