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Analgesia, Sedation and Neuromuscular Blockade in Critically Ill Patients: A Practical Approach for Intensivists

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A practical approach to analgesia, sedation and neuromuscular blockade of critically ill patients and a discussion on potential benefits, adverse effects and current professional international recommendations.

Introduction

Patients hospitalised in the Intensive Care Unit (ICU) are naturally prone to experience pain. They may require administration of sedatives and even neuromuscular blockade (NMB) in some cases. At the present moment, there are several clinical practice guidelines in this regard by multiple professional associations. However, there are still some discrepancies on the optimal clinical approach of these patients, namely on drug selection alongside monitoring of their effects. In this paper, we introduce a practical approach to the analgesia, sedation and NMB of critically ill patients, whilst taking into account potential benefits, adverse effects and current professional international recommendations.

Evaluation and Management of Pain in the ICU

More than 50% of critically ill patients experience pain, a situation that is associated with adverse outcomes. These include increasing length of ICU stay and in-hospital stay, increasing days under invasive mechanical ventilation (IMV), and a higher incidence of delirium. Clinicians must implement strategies for the early detection, evaluation and management of pain, in an attempt to maximise patient comfort, since this is considered an essential part of the so-called Humanisation of Intensive Care Units.

The physiological response to pain commonly presents with tachycardia, hypertension, tachypnoea, respiratory alkalosis, among others. This response is related to haemodynamic instability, impairment of the immune system and hyperglycaemia, in addition to the release of catecholamines, cortisol and vasopressin. Persistence of pain predisposes to a wide variety of detrimental psychological effects including agitation, post-traumatic stress disorder, disorientation and depression.

The first step of this approach is to accurately identify pain, which may pose a challenge in patients in which verbal communication is not feasible, for instance, in patients under IMV or sedatives, as well as in patients with paralysis, neurological or neuromuscular disorders, among others. The most widely used scale for pain detection and assessment is the Critical-Care Pain Observation Tool (CPOT) (**Table 1**), which takes into consideration a handful of clinical parameters; of note, this scale can be used in patients who can verbally communicate and also in patients who cannot, such as those under IMV, as it considers facial expression, upper limb movements and compliance with mechanical ventilation.

Once pain is identified, an adequate analgesic treatment must be prompted. The

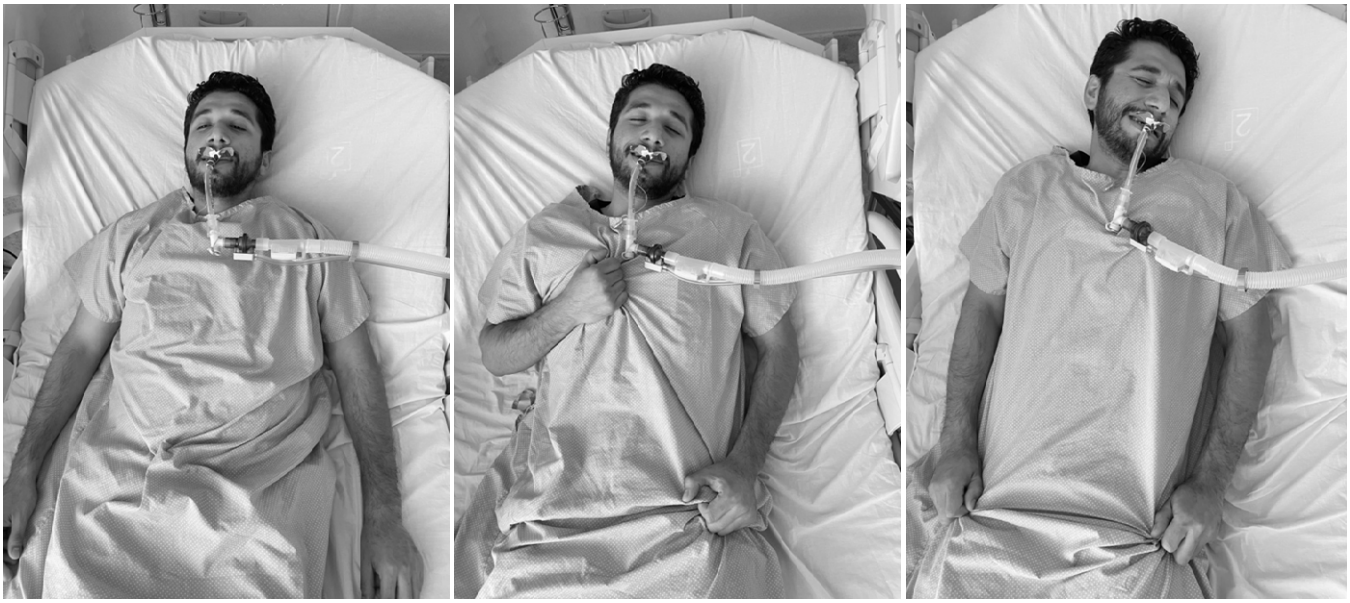

Figure 1. Left. CPOT 0: Facial expression relaxed, absence of movements, muscle tension relaxed, tolerating ventilator. RASS -2: Light sedation.
Middle. CPOT 4: Facial expression tense, body movements protection, muscle tension rigid, coughing but tolerating ventilator. RASS +2: Agitated.
Right. CPOT 8: Facial expression grimacing, body movements restlessness, muscle very tense or rigid, fighting. RASS +3: Very agitated.

