Maintaining comfort, cognitive function, and mobility in surgical intensive care unit patients

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Submitted: July 5, 2013, Revised: March 25, 2014, Accepted: March 31, 2014.
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DOI: 10.1097/TA.0000000000000282

CONTEXT OF THE DISCUSSION

As the quality of care in the intensive care unit (ICU) improves, the number of patients surviving to discharge increases. With this—and the need to be conscious of appropriate resource use—comes a shift in priorities in ICU care. No longer is it sufficient to merely assess mortality and discharge from the ICU. Instead, the focus has shifted to assessing and minimizing daily suffering of the critically ill ICU patient and the long-term impact of ICU admission.[1] Although minimizing suffering is certainly a laudable goal, excessive, open-ended analgesic, and sedative administration can result in significant ICU resource use and long-term addiction and neurologic impairment. This so-called "epidemic of the impact of critical illness" or cognitive impairment associated with ICU admission can persist after ICU and even hospital discharge with significant long-term impact on the patient and family.[1]

This review will focus on the current evidence for the management of pain, sedation, and mobility in the ICU. This year, the Society of Critical Care Medicine (SCCM) published an exhaustive set of clinical practice guidelines for the management of pain, agitation, and delirium in the ICU patient.[2] Interestingly, only one of its 21 authors is a surgical intensivist. The focus of this article will be the unique issues of maintaining comfort, cognitive function, and mobility in surgical ICU (SICU) patients.

DEFINING THE PROBLEM: PAIN IN THE SICU

Pain is extremely common in SICU patients, with significant pain reported by more than 55% of patients.[3,4] Of concern, the majority of patients report remembering pain during their ICU stay,[5] and the pain experience seems to be the strongest predictor of the development of post-ICU posttraumatic stress disorder.[6–8]

Pain experienced in the SICU is multifactorial, related to patient disease—either injury or surgical procedures and iatrogenic causes including ICU procedures, positioning, movement, and routine ICU care such as endotracheal tube suctioning. Uncontrolled pain has many negative consequences and may lead to increased morbidity. This is mediated through many pathways. For example, catecholamine release in response to pain may lead to reduced tissue perfusion due to small vessel vasoconstriction.[9] Hypermetabolism associated with pain has been associated with hyperglycemia[10] and increased catabolism and confers an increased infectious risk.[11–13]

An increased awareness of the negative consequences of pain has led many to study the best way to assess for pain in the ICU. The best method to screen for pain depends on the underlying disease process and the level of sedation required or achieved. Screening for pain has been shown to be associated with improved outcomes, including decreased length of ventilator support and ICU stay.[14]

TOOLS TO ASSESS PAIN IN SICU PATIENTS

Visual-analog scales or numerical rating scales are perhaps the most intuitive and historically most commonly used but are subject to intraobserver variation and contextual misinterpretation.[15] They are less likely to be effective in the noncommunicative ICU patient[16] and may be considered largely of historical interest. Nonetheless, as will be shown later, with an emphasis on allowing patients to be more awake and communicative in the ICU, there is nothing as simple and effective in determining whether a patient does or does not have pain than asking him or her.

The behavioral pain scale (BPS) was first described by Payen et al.[17] in 2001. This scale assesses facial expression, upper limb movement and position, and compliance with ventilation and has been used in both conscious and sedated patients.[18–20] A score is assigned ranging from 3 to 12, with a score of 5 or greater suggested as an indicator of significant pain.[17,21]

The Critical-Care Pain Observation Tool (CPOT) was first described by Gelinas et al.[22] in 2006. This tool assesses facial expression, body movements, muscle tension, and compliance with the ventilator or vocalization, and scores of 0 to 8 are awarded. Score greater than 2 is 86% sensitive and 78% specific for the prediction of significant pain in ICU patients.[23] The SCCM guidelines support using either of these two tools in assessment with a "B" level of evidence.[2] Patients unique to the SICU seem to be well-served by the use of these scales. The BPS is one of the recommended tools for the assessment of patients with disordered level of consciousness, such as traumatic brain injury.[24] The CPOT has been shown to be an accurate tool for pain assessment specifically after cardiac surgery.[22]

DEFINING THE PROBLEM: AGITATION AND THE NEED FOR SEDATION

Unlike pain management, many SICU patients do not need routine sedation. In fact, in most patients, adequate analgesia will provide sufficient comfort to reduce, if not eliminate, the need for strictly sedation medications. This concept of analgesia-based sedation, or analgosedation, has been shown to be effective and is gaining acceptance in many ICUs.[23] Analgosedation has been assessed as an effective tool in patients after orthopedic, general, and cardiac surgery and after neurologic injury.[25]

