Sedation in critical care

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Sedation of patients in critical care is commonly encountered in the everyday practice of anesthetists and intensivists. This educational article seeks to provide a broad outline of the principles of sedation in critical care and the aspects of the latest guidance in managing a patient's sedation.

Keywords:
agitation, critical care, delirium, pain, sedation

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Introduction

Every anesthetist will have an experience of managing sedated patients in critical care at some time during their career. For those who work in critical care routinely, managing sedation forms a part of their core skillset. All anesthetists should be competent in managing sedation for a patient on critical care, including its indication, titration to a desired therapeutic level, and the adverse effects of over-sedation. Protocolized sedation regimes within critical care are the standard of practice. This educational review will cover common sedative agents, principles, and approach to sedation in critical care, adverse effects, and a brief review of the recent literature.

Learning outcomes:

(1) Recognize rationale behind the principles of sedation in critical care.
(2) Knowledge of commonly used sedative agents.
(3) Appreciate the role of pain, agitation, and delirium assessment tools to guide use of analgesia and sedation in critical care.

Definitions

Sedation describes the use of drugs to inhibit consciousness and blunt a patient's awareness of their situation and surroundings. Classically, sedation is further described in relation to the patient's consciousness level:

Mild sedation – this equates to simple anxiolysis.

Moderate (conscious) sedation – verbal contact is maintained with the patient and they are able to follow commands. Airway reflexes, oxygenation, and hemodynamics are unaffected.

Deep sedation – loss of verbal contact with patient, only rousable to painful stimuli. Airway reflexes, oxygenation, and hemodynamics may be affected and intervention required.

General anesthesia – complete state of unconsciousness without response to painful stimuli, with significant effect on airway reflexes, oxygenation, and hemodynamics.

This description is less useful in critical care, where patients are routinely intubated with mechanical ventilation and often have hemodynamic support regardless of sedative interventions. Optimal sedation in critical care should allow for communication between the patient and the caregiver, while minimizing distress and pain from interventions such as the presence of an endotracheal tube, tracheal suctioning, and physiotherapy.

Indications for sedation

Sedation is typically implemented in critical care to allow a patient to tolerate advanced organ support, for example, mechanical ventilation via an endotracheal tube. It may also be used to optimize mechanical ventilation in disease states such as acute respiratory distress syndrome, as part of a neuroprotective strategy in traumatic brain injury and postcardiac arrest care, to

reduce oxygen consumption in sepsis, and combat agitation [1].

Risks and adverse effects

The 'ideal' sedative agent does not exist. However, existing drugs can be evaluated against the standard of an ideal agent, which would have the following properties:

(1) No effect on cardiac output, systemic vascular resistance, or blood pressure.
(2) Rapid onset and offset, easily titratable to desired effect.
(3) No active metabolites or accumulation.
(4) Excretion or elimination not dependent on hepatic or renal function.
(5) Cheap, with long shelf-life, and stored at room temperature.
(6) Consistent pharmacokinetic and pharmacodynamic profile across all age ranges and patient types.
(7) Absence of adverse effects, for example, nausea and pain on injection.
(8) No interaction with other medications.

Table 1 Complications of over-sedation and undersedation

Oversedation	Undersedation
Increased ventilator days	Catabolism
Increased ICU length of stay	Hypercoagulability
Increased risk of nosocomial infection	Immunosuppression
Reduced communication and cooperation with care	Sympathetic activation
Venous thromboembolism	Inadvertent displacement of indwelling devices (e.g. accidental extubation)
Delayed rehabilitation	Injuries to patient and staff