Critical Care Pain Observation Tool (CPOT)		
Facial expression	Relaxed	0
	Tense	1
	Grimacing	2
Body movements	Absence of movements	0
	Protection	1
	Restlessness	2
Muscle tension	Relaxed	0
	Tense, rigid	1
	Very tense or rigid	2
Compliance with the ventilator	Tolerating ventilator or movement	0
	Coughing but tolerating	1
	Fighting	2
Vocalisation	Talking in normal tone or no sound	0
	Sighing, moaning	1
	Crying out, sobbing	2
Goal: <3		

Table1. Critical Care Pain Observation Tool

drugs most frequently used for pain management in the ICU include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. Other drugs, such as ketamine, lidocaine, neuromodulators and magnesium sulfate, may also be used. Another strategy to be considered is that of regional analgesia, more widely used in post-surgical patients, which will not be addressed in this review.

Indications for therapeutic or prophylactic administration of pain medications in the ICU include the following:

1. Patients with endotracheal intubation and IMV
2. Polytrauma
3. Burns
4. Post-operative period
5. During procedures such as tracheostomy, placement of pleural tubes, dressing and debridement of wounds, drainage of fluid collections, catheter placements, etc.
6. Chronic pain (e.g., cancer)
7. Neuropathic pain
8. Palliative care

Opioids are considered first-choice drugs for analgesia in critically ill patients due to their high efficacy. These act on the μ, κ and δ receptors of the central nervous system (CNS). The most highly recommended of them are remifentanil, fentanyl, morphine and hydromorphone given their higher analgesic effectiveness. Other less advised opioid medications include buprenorphine, oxycodone, nalbuphine and codeine, which are associated with a higher incidence of adverse effects and a lower analgesic potency.

Opioid accumulation is associated with the following side effects: nausea, vomiting, ileus, haemodynamic instability and respiratory depression. Therefore, their use should be restricted to short periods of time. It is highly encouraged to use the minimum effective dose to achieve the desired effect, since higher doses might cause tolerance and desensitisation of receptors, thereby reducing their effect and, in turn, further requiring higher doses. To minimise adverse effects, a multimodal analgesia with adjuvant drugs may be used, with the aim of blocking the transmission of pain by other mechanisms at the peripheral level and at the level of the spinal cord-hypothalamus-cerebral cortex axis.

Opioid-induced hyperalgesia results from their use for prolonged periods of time along with excessive doses (Lee 2011). It is originated by an impaired action from N-methyl-D-aspartate (NMDA) glutamatergic receptors and an increase in spinal dynorphin levels, resulting in an excessive synthesis and a release of excitatory neuropeptides, thus shifting the balance between antinociceptive and pronociceptive systems. For the above reasons, opioids should be

withdrawn as early as possible - as soon as the cause of the pain is solved.

As a result of its ultra-short action and its elimination by plasmatic esterases, remifentanil is the opioid medication of choice. This drug is associated with lower days under IMV, lower time to extubation and lower length of ICU stay. Its pharmacokinetics are not affected by renal or hepatic impairment; therefore, it is safe in patients with liver or kidney diseases. Its major disadvantages include its high cost and lower availability compared to other opioid medications (Yang 2021). Fentanyl is associated with more days of IMV compared to remifentanil. Morphine is associated with hypotension due to histamine release, pruritus, and a higher incidence of nausea and vomiting. Along with hydromorphone, these drugs are reasonable options for analgesia (Devlin 2018).

Acetaminophen is recommended as an adjuvant analgesic in the opioid therapy of critically ill patients. Dose adjustment should be considered in chronic liver failure, and this drug must be avoided in acute liver failure and in cases of allergy. Nefopam is a histamine H1 receptor antagonist focused on the inhibition of monoamine uptake in synapses, which would lead to an increase in noradrenaline, dopamine and serotonin. It is advised as an adjuvant treatment to opioids and as a treatment alternative. However, it is seldom available worldwide.

NSAIDs remain an adequate alternative for analgesia. Their effect is comparable to low-potency opioids, thereby reducing opioid consumption, as well as their side effects. There is a wide variety of drugs included in this group such as COX-1, COX-2 and prostaglandin E2 inhibitors. Among critically ill patients, their adverse effects include acute kidney injury and gastrointestinal (GI) bleeding, with even higher risks for patients with pre-existing impaired renal blood flow, older adults, patients with heart disease, and patients with shock or those exposed to other nephrotoxic drugs (Thadhani 1996). Other lower incidence deleterious effects include cardiovascular and cerebrovascular complications, fluid retention, hypertension and thromboembolic events. In particular, ketorolac has been associated with a significant increase in the incidence of anastomotic leaks in post-operative patients (Wick 2017). However, NSAIDs are not recommended for routine use in critically ill patients.