Finally, for patients felt clinically to require sedation, the introduction of sedating medications should be coupled with a search for correctable factors leading to agitation. These include pain, delirium, hypoxemia, hypoglycemia, hypotension, drug or alcohol withdrawal, and excess stimulation. Patient-ventilator dyssynchrony has been cited by many as a reason for patients to require sedation in the SICU.[26] Dyssynchrony is a complex entity, involving patient factors and ventilator factors, which is associated with respiratory muscle injury and potentially prolonged mechanical ventilation.[27] It is important to recognize that, while increasing sedation is often an effective means of reducing patient-ventilator dyssynchrony, attempts must be made to use a more palatable ventilator strategy instead of simply increasing sedation indefinitely.[28]

TOOLS TO ASSESS AGITATION IN THE ICU

Many methods to monitor the need for sedation have been described; however, we will only highlight two well-studied scales that have proven useful in the ICU. The first is the Richmond Agitation-Sedation Scale (Table 1A). This scale was initially validated by Sessler et al.[29] in 2002. It is assessed by patient observation and subsequent interaction if the patient is not alert, and a score ranging from unarousable (−5) to combative (+4) is assigned.[29] This scale has been validated in

TABLE 1. The Richmond Agitation-Sedation Scale[29] and the Sedation-Agitation Scale[33]

A. Richmond Agitation-Sedation Scale

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on/removes tubes or catheters; aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement; patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but without aggressive or vigorous movements
0	Alert and calm	
−1	Drowsy	Not fully alert but with >10 s awakening with eye contact to voice
−2	Light sedation	<10 s awakening with eye contact to voice
−3	Moderate sedation	Any movement without eye contact to voice
−4	Deep sedation	No response to voice but movement with physical stimulation
−5	Unarousable	No response to voice or physical stimulation

B. Sedation-Agitation Scale

Score	Term	Description
7	Dangerous agitation	Pulling at Endotracheal tube (ETT) and catheter, thrashing, attempting to climb out of bed
6	Very agitated	Unable to calm with verbal reminding, requires physical restraints
5	Agitated	Anxious, attempts to sit up, but redirectable with verbal instructions
4	Calm, cooperative	Easily arousable, follows commands
3	Sedated	Difficult to arouse, awakens but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but not communicative or following commands
1	Unarousable	Minimal/absent response to noxious stimuli, does not follow commands

both medical ICU and SICU patients and for repeated measurements over time.[29–32]

The second scale is the Sedation-Agitation Scale (Table 1B), initially described by Riker et al.[33] and validated in a population of patients after cardiac surgery. This scale ranges from 1 (unarousable) to 7 (dangerous agitation). It has been shown to be reliable and reproducible when administered by ICU nurses.[34,35] The SCCM guidelines advocate using either of these two scales over numerous others with a "B" level of evidence owing to their high interrater reliability, validation, discrimination, and feasibility.[2] While these two scales provide the basis for the majority of sedation assessment completed in the ICU, it is important to recognize that, if a patient is receiving neuromuscular blocking agents, additional objective measures may be required. These include auditory evoked potentials, bispectral index, narcotrend index, and state entropy, a complete description of which is beyond the scope of this review.

The importance of regular assessment of sedation needs and attempts to reduce the use of sedating medication wherever possible cannot be emphasized strongly enough. Much has been written recently on the impact of protocols for daily interruptions of sedation if clinically appropriate.[36–39] These daily "sedation vacations" should, wherever possible, be combined with attempts to liberate the patient from the ventilator, starting with a spontaneous breathing trial. The use of such protocols has been shown to improve outcomes in the SICU, including a decreased duration of mechanical ventilation, decreased lengths of stay in both the ICU and hospital, and improved neurocognitive incomes including fewer instances of delirium and long-term cognitive dysfunction.[40–43] Specifically in trauma patients, Robinson et al.[42] in 2008 published the results of their used of an analgesia-delirium-sedation protocol and demonstrated a reduction in the length of both mechanical ventilation and hospital stay. A similar view was supported in a review by Banerjee et al.[44] in 2011. Of interest, the most recent publication on this topic, a multicenter randomized controlled trial (RCT) published by the Canadian Critical Care Trials Group compared patients who received protocolized sedation to those who received protocolized sedation with daily sedation interruptions in a mixed ICU population.[45] This study demonstrated no significant difference in the duration of mechanical ventilation or the length of ICU stay between groups, suggesting that a daily interruption of sedation may not be required. Of note however, the protocolized sedation used in this study was aimed to achieve only light sedation, potentially contributing to the conflicting results seen between this and other studies on this topic.