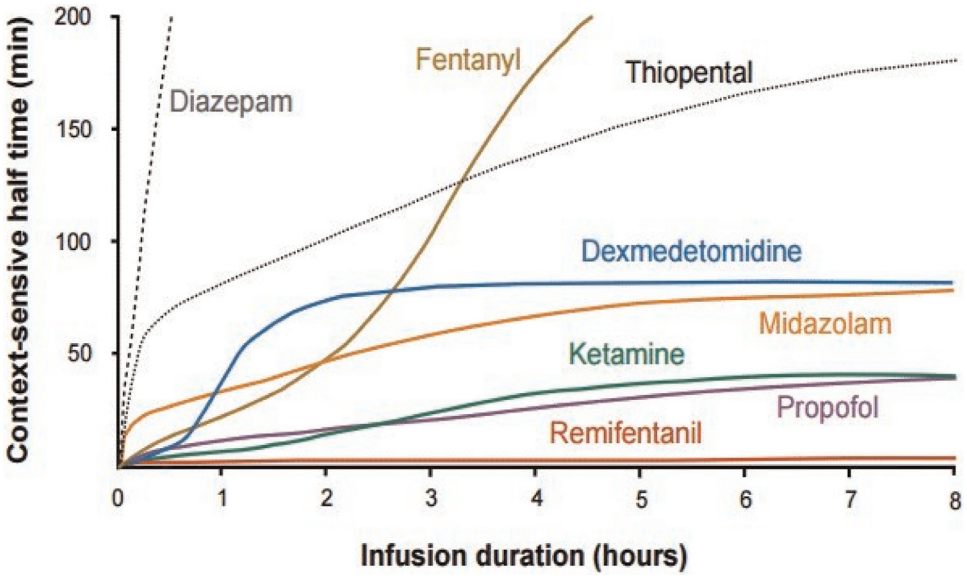
The most commonly encountered adverse effects of sedative agents in critical care include hypotension, dysrhythmia, myocardial depression, respiratory depression, delirium, and tolerance and withdrawal states.

Regardless of the drug used and its specific adverse effect profile, inappropriate depth of sedation can lead to adverse effects with significant consequences to the patient and the critical care service. These are listed in Table 1.

Context-sensitive half-time

The context-sensitive half-time (CSHT) is an important concept in sedation. It explains why many drugs that have short duration of action after a single bolus can appear to become long-acting after several hours of infusion and give rise to significant ongoing sedative effects for some time after the infusion is stopped. CSHT describes the accumulation of drug in the tissues during the course of an infusion. As the tissues become loaded, a reservoir of the drug builds up within the body. The result of this is that offset time of the drug's effect (measured in 'half-times') tends to increase the longer the infusion has been running (as this gives more time for the drug to accumulate). The notable exception is remifentanil, which is constantly metabolized in all tissues by ubiquitous enzymes called plasma esterases and so does not accumulate. Figure 1

Figure 1



Context-sensitive half-times of common sedative agents. Tissue loading results in a prolonged duration of action even after cessation of the infusion.

shows the offset times of various sedative drugs after cessation of an infusion of varying length ('context').