In subanaesthetic doses, ketamine exerts an analgesic effect comparable to morphine, with a similar need for rescue doses. This drug reduces chronic hyperalgesia mediated by NMDA receptors, as well as that induced by opioid medications (Hirota 2011). Its advantages include the fact that it does not cause respiratory or haemodynamic depression, hence it is useful in patients with shock (Eikermann 2012). Its adverse effects are dose-dependent, and they include hypersalivation, nausea and vomiting, vivid dreams, blurry vision, hallucinations, nightmares and delirium. Due to its dissociative effects, ketamine proves useful in the pain management of severely burned patients or in those with a large number of invasive devices and procedures. It can also be safely used in patients with intracranial hypertension. Ketamine is metabolised via the liver and excreted by the kidneys, nevertheless, no significant adverse effects over hepatic and renal functions have been noted at subanaesthetic doses.

	Mechanism of action	Comments	Dose	Onset; half-life	Contraindications/ cautions	Adverse effects
Acetaminophen	Inhibition of cyclooxygenases (COX-1, COX-2, and COX-3). Acts upon the endocannabinoid and serotonergic systems and influences transient receptor potential channels (TRP) and voltage-gated Kv7 potassium channels. Inhibition of Cav3.2 T-type calcium channels. Acts on L-arginine in the nitric oxide (NO) synthesis pathway.	Reduces opioid consumption. First-line treatment for mild to moderate pain. Weak anti-inflammatory action.	PO/IV: 1 g every 6-8 h Maximum dose: 4 g in 24 h	Onset: IV: 5-10 min PO: 30-60 min t½: 4-6 h	Caution in patients with significant liver dysfunction. Caution in malnutrition.	Associated with hypotension (IV administration). Liver failure (high doses).
Nefopam	Histamine H1 receptor antagonist focused on the inhibition of monoamine uptake in synapses, which would lead to an increase in noradrenaline, dopamine and serotonin.	Seldom available worldwide	20-30 mg every 6-12 h Maximum dose: 120 mg in 24 h	Onset: PO: 15-20 min IV: 15-20 min t½: 3-8 h	History of convulsive disorders. IM/IV: Urinary retention linked to urinary or prostate disorders, angle-closure glaucoma. Oral: Concomitant use with MAOIs.	Blurred vision, xerostomia, constipation, urinary retention, tachycardia, palpitations, angina. Nausea, vomiting, diarrhoea, abdominal pain. Dizziness, drowsiness, headache, paraesthesia, tremor, convulsion, light-headedness. Hypotension, syncope.

Tramadol	Acts on the CNS. Binds to μ-opioid receptors and blocks noradrenaline and serotonin reuptake by binding to monoaminergic receptors.	Partial antagonism by naloxone. Considered a mild opioid.	PO/IV: 50-100 mg every 4-6 h Maximum dose: 400 mg in 24 h	Onset: IV: 5-10 min PO: up to 1 h t½: 4-6 h	Accumulation in renal or liver failure. Associated with seizures in patients with epilepsy. Contraindicated with concurrent use of monoamine oxidase inhibitors (MAOIs).	Respiratory depression (less than other opioids). Nausea/vomiting. Ileus.
Gabapentin	Binds to α2δ subunits of voltage-gated calcium channels.	Useful for neuropathic pain. Reduces incidence of hyperalgesia and central sensitisation. Anticonvulsant. Reduces opioid consumption (multimodal analgesia in the ICU).	Start with 100 mg PO every 8 h Maintenance dose: 900-3600 mg/day	Onset: N/A t½: 4.8–8.7 h	Requires renal dosage adjustment. Absorbed in a relatively small portion of the duodenum. Ineffective in patients under jejunal feeding.	Sedation. Confusion. Ataxia. Dizziness.
Pregabalin	Neuromodulator. With potent binding to the α2-δ subunit, reduces calcium influx into presynaptic nerve terminals, with release of excitatory neurotransmitters such as glutamate, norepinephrine, and substance P.	Useful for neuropathic pain. Reduces incidence of hyperalgesia and central sensitisation. Anticonvulsant.	50–300 mg PO every 8-12 h	Onset: N/A t½: 5.5–6.7 h	Requires renal dosage adjustment.	Sedation. Confusion. Ataxia. Dizziness.
Carbamazepine	Blockade of voltage-gated sodium channels. Potent anticholinergic that acts at the level of muscarinic and nicotinic receptors.	Anticonvulsant. Reduces opioid consumption (multimodal analgesia in the ICU).	Start with 50-100 mg PO every 12 h Maintenance dose: 100-200 mg every 4-6 h Maximum dose: 1200 mg/day	Onset: 4-5 h t½: 5-26 h	Caution in AV block. History of myelosuppression and hepatic porphyrias. Caution with concurrent use of monoamine oxidase inhibitors (MAOIs).	Dizziness Ataxia Drowsiness Fatigue Headache Diplopia Urticaria Leukopenia Eosinophilia Thrombocytopenia
Lidocaine	Blockade of voltage-gated sodium channels, leading to a reversible blockade of the propagation of action potentials.	Reduces opioid consumption (when used in infusion). Shortens duration of perioperative ileus. Decreases the incidence of nausea/vomiting.	IV bolus: 1.5-2 mg/kg Infusion: 1.5-3 mg/kg Maximum dose: 5 mg/kg	Onset: immediate (IV) t½: 90-120 min	Caution in congestive heart failure and liver failure.	Dizziness Tinnitus Fasciculations Visual disturbances Arrythmias