DEFINING THE PROBLEM: DELIRIUM IN THE SICU

Delirium is defined as an acute alteration of attention and cognition with waxing and waning disturbance of consciousness.[46] The complete diagnostic criteria, as outlined in the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-IV-TR), can be found in Figure 1*A*. Delirium is, unfortunately, a common problem in the ICU, reported to occur in up to 60% to 80% of ICU patients.[1,47–49] Not all ICU-associated delirium is acquired, and an understanding of delirium present at the time of ICU admission is essential for effective identification and management.

Multiple pathophysiologic theories as to why delirium develops in the ICU exist. Most can be broken down to anatomic or physiologic theories. Anatomic theories include the presence of discrete anatomic lesions such as ischemia or hemorrhage, diffuse leukoencephalopathy, and an increase in permeability of the blood-brain barrier. Physiologic theories include alterations in neurotransmitters, inflammatory mediators, and hormones. Neurotransmitters previously implicated in

A

- Disturbance in consciousness manifested by a reduced clarity of awareness of the environment
- Accompanying changes in cognition, which may include memory impairment, disorientation, or language disturbance
- Development of a perceptual disturbance, which may include misinterpretations, illusions, or hallucinations
- The disturbance develops over a short period of time and tends to fluctuate during the course of the day. There is evidence from the history, physical examination, or laboratory tests that the delirium is a direct physiologic consequence of a general medical condition, substance intoxication or withdrawal, use of a medication, toxin exposure, or a combination of these factors

B

The diagnosis of delirium is made based on:

Feature 1: Acute mental status changes or fluctuating course
- Acute mental status change from baseline
- Fluctuating over the preceding 24 hours

AND

Feature 2: Inattention
- Difficulty focusing attention
- Reduced ability to shift attention

In combination with either

Feature 3: Disorganized thinking
- Disorganized or incoherent thinking
- Inability to follow questions or commands

OR

Feature 4: Altered level of consciousness
- Vigilant or hyper-alert
- Lethargic
- Stupor
- Coma

Figure 1. *A,* Diagnosis of delirium: DSM Criteria for the diagnosis of delirium.[116] *B,* Diagnosis of delirium: Components of the Confusion Assessment Method for the ICU.[46] *C,* Diagnosis of delirium: ICDSC.[117]

the development of delirium include acetylcholine, dopamine, serotonin, and γ-aminobutyric acid. Inflammatory mediators, including cytokines, have been postulated to impact the brain owing to pathologic increases in blood-brain barrier permeability. Hormones play an important role in the aberrant stress response. In patients predisposed by age or preexisting neurologic disease, the neurotoxic effects of corticosteroids may be implicated in the development of delirium.

Perhaps, the most important pathophysiologic theories however may be considered patient and disease factors. Preexisting disease states such as dementia, alcoholism, and hypertension put patients at risk for the development of delirium. The event precipitating ICU admission also plays a role, with patients admitted with neurologic deficits or higher disease severity also more prone to delirium. The ICU environment, with loss of normal sleep-wake cycles, prolonged immobilization, and the use of chemical and physical restraints, can worsen and even create delirium states. Finally, therapeutics frequently used in the ICU setting, especially the use of opioid analgesics and benzodiazapines, have been associated with delirium. Specifically among SICU patients, numerous risk factors for delirium have been identified. These include older age, a greater number of comorbidities, premorbid alcohol use, more severe illness, admission after emergency surgery or trauma, the need for blood transfusion, the presence of infection, and the use of benzodiazepines and opioids.[50–54] Although thought to occur most commonly among intubated patients, the incidence of delirium even among nonintubated patients in the SICU is nearly 10%.[50] It is important to recognize the prevalence of these risk factors in the ICU setting, and as such, when delirium results, it is often multifactorial in its cause.

Patients presenting in the SICU with delirium typically present in one of two distinct clinical patterns.[55] The first is hypoactive, presenting with decreased responsiveness and apathy. This is the most common presentation of delirium in the ICU. Less commonly patients will present with the classical hyperactivity associated with delirium and will appear agitated and emotionally labile. Overall, it is estimated that, in the absence of screening protocols, up to 75% of ICU delirium may be underrecognized.[1,55]

Failure to recognize and appropriately manage ICU-associated delirium has consistently been associated with poor outcomes.[56–61] Patients will have a longer hospital stay and an associated cost of $4 to $16 billion annually in the United States.[58,62] Patients with ICU-associated delirium are at higher risk of death compared with their counterparts who do not develop this complication.[57,62] For those who do survive, more than half will experience long-term cognitive dysfunction.[60] The degree of persistent cognitive dysfunction varies; however; most of these patients experience a dementia-like

C

Based on the prior 8 hour shift or from previous 24 hours.