Commonly used agents

Anesthetic agents

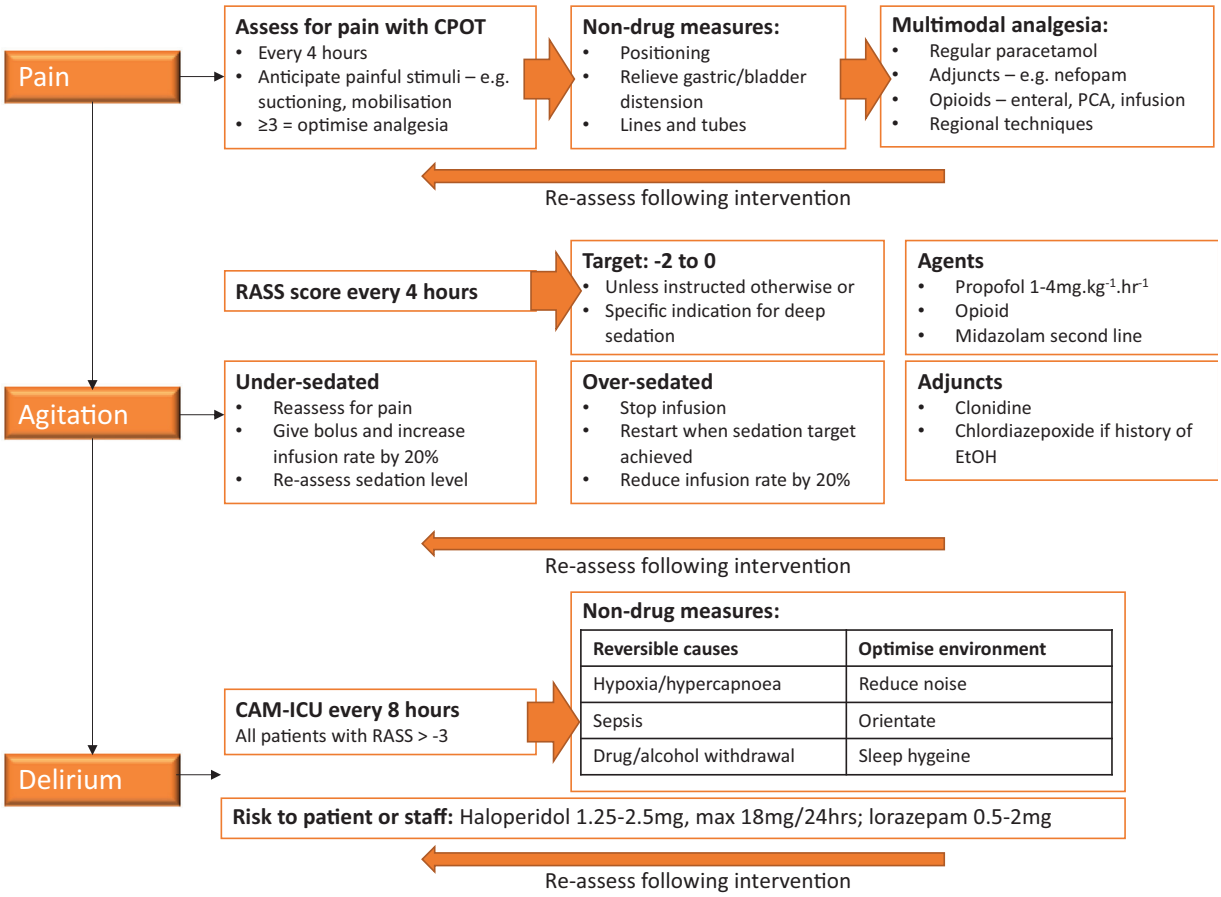
Propofol

Propofol is a commonly used agent. Its primary advantage for its use in critical care is a short (CSHT; see Fig. 1). This is ~20 min after a 2 h infusion, 30 min after a 6 h infusion, and 50 min after a 9 h infusion [2]. This allows for titration of sedation and aids in the rapid assessment of neurological status during a sedation hold. The typical dose for a propofol infusion is 1–4 mg/kg/h. Adverse effects are predictable, dose dependent, and in some cases desirable. Of note, hypotension is common (via decreased systemic vascular resistance and/or direct myocardial depression). Other, more desirable, effects include reduced cerebral metabolic requirement for oxygen ($CMRO_2$), reduced intracranial pressure (ICP), and reduced intraocular pressure (Fig. 2). Propofol has profound anti-seizure effects and is used to treat status epilepticus. The adverse effect profile is significantly worsened in patients with hypovolemia, vasoplegia, or existing myocardial impairment [3]. Caution must be exercised in patients requiring higher dose infusions (>4 mg/kg/h) for greater than 48 h owing to the risk of propofol infusion syndrome, which presents as rhabdomyolysis, metabolic acidosis, hyperkalemia, and myocardial failure.

Thiopentone

Thiopentone (thiopental) is less familiar to more junior clinicians, as its use has been largely superseded by propofol. The adverse cardiovascular adverse effects in response to bolus dose are more pronounced compared with propofol. Moreover, the pharmacokinetics of thiopentone are not conducive for ICU sedation: it is cleared via zero order (saturable) kinetics, leading to pronounced accumulation during infusions. Patients treated with thiopentone may remain in coma for several days following cessation of infusion ($t_{1/2}$ 53–120 h [3]). Thiopentone historically was used as an infusion in status epilepticus and raised ICP and may occasionally be seen used in these conditions today.

Figure 2



An example of an ICU sedation protocol.

