Section A -Research paper

Sedation in septic patients in Intensive Care Unit: Review Article

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Abstract:

As most critically ill or injured patients will require some degree of sedation, the goal of this paper was to comprehensively review the literature associated with the indication of use of sedative agents and their types in the intensive care unit (ICU).

Keywords: Sedation, sepsis, Intensive Care Unit.

Introduction:

ICU patients with sepsis are clinically treated by sedative treatment, because of the great discomfort and pain caused by invasive operation for ICU patients. Traditional anesthetics like propofol,ketamine, midazolam and dexmedetomidine have strong sedative, analgesic and certain anti-inflammatory effects on ICU patients with sepsis, and they can relieve the anxiety and discomfort of the patients. Studies worldwide are usually limited to the sedative treatment with anesthetics, and which drug is the most suitable for ICU patients with sepsis remains controversial (1).

Sedation has been a ubiquitous and essential component of critical care since its beginnings and plays a cardinal role in allowing therapies to be undertaken whilst minimising patient distress. Sedation requirements vary widely between patients and at different times of their illness. Being ill in an ICU is nearly always very frightening and may require a number of painful or uncomfortable procedures. The sedative regimen must be tailored to the individual patient, necessitating a multimodal and multidisciplinary approach and does not simply involve the use of drugs. Adequate analgesia should be a fundamental part of this approach; sedation should never be given as a substitute for analgesia. The term ‘sedation’ has become a catch-all phrase to describe everything from anxiolysis – ‘a little something to help you sleep’ – to a state of unresponsiveness that mimics general anaesthesia. This imprecision in terminology emphasises the need to define precisely our aims when the decision to ‘sedate’ is made The medical and nursing teams should always strive to use the minimum dose of sedation to achieve the desired effects without compromising

patient comfort and safety. There may, however, be situations where high doses of drugs are necessary to induce deep sedation verging on general anaesthesia(2).

Indications for the use of sedative drugs in the ICU include:

- To alleviate pain
- To facilitate the use of an otherwise distressing treatment and minimize discomfort e.g., tolerance of endotracheal tubes and ventilation To augment the effectiveness of a treatment e.g., inverse ratio ventilation As a treatment in its own right e.g., seizure control or management of intra cranial pressure
- To reduce anxiety
- To control agitation
- For amnesia during neuromuscular blockade

A variety of medications may be used for sedation and analgesia. These include opioids, benzodiazepines, intravenous and inhaled general anaesthetic agents, neuroleptic drugs, phencyclidine derivatives, phenothiazines, α-agonists and barbiturates.

While these drugs are used to help the patient, they carry with them the potential for harm.Those who sedate patients in the ICU should be fully informed of the benefits and problems associated with each drug they use and be fully appreciative of possible adjuncts to pharmacological sedation.

High quality care does not solely rest on the judicious use of drugs but also requires an understanding of the causes of the distress and the creation of an environment that reduces stress. The ICU patient may have a limited number of ways to express themselves and a patient who is pulling at monitoring lines may be distressed, in pain, delirious or a combination of all three. Prolonged sedation is an intervention whose adverse effects are often underestimated. Over-sedation may be responsible for prolongation of artificial ventilation, hypotension and under-perfusion, prolonged recovery and increased need for tracheostomy, delay in weaning from respiratory support, critical illness myopathy and muscle wasting, an increase in delirium, immunosuppression, ileus of the gastro-intestinal tract, thrombosis and DVT, with down regulation of receptors and increased risk of nosocomial pneumonia. Conversely, under-sedation not only causes generalised discomfort and tracheal tube intolerance but also hypercatabolism, increased sympathetic activity leading to hypertension, tachycardia, increased oxygen consumption, myocardial ischaemia, atelectasis, infection and psychological trauma. However, the perception that by sedating our patients we are protecting them from an unpleasant experience is probably not entirely correct. Patients who can only recall delusional memories are more likely to develop anxiety and post-traumatic stress disorder (PTSD) following discharge.