1. **Altered level of consciousness**
   - A. No response (0)
   - B. Response to intense and repeated stimulation (0)
   - C. Response to mild or moderate stimulation (1)
   - D. Normal wakefulness (0)
   - E. Exaggerated response to normal stimulation (1)
2. **Inattention** (1)
   - Difficulty following conversation or instructions
   - Easily distracted by external stimuli
   - Difficulty shifting focus
3. **Disorientation** (1)
   - To time, place, or person
4. **Hallucination, delusion or psychosis** (1)
   - Clinical manifestations of hallucination or delusion
   - Gross impairment in reality testing
5. **Psychomotor agitation or retardation** (1)
   - Hyperactivity requiring sedative drugs or restraints
   - Hypoactivity or psychomotor slowing
6. **Inappropriate speech or mood** (1)
   - Disorganized or incoherent speech
   - Inappropriate display of emotion related to situation
7. **Sleep/wake cycle disturbance** (1)
   - Sleeping less than 4 hours or waking frequently at night
   - Excessive daytime sleeping
8. **Symptom fluctuation** (1)
   - Fluctuating manifestations of any of the above over the observation period (typically 24-hours)

Figure 1. (Continued).

TABLE 2. Selected Medication for Analgesia in the SICU[2]

Drug Class	Pros	Cons	Dosing
Opioids	Excellent pain control when appropriately titrated	Respiratory depression	IV best in ICU
Fentanyl		Hemodynamic effects	SC, transdermal, PO also appropriate in some settings
Remifentanil		Accumulation with hepatic or renal impairment	(see Table 4)
Morphine		Neurogenic toxicity with meperidine	
Hydromorphone			
Methadone			
Meperidine			
Nonsteroidal anti-inflammatories	Anti-inflammatory	Renal dysfunction	Ketorolac:
Ketorolac	Excellent coanalgesic properties	Contraindicated with gastrointestinal bleeding and platelet dysfunction	15–30 mg IV/IM q 6 h to maximum 5 d
Ibuprofen		Contraindicated after coronary artery bypass surgery	Ibuprofen: 400–800 mg IV q 6 h to maximum 3.2 g/d 400–600 mg PO q 4 h to maximum 2.4 g/d
Acetaminophen	Excellent coanalgesic properties	Longer time to onset (up to 60 min) for PO and PR	325–1,000 mg q 4–6 h to maximum 4 g/day PO
		Contraindicated with significant hepatic dysfunction	650–1,000 mg q 4–6 h to maximum 4 g/day IV
Gabapentin	Coanalgesia for neuropathic pain	Excessive sedation	100–1,200 mg PO q 8 h
		Confusion	
		Dizziness and ataxia	
		Dose adjustment in renal failure	
		Requires tapering to avoid drug withdrawal	
Carbamazapine	Coanalgesia for neuropathic pain	Sedation	50–200 mg q 4–6 h to maximum 1,200 mg/d
		Dizziness and lightheadedness	
		Occular symptoms (diplopia, nystagmus)	
		Rare association with Stevens-Johnson syndrome, apastic anemia, and agranulocytosis	
Ketamine	Rapid onset of action (30–40 s) Amnestic properties	Hallucinations and psychological disturbance possible	IV loading dose 0.1–0.5 mg/kg followed by infusion at 0.05–0.4 mg/kg/h

IV, intravenous; SC, subcutaneous; PO, per os (oral administration); PR, per rectum.

illness that may prevent a return to their premorbid level of functioning.

TOOLS FOR ASSESSING DELIRIUM

The negative consequences of delirium underscore the importance of screening and prevention strategies. As such, the presence of delirium should be assessed for daily in ICU patients. Two common methods for the assessment have been proposed: the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium-Screening Checklist (ICDSC). Both are given an "A" level of evidence in the current SCCM guidelines.[2] The CAM-ICU assesses both the level of consciousness and the content of consciousness. Details can be found in Figure 1*B*. The ICDSC consists of eight areas for assessment, including level of consciousness, symptom fluctuance, as well as specific psychological and motor symptoms (Fig. 1*C*). It is designed to be assessed by nursing staff over an entire shift or using data from the previous 24 hours.