Ketamine

Ketamine is phencyclidine derivative that acts as an NMDA receptor antagonist. It causes a dissociative state: patients' eyes may be open, and they may move, but their consciousness is completely divorced from reality. Ketamine for sedation on critical care may be used as an infusion of 0.5–3 mg/kg/h. Ketamine's adverse effect profile suits its use in the prehospital setting: it is profoundly analgesic; cardiac output is maintained via direct myocardial and sympathetic activation; and airway reflexes are also maintained, facilitating spontaneous ventilation. Regarding its use in critical care, it is rarely used as a sole agent and more often acts in an adjunctive capacity when deeper levels of sedation are required (e.g. raised ICP), to facilitate ventilation in severe bronchospasm, or during painful procedures (e.g. burn care). Emergence delirium may be distressing for patients receiving ketamine sedation: it is usual practice to co-administer a benzodiazepine with ketamine, to suppress any unpleasant hallucinations.

Opioids

Morphine

Morphine is a naturally occurring opiate whose use is commonplace in critical care. It can be used safely as a prolonged infusion, although caution must be exercised in instances of renal failure, as its active metabolite, morphine-6-glucoronide, is excreted by the kidney and high levels will contribute to a prolonged duration of action. The dose for infusion is 0.04–0.2 mg/kg/h. Morphine also carries significant long-term adverse effects with its prolonged usage, such as reduced gastrointestinal transit time, tolerance, dependence and withdrawal, and immunosuppression via its effects on lymphocyte function.

Fentanyl

Fentanyl is a synthetic opioid. It is 100 times more potent than morphine and tends to accumulate with prolonged infusion (the increase in CSHT is exponential), particularly in elderly patients. Fentanyl (along with alfentanil and remifentanil) has the advantage over morphine that its metabolites are inactive, and it does not accumulate in renal failure. Only 10% is renally excreted. Infusion is initiated at 1–10 μg/kg/h.

Alfentanil

Alfentanil is synthesized from fentanyl and has a smaller volume of distribution, leading to less accumulation and therefore a shorter CSHT in comparison (see Fig. 1). Infusion is initiated at 0.5–2 μg/kg/h.

Remifentanil

Remifentanil is an ultra-short-acting μ agonist. It is metabolized by plasma esterases (found in all tissues) into inactive metabolites, and therefore does not rely on hepatic metabolism or renal excretion. Its short CSHT (3 min irrespective of the length of infusion) allows for fast offset of its effects – around 10 min after stopping an infusion. Remifentanil is used in ICU sedation, but it is costly and requires additional staff training. It should not be administered as a bolus, as this may provoke significant bradycardia and hypotension. It is used as an infusion for sedation at 0.05–0.2 μg/kg/min. Although remifentanil's pharmacokinetic profile appears very favorable for ICU sedation, a study has shown no difference in time to extubation in comparison with fentanyl [4]. Remifentanil induces rapid tolerance and withdrawal symptoms. Its use is associated with opioid-induced hyperalgesia, a paradoxical increase in sensitivity to painful stimuli following opioid exposure.

Benzodiazepines

Midazolam

At first glance, midazolam might appear to be an ideal sedative agent as it has quick onset of action and few cardiorespiratory adverse effects. However, its adverse features far outweigh its benefits in many cases. Midazolam is reliant on hepatic metabolism via the cytochrome p450 enzyme, CYP3A4. Action of this enzyme is dependent on hepatic function and blood flow, along with interaction with other substrates for this enzyme such as alfentanil. Active metabolites are produced which require renal excretion and are not cleared by renal replacement therapy due to their high protein binding. When used as an infusion, the dose is 0.05–0.1 mg/kg/h. Prolonged infusion leads to considerable delay in waking times and extubation, tachyphylaxis, and withdrawal on cessation of the infusion. In common with other benzodiazepines, midazolam also produces a significantly higher incidence of delirium, and has deleterious immune effects such as impaired neutrophil function and inhibition of cytokine production by macrophages. There are some instances when midazolam may be preferable over propofol, for example, in patients with significant cardiovascular instability. Its usage also increased during the recent COVID-19 pandemic, often owing to high patient sedation requirement and shortages of propofol. Flumazenil exists as an inverse agonist to benzodiazepines but must be used with caution owing to its tendency to provoke generalized seizures.

Lorazepam

Lorazepam is less favorable as a primary sedative agent owing to its slow onset of action, long CSHT, and long

elimination half-life. It is more frequently used as a bolus dose (0.5–2 mg) as adjunct to other sedative agents, or in the treatment of status epilepticus. It has inactive metabolites. It is important to note that lorazepam comes prepared in solvents such as polyethylene glycol, which may provoke hyperosmolar states, lactic acidosis, or renal tubular acidosis [5].