Types of sedation in septic patients

The most commonly used agents are intravenous anaesthetic agents (Benzodiazepines often in combination with opioids, Dexmedetomidine,Propofol and Ketamine). The current literature supports modest benefits in outcomes with non-

benzodiazepine-based sedation versus benzodiazepines (3).

Benzodiazepines are commonly used for sedation in the critically ill. They bind to the GABA receptor complex modulating GABA release in the CNS causing downregulation of neuronal excitation. This causes sedation, anxiolysis or hypnosis depending on the doses used and the number of receptors occupied. They do not cause general anaesthesia, but will depress the respiratory centre and cause cardiovascular depression. They are bound to plasma proteins and are not removed by dialysis.

Midazolam is a short-acting, water-soluble benzodiazepine that becomes lipophilic in the blood and rapidly enters the CNS. Anterograde amnesia occurs almost immediately after intravenous administration and usually persists for 20–40 min after a single dose. Midazolam is hydroxylated by CYP3A4 and its metabolism can therefore be affected by hepatic function, blood flow and administration of other drugs (e.g., diltiazem, macrolides, cimetidine and ranitidine). Midazolam has an active metabolite, α1-hydroxymidazolam, which accumulates in renal failure. Consequently midazolam has a large variability in its elimination half-life and an unpredictable offset of action following prolonged administration. A wide inter-patient variability in the pharmacokinetic properties of midazolam in critically ill patients with multiple organ failure has been reported, which can lead to prolonged sedation after midazolam therapy is stopped. Unpredictable awakening times and prolonged extubation times have been reported when midazolam is administered by infusion for longer than 72 hours. Tolerance and tachyphylaxis may occur, particularly with longer-term infusions (>= 3 days). Benzodiazepine withdrawal syndrome has also been associated with high dose/long-term midazolam infusions (4).

Compared with propofol infusions, midazolam infusions have been associated with a decreased occurrence of hypotension but a more variable time course for recovery of function after the cessation of the infusion. Midazolam is most commonly administered via a continuous infusion titrated between 0.25 and 1.0 μg/kg/min. Sedation holds should be used in patients not requiring deep sedation to ensure optimal wake up times. One review suggested that bolus administration may be used as an alternative to infusion, reducing mechanical ventilation duration and ICU length of stay. Doses of 0.5–2 mg IV every 5–10 minutes can be administered as needed. Diazepam and Lorazepam are used less often to sedate patients in the ICU and can only be administered intravenously by intermittent infusion due to a long elimination half-life .The active metabolites can accumulate with prolonged administration, especially in the context of renal dysfunction.

Opioids such as morphine, fentanyl, alfentanil and remifentanil are the mainstays of the treatment of pain in the ICU. They are central nervous system μ receptor agonists that invoke analgesia, sedation, respiratory depression, constipation, urinary retention, nausea, and confusion. When administered

parenterally in equivalent doses, there are no differences in analgesic effect, but pharmacokinetics, metabolism and side effects vary. The choice of agent therefore depends on the desired onset and duration of action and the potential adverse effects of the agent. In order to cross the blood brain barrier an opioid needs to be lipid soluble. Consequently when given as a bolus dose, duration of action of many opioids tends to be short due to redistribution into the large volume of fat stores; following infusion this compartment can become saturated and the effect substantially prolonged. There are few trials comparing the various opioids to each other in critically ill patients. There are no dosing recommendations given in this document as doses need to be titrated to the needs of each individual.

Dexmedetomidine is a marvelous α2-agonist with analgesic, sedative, sympatholytic and anxiolytic properties. It demonstrates a much higher affinity to the alpha2 receptor than clonidine which makes its sedative effects much more prominent than clonidine. Sedation by α2-agonists appears to be unique in that patients can be roused readily and performance on psychomotor tests is reasonably well preserved. Consequently, patients sedated with α2-agonists may be more cooperative and communicative than patients sedated with other drugs in the intensive care setting. Dexmedetomidine depresses the gag reflex and improves endotracheal tube tolerance when compared with other sedatives. The cardiovascular effects should not be under emphasised however. Basic and translational studies showed that among the recommended sedatives, dexmedetomidine has anti-inflammatory and anti-bacterial effects, which are superior to those of gammaaminobutyric acid agonists, such as benzodiazepines and propofol. Furthermore, it also reduces neuronal apoptosis and promotes biomimetic sleep—all of which could improve clinical outcomes (5).