Although recognition of delirium is important, strategies to prevent the development of ICU-associated delirium will be far more effective than those designed to treat it. There are currently no medications shown to be effective in the prevention of ICU-associated delirium. Prevention strategies proven to be effective include environmental and activity-based interventions as well as those related to medication. A recent trial compared patients who were subjected to early mobilization with those who continued with current practice and demonstrated both a reduction in incidence of delirium and a

TABLE 3. Dose Ranges for Commonly Used Opioid Medication[2]

Opioid	Intermittent Dosing	Infusion Dosing
Fentanyl	0.35–0.5 μg/kg IV q 0.5–1 h	0.7–10 μg/kg/h
Remifentanyl	N/A	Load: 1.5 μg/kg IV then 0.5–15 μg/kg/h
Morphine	2–4 mg IV q 1–2 h	2–30 mg/h
Hydromorphone	0.2–0.6 mg IV q 1–2 h	0.5–3 mg/h
Methadone	10–40 mg q 6–12 h PO 2.5–10 mg q 8–12 h IV	N/A

IV, intravenous; SC, subcutaneous; PO, per os (oral administration); PR, per rectum; NA, not applicable.

decreased duration in patients who did develop delirium.[63] Based on this and other studies, the current SCCM guidelines suggest (1B recommendation) early mobilization to reduce the incidence and duration of delirium.[2] Both maintenance of premorbid sleep-wake cycles and frequent reorientation have been shown to prevent and mitigate the effects of confusion. The importance of noise control in maintaining sleep-wake cycles was assessed in a trial of 69 patients randomized to sleep with and without earplugs at night and demonstrated a 35% risk reduction in the incidence of confusion.[64] A recent RCT assessed the effect of a patient-directed music intervention delivered through noise-cancelling headphones and demonstrated a reduction in anxiety and the use of medications for sedation.[65] Finally, providing adequate medication to allow good pain control while minimizing sedating medications will also decrease the incidence of ICU-associated delirium. The concept of pharmacologic prevention strategies has been raised in recent years. A review published in 2009 assessed evidence for the use of antipsychotics, acetylcholinesterase inhibitors, melatonin, hypnotics, and gabapentin and concluded that the inconsistent and often conflicting data supporting the use of these medications to prevent delirium precluded a recommendation for routine use.[66] More recently however, Wang et al.[67] published the results of an RCT in which 475 patients at least 65 years of age admitted to the ICU after noncardiac surgery were randomized to receive either a continuous infusion of haloperidol or placebo for 12 hours. Those randomized to receive haloperidol were significantly less likely to develop delirium in the first seven postoperative days (15% vs. 23%), with no significant adverse effects noted. While this finding warrants further investigation, the data continue to remain unclear, and as such, the SCCM guidelines provide no recommendation for pharmacologic prevention of delirium.[2]

MEDICATIONS FOR THE MANAGEMENT OF PAIN, AGITATION, AND DELIRIUM IN THE SICU

Analgesia

Almost all patients in the ICU will have pain, and as such, medication for the purposes of analgesia should be considered in all ICU patients in conjunction with nonpharmacologic management. Analgesic needs will differ for different patients and at different times throughout their ICU stay. Although baseline analgesia requirements may be low, consider additional analgesia before invasive procedures or movement out of the ICU setting for diagnostic or procedural interventions. Furthermore, it is imperative to recognize the unique needs of the postoperative patients with respect to pain management. While not routinely beneficial, the use of a thoracic epidural has been shown to be superior to most other forms of pain management in patients recovering from abdominal aortic aneurysm repair or traumatic rib fractures.[68–71]

Tables 2 and 3 list the commonly used analgesics in the ICU. For nonneuropathic pain, opioids will be the mainstay in most patients.[2,72] The multiple routes and doses make these excellent for the complex ICU patient, and when titrated appropriately, all should allow for adequate pain control. Caution should be used however especially in the trauma population. Much has been written recently on the long-term effects of opioids, the potential for addiction, and the important role the physician plays in this pathway.[73,74] While short-term opioid use is effective for pain control and associated with low risk for addiction,[75] chronic use can predispose to addiction and even death. Prescription of opioid analgesia is on the rise for both acute and chronic pain.[76,77] Of patients prescribed opioids for chronic pain, up to 12% will develop aberrant drug-related behaviors, and up to 6% will develop addiction.[74,78] Physicians prescribing opioid analgesia are creating iatrogenic addictions,[79] a process that may start in the SICU. Interestingly, when studying a cohort of postoperative patients, 6% of whom remained on new opioids at least 150 days after surgery, the strongest predictor for prolonged opioid use was not pain or its severity but rather self-perceived risk of addiction and depressive symptoms.[80] Regardless of the inciting factor, these iatrogenic addictions have major consequences, with the Centers for Disease Control and Prevention estimating that 74% of deaths caused by prescription drug overdose are related to opioids.[76] As such, it is incumbent on the ICU physician to remember that, as soon as possible, opioid medications should be discontinued in favor of less addicting medications.