Morphine	Stimulates μ, κ and δ receptors distributed in the CNS and peripheral tissues.	Metabolised by glucuronidation. Active metabolites: M6G and M3G. Releases histamine from mast cells, causing vasodilation.	IV bolus: 0.1-0.2 mg/kg Infusion: 0.05-0.1 mg/kg/h	Onset: 5-10 min t½: 3-5 h	Metabolites accumulation in renal failure. Causes histamine release.	Immunosuppression Delirium, sedation, and respiratory depression Tolerance within 48 h Withdrawal symptoms after discontinuation Hyperalgesia and other pain syndromes with long-term use Ileus/constipation/nausea/vomiting Urinary retention Bradycardia
Hydromorphone	Semi-synthetic opioid agonist. Stimulates μ receptors (and δ receptors to a lesser degree) at the supraspinal and spinal levels.	Metabolised mainly into dihydroisomorphine glucuronide and hydromorphone-3-glucuronide (H3G). May require higher doses in patients with history of prior opioid use	IV bolus: 0.2-0.6 mg Infusion: 0.5-5.0 mg/h PO: 2-8 mg/3-4 h	Onset: 10-20 min t½: 2-6 h	Decrease dose in older adults. Requires dose adjustment in patients with morbid obesity, liver/renal failure, COPD, or restrictive lung diseases.	Delirium, euphoria, miosis, drug dependence, tolerance Constipation, nausea, vomiting Pruritus Respiratory depression Urinary retention
Fentanyl	Stimulates μ, κ and δ receptors distributed in the CNS and peripheral tissues.	Synthetic opioid. Fat-soluble. Causes less hypotension than morphine. Hepatic metabolism without active metabolites	IV bolus: 0.3-0.5 mcg/kg Up to 2 mcg/kg Infusion: 1-10 mcg/kg/h	Onset: 1-2 min t½: 1-4 h	Administration should be based on ideal body weight in obese patients. Older adults may require lower doses. Caution in uncontrolled hypothyroidism, lung diseases, decreased respiratory reserve, alcoholism, functional liver/renal damage. Muscle stiffness when rapidly infused.	Sedation, delirium Tolerance within 48 h Withdrawal symptoms after discontinuation Hyperalgesia and other pain syndromes with long-term use Respiratory depression Ileus, constipation, nausea, vomiting Urinary retention Bradycardia
Remifentanil	μ receptor selective agonist, with rapid onset and short duration.	Hydrolysis by plasmatic esterases, without active metabolites. Allows for an early neurologic assessment in neurointensive care. Does not increase histamine.	IV bolus: 1 mcg/kg Infusion: 0.05-2 mcg/kg/h	Onset: 1-3 min t½: 3-10 min	No accumulation in patients with liver/renal failure. Administration should be based on ideal body weight in obese patients. Muscle stiffness may occur.	Immunosuppression Sedation, delirium Respiratory depression Tolerance within 48 h Withdrawal symptoms after discontinuation Hyperalgesia and other pain syndromes with long-term use Ileus, constipation, nausea, vomiting Urinary retention Bradycardia

Sufentanil	High affinity to the μ receptor. Slow dissociation.	Synthetic opioid. 7 to 10 times more potent than fentanyl. Accumulation unlikely.	IV bolus: 0.1-0.3 mcg/kg Infusion: 0.1-1 mcg/kg/h	Onset: 1-3 min t½: 0.5-2 h	Caution with concurrent use of monoamine oxidase inhibitors (MAOIs).	Sedation, delirium Respiratory depression Tolerance or withdrawal symptoms Ileus/constipation Nausea/vomiting Urinary retention Bradycardia
Diclofenac	COX-1 and COX-2 inhibition, which regulate production of prostaglandins and thromboxane from arachidonic acid.	Analgesic, antipyretic, and anti-inflammatory. PO is 100% absorbed.	IV bolus: 75 mg Infusion: 0.04 mg/kg/h	Onset: 15-30 min t½: 2 h	Avoid in patients with risk of acute kidney injury: e.g., hypovolaemia or inotrope-dependent shock. Avoid in patients with risk of GI bleeding: burns, platelet abnormalities, coagulopathy, concomitant use of ACE inhibitors, congestive heart failure, cirrhosis.	Acute kidney injury. GI bleeding. Hypotension.
Ibuprofen	COX-1 and COX-2 inhibition, which regulate production of prostaglandins and thromboxane from arachidonic acid.	Analgesic, antipyretic, and anti-inflammatory.	PO: 400-600 mg every 4 h Maximum dose: 2.4 g/day	Onset: 25 min t½: 1.8-3.5 h	Avoid in patients with risk of acute kidney injury: e.g., hypovolaemia or inotrope-dependent shock. Avoid in patients with risk of GI bleeding: burns, platelet abnormalities, coagulopathy, concomitant use of ACE inhibitors, congestive heart failure, cirrhosis.	Acute kidney injury. GI bleeding.
Ketorolac	COX-1 and COX-2 inhibition, which regulate production of prostaglandins and thromboxane from arachidonic acid.	Analgesic, antipyretic, and anti-inflammatory.	IV: 10-30 mg every 4-6 h, in no less than 15 s Infusion: 5 mg/h	Onset: 10 min t½: 4-6 h	Avoid in patients with risk of acute kidney injury: e.g., hypovolaemia or inotrope-dependent shock. Avoid in patients with risk of GI bleeding: burns, platelet abnormalities, coagulopathy, concomitant use of ACE inhibitors, congestive heart failure, cirrhosis.	Acute kidney injury. GI bleeding. Anastomotic leak.