Boluses of dexmedetomidine result in a biphasic response; there is an initial peripheral effect causing vasoconstriction resulting in hypertension and a reflex bradycardia and ultimately, a central effect causing vasodilation, bradycardia and hypotension. Arrhythmias and sinus arrest have both been reported. Boluses of Dexmedetomidine are not recommended. Dexmedetomidine decreases the duration of mechanical ventilation when compared to benzodiazepines but not when compared to propofol. The MIDEX trial demonstrated a shorter duration of mechanical ventilation compared to midazolam (123 versus 164 hours). The ability to have an awake, comfortable and ETT-tolerant patient without respiratory depression makes Dexmedetomidine close to the ideal sedative(6).

Following infusion, dexmedetomidine exhibits a rapid distribution phase with a halflife of about 6 minutes. A loading infusion of 1 mcg/kg over a 10-minute period provides clinically effective onset of sedation generally within 10 to 15 minutes. Maintenance doses of 0.2- 0.7mcg/kg/hr can be titrated to achieve the target level of sedation. For patients being converted from alternate sedative therapy, a loading dose

may not be required. The terminal elimination half-life of dexmedetomidine is approximately 2 hours. Dose reductions should be considered in the elderly and those with renal or hepatic impairment, and it should be used with caution in patients with any form of heart block.

Many tools exist for evaluating depth of sedation; however without a gold standard against which to evaluate, it is difficult to establish which is optimal. Broadly speaking we can use subjective clinical sedation scales or objective physiological tools – in every day practice however, clinical sedation scores are the most useful. The most commonly used scales are Richmond Agitation Sedation Score (RASS), Ramsay Sedation Scale and **Riker Sedation-Agitation Scale (SAS)**. The Richmond Agitation Sedation Score (RASS) (table 1) is a ten point scale that assesses both degrees of agitation and sedation (7).

Table (1):Richmond Agitation-Sedation Scale score

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitation	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
−2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

When assessing sedation it differentiates between verbal and physical stimulation; it also makes a basic assessment of attention, providing a possible indicator of delirium. This tool has also been validated against BIS index and drug doses, it also integrates with the Confusion Assessment Method for the ICU (CAM-ICU) for assessing delirium .

References:

1. Gulla KM, Sankar J, Jat KR, Kabra SK, Lodha R. Dexmedetomidine vs Midazolam for Sedation in Mechanically Ventilated Children: A Randomized Controlled Trial. Indian Pediatr. 2021 Feb 15;58(2):117-122.
2. Ma Y, Yu Xy and Wang Y. Dose-related effects of dexmedetomidine

onimmunomodulation and mortality to septic shock in rats. World J EmergMed 2018;9:56–63 .

3. Nakashima T, Miyamoto K, Shima N, Kato S, Kawazoe Y, Ohta Y et al. Dexmedetomidine improved renal function in patients with severe sepsis: an exploratory analysis of a randomized controlled trial. j intensive care 2020 **8,** 1.
4. Palomino J, Echavarria R, Franco-Acevedo, Moreno-Carranza B and Melo Z: Opoids preconditioning upon renal function and ischemia-reperfusion injury: A Narrative Review.Medicina (Kaunas) 2019; 55: 522.
5. Mei B, Li J, Zuo Z. Dexmedetomidine attenuates sepsis-associated inflammation and encephalopathy via central α2A adrenoceptor. Brain Behav Immun. 2021;91:296–314
6. Wang K,Wu M,Xu J, Wu C, Zhang B, Wang G et al.Effects of dexmedetomidine on perioperative stress, inflammation, and immune function: systematic review and meta-analysis,British Journal of Anaesthesia 2019,Volume 123, Issue 6.
7. Sessler CN, Gosnell MS, Grap MJ et al. The Richmond agitation–sedation scale validity and reliability in adult intensive care unit patients. Am J Resp Crit Care Med 2002; 166: 1338–1344.