The addition of nonsteroidal anti-inflammatories may provide additional pain relief in surgical and trauma patients but is contraindicated in a variety of settings including renal dysfunction, gastrointestinal bleeding, and after coronary artery bypass surgery and must therefore be used with caution.[2,81] Acetaminophen has also been shown to have excellent coanalgesic properties in the postoperative patient[2,82,83] and should be considered for routine administration in the absence of contraindications. For patients with neuropathic pain, coanalgesia with gabapentin or carbamazepine has been shown to be beneficial.[84] Finally, in extreme circumstances, ketamine for analgesia in the ICU may be warranted, although there are no Level I studies specific to ICU.[85,86]

Sedation

In addition to adequate analgesia, a smaller proportion of patients will require the addition of medication for sedation. In general, when sedation is required, light sedation is preferred. This means that the patient will remain arousable and able to follow simple commands. Sedation to these end points has been associated with both a decreased duration of ventilator support and a decreased length of stay in the ICU.[36,39,87] Certain patients may require deeper sedation, meaning that the

TABLE 4. Selected Medications for Sedation in the SICU

Drug	Pros	Cons	Dosing
Benzodiazepines	Generally fast onset of sedation (midazolam and diazepam > lorazepam)	Greater sensitivity in elderly	Midazolam recommended only for short-term use (1–2 d maximum)
Midazolam		Risk of respiratory depression	Lorazepam better for longer-term sedation
Lorazepam		Risk of hypotension	Diazepam is least potent
Diazepam		May induce cardiopulmonary instability in critically ill patients	
		Tachyphylaxis	
		Should be use with caution in patients with liver and renal dysfunction	
		Potential toxicity with propylene glycol used to dilute parenteral lorazepam	
		Increased length of ICU stay	
		Withdrawal syndromes with prolonged use	
Propofol	Good for patients requiring frequent awakening (i.e., patients with neurologic injuries)	Long-term use may saturate peripheral tissues and lead to prolonged emergence from sedation	Loading dose of 5 μg/kg/min over 5 min if no significant concern for hypotension
	Highly lipid-soluble so crosses the blood-brain barrier quickly (rapid onset of action; 1–2 min) and similarly rapid redistribution into peripheral tissues and clearance	Respiratory depression	Infusion at 5–50 μg/kg/min
	No active metabolites	Hypotension due to systemic vasodilation	
		Pain at peripheral injection site	
		Hypertriglyceridemia	
		Acute pancreatitis	
		Myoclonus	
		Allergic reactions possible in patients with egg or soybean allergy	
		PRIS	
Dexmedetomidine	Lower incidence of delirium	Onset of action at 10–15 min with peak sedation occurring only within an hour of initiation of infusion. This can be hastened by giving a loading dose, but hemodynamic instability has been shown to result in ICU patients	Loading dose of 1 μg/kg over 10 min then infusion of 0.2–0.9 μg/kg/h for up to 24 h
	Shorter duration of delirium	Hypotension	
	More easily arousable	Bradycardia	
	Minimal respiratory depression	Potential loss of airway reflexes important in nonintubated patients	
	Can continue use after extubation with continuous respiratory monitoring		
	May reduce opioid requirements		
	Lower incidence of withdrawal		
Ketamine	Short duration of action	No studies in ICU patients	
	Amnestic effects		

patient is kept unresponsive to painful stimuli; however, this should be avoided whenever clinically possible. Furthermore, the need for continued deep sedation should be evaluated at a minimum on a daily basis, and sedation should be lightened as soon as clinically appropriate.

Medications commonly used for sedation in the ICU are listed in Table 4. Throughout North American ICUs, benzodiazapines are the most frequently used sedating agents. Benzodiazapines work by activating γ-aminobutyric acid A ($GABA_A$) neuronal receptors in the brain, conferring amnestic effects that are greater than their sedative effect. Benzodiazepines are metabolized by the liver through cytochrome p450 system and glucuronide conjugation and, as such, may interfere with other cytochrome p450–mediated medications.[88,89] In

A

1. Safety screen for spontaneous awakening trial
   - No active seizure
   - No alcohol withdrawal
   - No agitation
   - No paralytics
   - No myocardial ischemia
2. Spontaneous awakening trial if safe
   - Failure for any of:
     - Pain, anxiety, agitation
     - RR > 35/min
     - SpO2 < 88%
     - Respiratory distress
     - Cardiac distress
     - If fail, restart sedatives at half the previous dose
3. Spontaneous breathing trial safety screen if pass spontaneous awakening trial
   - No agitation
   - SpO2 >= 88%
   - FiO2 < 50%
   - PEEP <= 7.5 cm H20
   - No myocardial ischemia
   - Off vasopressors
   - Making inspiratory efforts
4. Spontaneous breathing trial if safe
   - Failure for any of
     - RR > 35/min or < 8/min
     - SpO2 < 88%
     - Respiratory distress
     - Cardiac distress
     - Mental status changes
     - If fail, return to previous ventilatory support
5. Consider extubation if pass spontaneous breathing trial