Table 3. Analgesics

CNS: Central nervous system, MAOIs: Monoamine oxidase inhibitors, COPD: Chronic obstructive pulmonary disease, ACE: Angiotensin converting enzyme, GI: Gastrointestinal bleeding.

Sedation

Although maintenance sedation is a commonly used approach in critically ill patients, it is intrinsically harmful. This intervention is associated with patient weakness, delirium, increasing days on mechanical ventilation and increasing days of hospitalisation and ICU stay (Nedergaard 2022). However, it might be necessary in some specific scenarios. Indications for maintenance sedation include the following (Reade 2014):

1. Moderate to severe acute respiratory distress syndrome (ARDS).
2. Intracranial hypertension (e.g., severe traumatic brain injury with concurrent mass effect).
3. Status epilepticus (when non-responsive to first-line or second-line therapy).
4. Consider in abdominal compartment syndrome, flail chest and patients requiring major surgery, or inability to perform regional anaesthesia.

If opting for sedation, it is highly recommended that the dose of the medications is titrated according to predefined goals based on the patient's condition, as well as continuous monitoring. There are several ways to monitor the sedation state of a critically ill patient; the RASS scale is the most widespread tool for this purpose. If a given patient has an indication for deep sedation (e.g., ARDS or refractory intracranial hypertension) it is recommended that they remain at a level <-3. However, if only minimal sedation is planned (such as in a patient under a weaning protocol), it is reasonable to remain in levels from 0 to -1. It is difficult to find a justification for maintaining a moderate sedation (RASS 2 to 3). There are different technological sedation monitors such as the unilateral or bilateral bispectral index (BIS), entropy monitoring, among others, although none has been shown superior to the RASS scale (**Table 2**), and they could indeed prompt additional expenses.

Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS) guidelines endorse propofol and dexmedetomidine as first-choice sedatives. Benzodiazepines are not recommended as maintenance sedatives due to their association with delirium (Devlin 2018). Ketamine might also be considered as a sedative for critically ill patients, even showing benefits in patients with shock including lower rates of hypotension and bradycardia (Umunna 2015).

The haemodynamic changes associated with propofol may include myocardial depression, bradycardia and hypotension. It must be taken into consideration that propofol provides up to 1.1 kcal per millilitre; therefore, it may cause hypertriglyceridaemia, pancreatitis or overfeeding. With regard to dexmedetomidine, this drug frequently causes bradycardia, and it may also contribute to hypotension in patients with shock; nevertheless, its safety profile appears to be better than other sedatives and it has even been associated with greater haemodynamic stability in patients with septic shock. Unfortunately, despite many recommendations discouraging the use of benzodiazepines, midazolam remains the most commonly used sedative in continuous sedation among many hospitals (Luz 2022). It is recommended to consider the use of anti-psychotic agents, volatile anaesthetics or intermittent benzodiazepines in patients with ARDS who do not achieve deep sedation with propofol and dexmedetomidine.

It is important to emphasise that the condition that leads the patient to require sedation must be solved as soon as possible, and a wake-up test must be performed early in the course to prompt a timely ICU discharge, which should be repeated every day until the patient can be safely withdrawn from mechanical ventilation. This procedure is associated with fewer days on IMV, and fewer days of ICU stay.