Chlordiazepoxide

This long-acting benzodiazepine is typically used in the management of alcohol withdrawal, alongside Clinical Institute Withdrawal Assessment for Alcohol scale scoring [6]. It is administered via the enteral route. Prompt recognition and management of alcohol withdrawal will avoid unnecessary over-sedation with intravenous sedative agents.

Neuroleptics

Haloperidol

Haloperidol is an atypical antipsychotic that acts as an antagonist at the D_2 receptor, both in the periphery and the CNS. It is most commonly used in control of agitated states in hyperactive delirium as it is available in an intravenous preparation. It is administered as an intravenous bolus dose in increments of 1.25–2.5 mg, titrated to effect. Adverse effects include QTc prolongation, torsades des pointes, neuroleptic malignant syndrome, and extrapyramidal features.

α-2 agonists

Clonidine

Clonidine is an α-2 adrenoreceptor agonist that has sedative and analgesic properties. It may be used in an awake patient to aid in the management of agitation and anxiolysis and also in patients as an adjunct to a primary sedative agent. When used, it may be given as an infusion of 0.5–2 μg/kg/h or via the enteral route, usually 50 mg TDS. It may aid in the management of hypertension but also precipitate bradycardia. It has a long $t_{1/2}$ (6–24 h) and can produce rebound hypertension if abruptly withdrawn. It is reliant on renal excretion and may accumulate in renal failure. Clonidine has been shown to reduce delirium, facilitate patient cooperation with ventilation, and improve weaning [7]. However, it has not demonstrated a mortality benefit, reduced duration of ventilation, or reduced ICU length of stay when compared with nontreatment with clonidine [8].

Dexmedetomidine

Dexmedetomidine is eight times more selective for the α-2 receptor than clonidine [9]. It has a favorable pharmacokinetic profile for ICU sedation, with a distribution half-life of 6 min. It is highly protein bound and undergoes hepatic metabolism, so reduced doses should be used in hepatic impairment and hypoalbuminemia. Adverse effects are dose dependent and more apparent on a loading dose. It can precipitate hypertension, which is then superseded by hypotension and bradycardia owing to its inhibitory effect on sympathetic outflow. The PRODEX and MIDEX trials showed that dexmedetomidine is as effective as propofol and midazolam in maintaining light to moderate sedation [10]. SPICE-III did not show any mortality benefit in using dexmedetomidine compared with usual care but did demonstrate a reduction in ventilator days and delirium. This was balanced by increased adverse outcomes such as bradycardia, hypotension, and asystole [11]. One potential barrier to routine dexmedetomidine usage is cost. Treatment of one 70 kg patient for 24 h costs £30–£250 (infusion rate of 0.2–1.2 μg/kg/h). In comparison, an equivalent infusion of clonidine would cost £12.50–£50 for 24 h (infusion rate 0.5–2 μg/kg/h^{-}; prices from the British National Formulary, June 2020).

Scoring systems

Sedation scoring systems produce a numerical value to describe the depth of sedation. This allows for reproducibility in the delivery of sedation and continuity of clinical practice. There are various scores validated for this use, and no particular score has a significant advantage over another. It is important that only one score is in use for a particular critical care unit, to ensure consistency of approach.

Titrating sedation to the optimal depth that allows for the patient to be free from pain and agitation, cooperative with caregiver interventions, while avoiding adverse effects from either the drugs or over/undersedation is complex and requires expertise. A sedation scoring system can be used as an aid in guiding the titration of sedation.

Ramsay scoring scale

This was the first scoring system to be developed. It describes six levels of sedation and can be used on all patients in critical care (Table 2).