B

1. Safety screen
   - RASS >= -3
   - FIO2 <= 60%
   - PEEP <= 10 cm H20
   - No dose escalation on vasopressors for at least 2 hours
   - No evidence of active myocardial ischemia for at least 24 hours
   - No arrhythmia requiring administration of new antiarrythmic agent for at least 24 hours
2. If pass safety screen proceed with exercise and mobility therapy
   - Physical and occupational therapy directed care
     - Active movements in bed
     - Participation in routine care and grooming
     - Moving from bed to chair
     - Ambulating

Figure 2. *A,* Components of the Awakening and Breathing Coordination of daily sedation and ventilator removal (ABCDE) bundle.[36,114] *B,* Components of mobility assessment associated with the ABCDE bundle.[36]

patients with renal dysfunction and elderly patients, active metabolites may accumulate and a prolonged effect may be seen.[89–91] For many years, propofol was seen as one of the only alternatives to benzodiazapines. Propofol binds multiple central nervous system receptors to block neural transmission (GABA-A, glycine, nicotinic, M1 muscarinic).[92] It is a complex drug with not only sedative properties but also hypnotic, anxiolytic, amnestic, antiemetic, and anticonvulsant effects. Fear over the risk of propofol infusion syndrome (PRIS) has likely limited its use. PRIS is rare, occurring in approximately 1% of patients who receive propofol infusions.[93] It is typically associated with high-dose infusions (>70 μg/kg/min) but has also rarely been reported with low-dose infusions as well as in pediatric patients.[93,94] The signs and symptoms are nonspecific and include metabolic acidosis, hypertriglyceridemia, hypotension, and arrhythmia. Rarely, acute kidney injury, rhabdomyolysis, and liver dysfunction have been reported.[95,96] There is no specific management for PRIS, and patients should be supported throughout the course. Despite supportive care and even after discontinuation of the infusion, mortality in patients with PRIS is reported to be up to 33%.[95,97]

More recently, there has been a great deal of interest in the use of dexmedetomidine to achieve moderate-to-light sedation. Dexmedetomidine is a selective α_2-receptor agonist that works as a sedative, analgesic, and sympatholyitic.[98] It is rapidly redistributed into peripheral tissues and is metabolized by the liver, and therefore, prolonged clearance may be seen in patients with severe hepatic dysfunction. Currently, it is approved only in North America for short-term sedation in the ICU (<24 hours), although many studies support its safe use in higher doses (1.5 μg/kg/h) and increased duration (up to 28 days).[59,99–101] In a recent trial, dexmedetomidine was compared with both midazolam and propofol in critically ill medical ICU and SICU patients.[102] Dexmedetomidine was found to be noninferior with respect to sedation and was found to be superior to midazolam with respect to duration of mechanical ventilation. Further dexmedetomidine was found to be superior to both drugs with respect to patient communication. An RCT of 306 patients randomized to received dexmedetomidine or morphine and propofol after cardiac surgery demonstrated dexmedetomidine to be associated with a decreased duration of delirium, although not with a decrease in the incidence of delirium.[59] Specifically in trauma patients, standard dose dexmedetomidine has been shown to be equivalent to propofol in a retrospective review of 127 patients.[103] There has been much interest in the use of dexmedetomidine in patients with traumatic brain injury, although only small studies have been published, warranting further research in this area.[104]

Delirium

It is important to note that pharmacologic management of delirium has not been consistently shown to improve outcomes. Nonpharmacologic management should be initiated first, including verbal de-escalation, positioning, relaxation techniques, maintenance of the sleep-wake cycle, frequent reorientation, mobilization, and music therapy. When these techniques are not sufficient for safe and comfortable patient care however, medication may be required. The most commonly used medication in this setting is haloperidol (Haldol), a first generation or typical antipsychotic that acts through dopimanergic blockade. Although adverse effects exist, including a risk of QT prolongation and extrapyramidal adverse effects with significant doses, it is considered by many to be the first line of treatment for ICU-associated delirium.[2,105] Despite this, there is currently no evidence that treatment with haloperidol reduces the duration of delirium.[2] More recently, atypical (or second-generation) antipsychotics have been used more frequently in the control of agitation and delirium. These include olanzapine, quetiapine, risperdol, and ziprasidone, which are all D2 receptor antagonists with the additional seritonergic activity and faster dissociation from dopaminergic receptors, which separate these drugs from the first generation antipsychotics. These are equally effective in the treatment of delirium when compared with haloperidol, but additional dosing forms are available which broadens the clinical applicability.[106] Based on a small RCT of 36 patients in a medical ICU where the use of quetiapine in combination to haloperidol,