Richmond Agitation Sedation Scale (RASS)		
Combative	Overtly combative, immediate danger to staff	+4
Very agitated	Pulls on or removes tube (s) or catheter (s) or has aggressive behaviour toward staff	+3
Agitated	Frequent non-purposeful movement or patient-ventilator dyssynchrony	+2
Restless	Anxious or apprehensive but movements not aggressive or vigorous	+1
Alert and calm	Spontaneously pays attention to caregiver	0
Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact to voice	-1
Light sedation	Briefly (less than 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

Table 2. Richmond Agitation Sedation Scale

	Mechanism of action	Comments	Dose	Onset; half-life	Contraindications/ cautions	Adverse effects
Propofol	Potentiates activation of GABA-mediated ion channels. Inhibition of NMDA receptors.	Sedative-hypnotic, anxiolytic. Antiemetic.	IV bolus: 1-2 mg/kg Infusion: 20-50 mcg/kg/min ≥60 mcg/kg/min associated with propofol infusion syndrome	Onset: 15-30 s t½: 5-10 min	Hepatic metabolism. Renal excretion. Avoid with triglycerides ≥800 mg/dl.	Respiratory depression Metabolic acidosis Immunosuppression Pancreatitis Hypotension QT prolongation Myocardial depression Green urine
Dexmedetomidine	α2 receptor agonist. α2 selectivity over α1 receptors (1600:1). Induces sleep by decreasing the firing of noradrenergic neurons of the locus coeruleus in the brainstem, and by activating endogenous pathways that promote non-rapid eye movement (NREM) sleep.	Conscious sedation, sympatholytic, anxiolytic, analgesic. Decreases risk of delirium. Regulates sleep. Reduces opioid consumption (multimodal analgesia).	IV bolus: no Infusion: 0.2-0.7 mcg/kg/h >1.5 mcg/kg/h associated with risk of cardiotoxicity.	Onset: 15-20 min t½: 3-4 h	Caution with concurrent use of esmolol. Consider dose reduction in patients with liver disease.	Hypotension Bradycardia Dry mouth Nausea
Ketamine	NMDA antagonist. Acts upon opioid receptors and monoaminergic receptors. Inhibition of muscarinic receptors. Promotes GABAergic transmission.	Dissociative anaesthesia, sedation, and analgesia. Prevents neuropathic pain. Confers haemodynamic stability (positive chronotropism, increases blood pressure). Bronchodilation. Preserves airway reflexes.	IV bolus: 0.2-4.5 mg/kg IM: 6.5-13 mg/kg Infusion: 2.5-5 mcg/kg/min > 20 mg/kg associated with myocardial depression	Onset: 30-40 s t½: 10-15 min	Porphyria Thyroid diseases	Sialorrhea Laryngospasm Drug dependence Dysuria Urinary incontinence Hallucinations
Etomidate	Modulates and activates $GABA_A$ receptors that contain β2 and β3 subunits.	Anaesthetic, hypnotic. Haemodynamic stability (attenuates responses to ACO and bradykinin). 34% decrease in cerebral blood flow and 45% decrease in cerebral metabolic rate of oxygen (CMRO2) without mean arterial pressure (MAP) being affected. Anticonvulsant.	IV bolus: 0.2-0.6 mg/kg Infusion: no	Onset: 30-60 s t½: 2.5-5.5 h	Hepatic metabolism. Renal excretion. Interaction with metamizole (dipyrone).	Inhibition of adrenocortical axis Myoclonus Nausea/vomiting Injection site pain Nystagmus Hiccups

Midazolam	GABA agonist. Increases the opening frequency of chloride channels.	Hypnotic, sedative, anxiolytic, and amnesic activity. Anticonvulsant (first-line therapy in status epilepticus).	IV bolus: 0.01-0.05 mg/kg Infusion: 0.02-0.1 mg/kg/h	Onset: 2-3 min t½: 3-72 h	Clearance depends on hepatic and renal function.	Hypotension Bradycardia Thrombosis Respiratory depression Delirium Tachyphylaxis Immunosuppression Ataxia Polyneuropathy/Critical illness myopathy
Lorazepam	GABA agonist. Increases the opening frequency of chloride channels. This change results in hyperpolarisation and stabilisation of cell plasma membrane.	Anterograde amnesia. Sedative. Anxiolysis. Anticonvulsant.	PO: 2-3 mg every 8-12 h IM: 0.05 mg/kg IV bolus: 0.02-0.04 mg/kg Infusion: 0.01-0.1 mg/kg/h	Onset: 1-3 min (IV), 15-30 min (IM) t½: 14 h Peak plasma time: 2 h (PO)	Myasthenia gravis, acute angle-closure glaucoma. Caution in obstructive sleep apnoea and severe respiratory failure.	Hypotension Respiratory depression Diarrhoea Delirium Tachyphylaxis
Diazepam	GABA agonist. Increases the opening frequency (but not opening duration) of chloride channels.	Anterograde amnesia, sedation. Highly fat-soluble. Crosses the blood-brain barrier.	IV bolus: 0.1-0.2 mg/kg Infusion: no	Onset: 2-5 min t½: 20-120 h Biphasic half-life with a rapid initial distribution phase and a prolonged terminal elimination phase of 1 to 2 days.	Diazepam and desmethyldiazepam (active metabolite) accumulate with repeated dosing. Accumulation occurs mostly in newborns, older adults and in patients with liver diseases.	Hypotension Respiratory depression Phlebitis Delirium Tachyphylaxis

Table 4. Sedatives
NMDA: N-methyl-D-aspartate, GABA: Gamma-aminobutiryc acid.