Richmond agitation and sedation scale

This is another scale that describes ten levels of sedation and assigns a numeric value. It is more intuitive than the Ramsay score in that zero describes an awake, calm, and cooperative patient, with the score being positive for increased arousal/agitation and negative for increased sedation. Another

Table 2 The Ramsay scoring scale

Scores	Description
1	Patient is anxious and agitated, restless, or both
2	Patient is cooperative, orientated, and tranquil
3	Patient responds to commands only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus.
6	Patient exhibits no response

Table 3 The Richmond agitation and sedation scale

Scores	Description
+4	Combative, violent, danger to staff
+3	Pulls or removes tube(s) or catheters; aggressive
+2	Frequent nonpurposeful movement; fights ventilator
+1	Anxious, apprehensive, but not aggressive
0	Alert and calm
−1	Awakens to voice (eye opening/contact) >10 s
−2	Light sedation, briefly awakens to voice (eye opening/ contact) <10 s
−3	Moderate sedation, movement or eye opening; no eye contact
−4	Deep sedation, no response to voice but movement or eye opening to physical stimulation
−5	Unrousable, no response to voice or physical stimulation

advantage is that it is validated alongside BIS values and drug dosage and also has stronger interrater agreement so is therefore more likely to produce a consistent standard of sedation on the critical care unit [12]. Richmond agitation and sedation scale (RASS) also integrates with the Confusion Assessment Method for ICU (CAM-ICU) score in the assessment of delirium (Table 3).

An approach to ICU sedation

There is strong evidence that interventions to optimize sedation lead to reduced duration of mechanical ventilation and reduced length of ICU stay [13]. A shift toward lighter sedation is advocated by the Pain, Agitation, and Delirium guidelines [14]. Vincent *et al.* [15] describe the eCASH (early comfort, using analgesia, minimal sedatives, and maximal humane care) approach, which uses a sedation strategy that eliminates the use of sedative agents at the earliest opportunity. A pragmatic approach to managing any patient in critical care would be to assess for and treat pain, agitation, and delirium.

Pain

Pain in critical care patients should be a treatment priority. Pain can be quantified by using either a verbal rating scale if the patient is able to communicate, and this remains the gold-standard rating method ('pain is what the patient says it is'). If the patient cannot communicate, a non-verbal scale can be used, such as the critical care pain observation tool [16] or behavioral pain scale [17], both of which are validated for the assessment in ICU patients. Pain should first be addressed by nonpharmacological means such as relieving gastric or urinary bladder distension, optimizing patient positioning, or removal of unnecessary drains, tubes, or catheters. If analgesia by pharmacological means is required, it should be delivered in a multimodal approach. The use of opioids should be kept to a minimum, and non-opioid adjuncts such as cyclooxygenase-2 inhibitors, α-2 agonists, neuropathic agents, and regional anesthesia should be used if appropriate (Tables 4 and 5).

Table 4 The behavioral pain scale – pain score is based upon highest score achieved from any behavior

Indicator	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g. brow lowering)	2
	Fully tightened (e.g. eyelid closing)	3
	Grimacing	4
Upper limb movements	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating the ventilator most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4
Score 3–4=no pain; 5–6=mild pain; ≥7=additional analgesia required		

Typical interventions and their associated pain scores are listed in Table 6 [18].

Agitation

Once pain has been adequately controlled, sedative agents can be titrated to achieve the desired level of sedation. Lighter sedation is usually preferable; however, there will be instances in which deeper levels of sedation are necessary, such as neuromuscular blockade, neuroprotection, or severe respiratory failure. Propofol is the most commonly used agent, and each critical care unit will have its own preferred first-choice opioid. Midazolam is not an ideal agent owing its adverse effects, as described before. Adjunctive agents such as clonidine and the sparing use of benzodiazepines should be considered in patients with high sedation requirements.

Table 5 The critical care pain observation tool – score taken following observation for one minute at rest as baseline, followed by reassessment during a nociceptive procedure