when compared with the use of haloperidol alone, was associated with a reduced duration of delirium.[107] Based on this, the recent SCCM guidelines suggest that the use of atypical antipsychotics may reduce the duration of delirium, although this is a Grade C recommendation.[2] More recently, a pilot RCT assessed the treatment of medical and surgical/trauma ICU patients with delirium with either zipasidone or haloperidol.[108] This pilot study demonstrated feasibility of continuing to a full trial, although with small numbers suggested no difference between ziprasidone and haloperidol with respect to either delirium-free days or adverse outcomes. It is clear that additional research is required to determine the role of atypical antipsychotics on the treatment of delirium. Finally, perhaps the most frequently used medications to control agitation and delirium are benzodiazepines. Although effective at providing rapid sedation, the adverse effects listed in Table 2 caution one against routine use in the management of agitation. Benzodiazepines should not be used in the treatment of delirium because this class of medication has been shown to increase the risk and duration of delirium. In fact, the most recent SCCM guidelines suggest that the use of benzodiazepine infusions be replaced by the use of dexmedetomidine to reduce the duration of delirium (Grade 2 B recommendation).[2]

Specific triggers for delirium deserve special attention. Alcohol withdrawal syndrome is characterized by a spectrum ranging from anxiety to delirium tremens and occurs in up to 25% of patients who are premorbid alcohol abusers.[46] Unlike in other conditions associated with delirium, the mainstay of treatment of alcohol withdrawal–related delirium is benzodiazepines.[46] Although some suggest the use of ethanol itself to prevent alcohol withdrawal syndromes, an RCT conducted in trauma patients admitted to the SICU with a history of significant daily alcohol intake compared a strategy of intravenous ethanol with one of scheduled benzodiazapines and found no difference in efficacy or adverse outcomes.[109] More recently Ungur et al.[110] published a systematic review of RCTs assessing prevention and therapy for alcohol withdrawal syndromes in trauma, surgical, and medical ICUs. The authors conclude that benzodiazepines are effective and safe for the prevention of alcohol withdrawal syndromes as well as for their treatment.

Multidisciplinary Protocols and Approaches

It has been consistently shown in recent literature that multidisciplinary approaches and, in many cases, protocolized care is associated with improved patient outcomes. Protocolized nurse-directed sedation during mechanical ventilation is associated with a decreased length of mechanical ventilation and sedation requirements, a lower rate of tracheostomy, less pain and agitation, a decreased incidence of ventilator-associated pneumonia, and a shorter ICU and hospital stay.[40,41,111] Protocolized daily interruption of sedation is associated with a decreased length of mechanical ventilation, a shorter ICU stay, and the requirement for fewer investigations for mental status changes.[42,43,112,113] Coordinated approaches where sedation interruption is coupled with attempts to liberate from the ventilator is associated with a greater number of ventilator-free days, increased rate of self-extubation with similar rate of reintubation, and a shorter stay in both the ICU and the hospital.[36,42,43,112] Furthermore, this strategy has been shown in one study to be associated with a 14% absolute mortality reduction at 1 year.[36]

A significant body of literature surrounding such protocols has been produced through Vanderbilt University.[36,114] This group has coined the Awakening and Breathing Coordination, Delirium Monitoring and Management (ABCDE) bundle.[114] This multidisciplinary approach is typically initiated by nursing staff and respiratory therapists and consists of a daily assessment for spontaneous awakening and breathing in all ventilated patients. Details of this bundle can be found in Figure 2. Patients are screened for safety of a spontaneous awakening trial, and if safe, sedation is weaned, and the patient is allowed to wake slowly. If the patient tolerates this awakening, a spontaneous breathing trial is initiated. If the spontaneous breathing trial is successful, extubation should be considered. A similar daily assessment for all ventilated patients for exercise and mobility therapy in conjunction with spontaneous awakening trial has been described (Fig. 2*B*). One third of patients will be able to successfully move from bed to chair, and 15% will be able to walk successfully on the ventilator.[63] Furthermore, the use of this protocol has been associated with more ventilator-free days, decreased duration of delirium, and a greater likelihood of return to independent function.[63] Further studies have demonstrated through the use of financial modeling that early rehabilitation programs can provide substantial financial savings in relation to modest implementation costs.[115]

CONCLUSION

The management of patients in the SICU should include early and aggressive attempts to control pain, with judicious use of sedation. A multidisciplinary approach including early mobility, nonpharmacologic interventions, and daily assessment for delirium should be undertaken to optimize outcomes for critically ill surgical and trauma patients.

AUTHORSHIP

This article was commissioned on behalf of the critical care committee of the American Association for the Surgery of Trauma. Drs. Vogt and Frankel contributed equally to both manuscript formation and editing.

DISCLOSURE

The authors declare no conflicts of interest.

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