Neuromuscular Blockade

Neuromuscular blockade (NMB) can be common among critically ill patients, especially in the course of ARDS treatment. Its indications are limited, and this modality is associated with several adverse effects such as venous thromboembolism, critical illness myopathy, patient awareness during paralysis, autonomic interactions, pressure ulcers, corneal ulcers and residual paralysis (Renew 2020).

Indications of NMB in the ICU include:

1. Rapid sequence intubation (RSI)
2. Moderate to severe ARDS
3. Consider in intracranial hypertension, refractory status asthmaticus, failed sedation, and to temporarily reduce intra-abdominal pressure in patients with intra-abdominal hypertension (IAH), among others (De Laet 2007).

The American Society of Anesthesiologists (ASA) recommends the use of NMB to reduce the number of intubation attempts, thereby decreasing the risk of airway injuries during direct laryngoscopy (Apfelbaum 2013). Rocuronium is the only non-depolarising drug indicated for induction and intubation during RSI.

Regarding the management of moderate to severe ARDS in patients under IMV, meta-analyses have shown a reduction in mortality in the ICU when using an infusion of cisatracurium (Ho 2020), and recently, it has shown greater utility if maintained under continuous infusion for more than 48 hours in patients with respiratory failure under IMV due to COVID-19 (Li 2021). The major advantage of cisatracurium relies on its metabolism by Hofmann elimination, which confers a rapid elimination of its

effects when withdrawn. Moreover, it does not depend on hepatic or renal depuration. A strategy that combines the use of NMB with cisatracurium and low tidal volume could reduce mortality, most likely due to a reduction of asynchrony events and improvement of pulmonary compliance and functional residual capacity, which would translate into an increase in oxygenation (Murray 2016; Battaglini 2021; Chang 2020).

Among neurocritical patients with acute brain injury, the use of NMB has been suggested in order to reduce the number of episodes of intracranial hypertension; however, the level of evidence for this recommendation is low (Renew 2020). Its main effect relies on the reduction of asynchrony events with the ventilator, cough limitation and any other condition that may cause Valsalva manoeuvre (Steingrub 2014). In patients with intra-abdominal hypertension and abdominal compartment syndrome, NMB has also been suggested in order to increase abdominal compliance by relaxation of the abdominal muscles (Malbrain 2005). Nonetheless, conclusive evidence in this regard is lacking.

There are other neuromuscular blocking agents (NMBA) not currently recommended as first-choice drugs; however, their use in specific scenarios may be justified when the latter are not available. In patients with ARDS that require NMB, vecuronium, atracurium or pancuronium may also be used, although with the risk of prolonging neuromuscular relaxation, thereby increasing side effects. In addition, when rocuronium is not available for RSI, succinylcholine can also be considered, which is a depolarising NMB of ultra-short action, although with the risk of hyperkalaemia and even malignant hyperthermia (Zamarrón-López 2019).

Train-of-four nerve stimulation (TOF) is a tool for the monitoring of NMB. A value <0.7 is considered an adequate paralysis (Murphy 2010). In a recent study that compared three strategies for using NMB (a fixed-dose of cisatracurium; titration based solely on TOF and a ventilator synchrony protocol), it was shown that a protocol using ventilator synchrony for cisatracurium titration required significantly less drug compared to TOF-based titration and a fixed dosing regimen (DiBridge 2021).

Several factors affect the duration of NMBA activity: for instance, the concomitant use of diuretics, antiarrhythmics, aminoglycosides, magnesium, lithium, as well as some conditions such as hypokalaemia, hypothermia and acidosis, all increase the potency of non-depolarising NMBA. NMBA potency is inversely related to its speed of onset (that is, the lower the potency of the drug, the faster the onset of neuromuscular blockade after its administration). Patients with myasthenia gravis and glaucoma are especially sensitive to the effects of NMB. On the other hand, patients with burns are resistant to the effects of NMBA due to the proliferation (upregulation) of nicotinic receptors in the sarcolemma (Murray 2016).