Indicator	Score	Description
Facial expression	0–Relaxed	No muscle tension observed
	1 – Tense	Presence of frowning, brow lowering, orbit tightening or any other change (e.g. opening eyes or tearing during nociceptive procedures)
	2 – Grimacing	All previous facial movements plus eyelid tightly closed (the patient may present with mouth open or biting the endotracheal tube)
Body movements	0 – absence of movements or normal position	Does not move at all (does not necessarily mean absence of pain) or normal position (movements not aimed toward the pain site or not made for the purpose of protection)
	1 – Protection	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements
	2 – Restlessness or agitation	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed
Compliance with ventilator (if intubated)	0 – Tolerating ventilator or movement	Alarms not activated, easy ventilation
	1 – Coughing but tolerating	Coughing, alarms may be activated but stop spontaneously
OR	2 – Fighting ventilator	Asynchrony: blocking ventilation, alarms frequently activated
Vocalization	0 – Talking in normal tone or no sound	Talking in normal tone or no sound
	1 – Sighing or moaning	Sighing or moaning
	2 – Crying out, sobbing	Crying out, sobbing
Muscle tension	0 – Relaxed	No resistance to passive movements
	1 – Tense, rigid	Resistance to passive movements
	2 – Very tense or rigid	Strong resistance to passive movements or incapacity to complete them
Total	/8	

The rating should be taken from the highest observed score. The assessment should be repeated following an intervention to promote analgesia, to evaluate the effectiveness of that intervention [16].

Table 6 BPS and CPOT scores following common ICU intervention

Procedure	BPS score	CPOT score
Resting	3	0
Changing position	4	3
Mouthwash	6	3
Secretion suctioning	7	4
Respiratory physiotherapy	4	1

BPS, behavioral pain scale; CPOT, critical care pain observation tool.

Delirium

Once pain and agitation have been adequately managed, the patient should be assessed for the presence of delirium. Delirium, according to the DSM-V, is the disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with a reduced ability to focus, sustain, or shift attention [19]. The presence of delirium may be detected by regular assessment with the CAM-ICU score.

ICU delirium is a well-documented complication of critical care. It is multifactorial, but injudicious sedative use is a contributing factor. Delirium is a frightening experience for the patient, and comes with an accompanied psychological morbidity, starting with mild effects on sleep to severe anxiety and post-traumatic stress disorder Moreover, ICU delirium increases the risk of mortality in critical care [20]. It may be tempting to increase a patient's depth of sedation with well-meaning intention of blunting any unpleasant experience that they may be having. This is often counterproductive: an adverse effect of deeper sedation is delirium, and the resultant prolonged stay in critical care as a result of over-sedation may amplify any psychological morbidity (Table 7).

If delirium is present, its first-line management should employ nonpharmacological methods. Reversible causes such as hypoxia/hypercapnia, hypo/hyperglycemia, sepsis, hypotension, and drug/alcohol withdrawal should be corrected. The patient should be given reassurance of their safety and reminded of their location and circumstances on a regular basis. The patient's environment should be addressed to facilitate orientation, for example, visible date and time, hearing/visual aids present, and communication aids. There should be promotion of good sleep hygiene by keeping ambient noise to a minimum, and minimizing light and intervention (e.g. measuring temperature and non-invasive blood pressure) during night-time hours.

Table 7 CAM-ICU scoring tool

Feature 1: acute onset or fluctuating course	Score
Is the patient different from his/her baseline mental status?	Present if yes to either question
OR	
Has the patient had any fluctuation in mental status over the past 24 h as evidenced by fluctuation in RASS, GCS, or previous delirium assessment?	
Feature 2: inattention	
Say to the patient: I am going to read you a series of 10 letters. When you hear the letter A, squeeze my hand.	Present if 2 or more errors
S A V E A H A A R T	
Errors encountered if hand not squeezed or squeezed on any other letter than A	
Feature 3: altered level of consciousness	
Present if RASS anything other than zero	Present if RASS not zero
Feature 4: disordered thinking	
Ask	Present if combined number of errors is greater than 1
1. Will a stone float on water?	
2. Are there fish in the sea?	
3. Does one kilogram weigh more than two kilograms?	
4. Can you use a hammer to hit a nail?	
Errors are counted when the patient incorrectly answers a question	
Say	
'Hold up this many fingers' (hold 2 fingers in front of patient)	
'Now do the same with the other hand'	
If the patient is unable to move both arms, for second part of command ask patient to 'Add one more finger'	
An error is counted if the patient is unable to complete the entire command	
CAM-ICU is positive if features 1 and 2 are present with either feature 3 or 4	

CAM-ICU, Confusion Assessment Method for ICU; GCS, Glasgow coma scale; RASS, Richmond agitation and sedation scale.

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Conflicts of interest

There are no conflicts of interest.

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