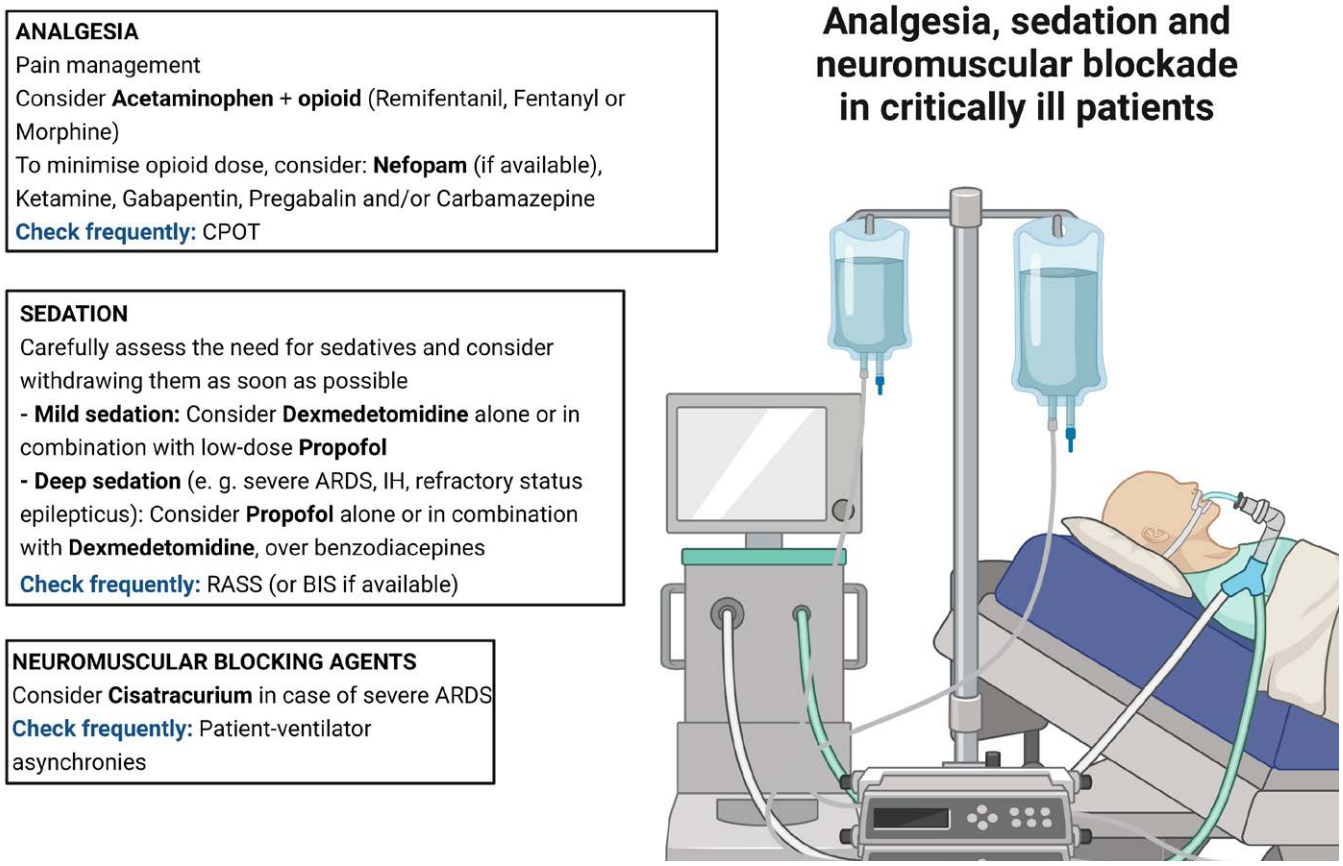

Figure 5. Analgesia, sedation and neuromuscular blockade in critically ill patients

NMBA	Mechanism of action	Comments	Dose	Onset; half-life	Contraindications/cautions	Adverse effects
Atracurium	nNMBs. Intermediate action.	Histamine release. Metabolite: laudanosine (decreases seizure threshold).	IV bolus: 0.4-0.5 mg/kg Infusion: 5-20 mcg/kg/min	Onset: 3-5 min t½: 2-20 min	Does not require dose adjustment in liver/renal failure.	Hypotension Seizures Skin flush Green urine
Cisatracurium	nNMBs. Elimination by plasmatic esterases.	First-line in continuous infusion.	IV bolus: 0.1-0.2 mg/kg Infusion: 1-4 mcg/kg/min	Onset: 2-3 min t½: 22-29 min	Does not require dose adjustment in liver/renal failure.	Histamine release in high doses
Pancuronium	nNMBs. Prolonged action.	Vagal blockade, sympathetic stimulation.	IV bolus: 0.05-0.1 mg/kg Infusion: 0.8-1.7 mcg/kg/min	Onset: 2-3 min t½: 89-161 min	Significant accumulation, prone to residual blockage (3-OH metabolite).	Hypotension Tachycardia Vagal blockade Catecholamine release
Rocuronium	nNMBs. Intermediate action.	Second-line in continuous infusion.	IV bolus: 0.6-1.2 mg/kg Infusion: 8-12 mcg/kg/min	Onset: 1-2 min t½: 1-2 h	Preferable over vecuronium in renal dysfunction.	Unpredictable in recurring doses
Vecuronium	nNMBs. Intermediate action.	Does not cause fasciculations.	IV bolus: 0.1 mg/kg Infusion: 0.8-1.7 mcg/kg/min	Onset: 3-4 min t½: 4 min	Preferable over rocuronium in liver dysfunction.	Vagal blockade with higher doses Arrhythmia Urinary retention

Table 5. Neuromuscular blocking agents
nNMBs: Non-depolarising neuromuscular blockers.

Conclusions

Analgesics, sedatives and neuromuscular blocking agents are commonly used medications in the ICU. An adequate protocol of care involves knowledge of their indications, adverse effects, their correct use and the selection of the most appropriate agent, with the aim of reducing morbimortality in critically ill patients.

Conflict of Interest

None. ■

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