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Analgosedation in Critically Ill Adults Receiving Extracorporeal Membrane Oxygenation Support

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Abstract

Extracorporeal membrane oxygenation (ECMO) is an increasingly utilized intervention for cardiopulmonary failure. Analgosedation during ECMO support is essential to ensure adequate pain and agitation control and ventilator synchrony, optimize ECMO support, facilitate patient assessment, and minimize adverse events. Although the principles of analgosedation are likely similar for all critically ill patients, ECMO circuitry alters medication pharmacodynamics and pharmacokinetics. Lack of clinical guidelines for analgosedation during ECMO, especially at times of medication shortage, can affect patient management. Here, we review pharmacological considerations, protocols, and special considerations for analgosedation in critically ill adults receiving ECMO support.

Introduction

Extracorporeal membrane oxygenation (ECMO) is an increasingly used form of prolonged mechanical cardiopulmonary support. The two main configurations of ECMO, veno-venous (VV) and veno-arterial (VA), provide extracorporeal gas exchange and circulatory support in patients with refractory respiratory and cardiac failure, respectively. ECMO support has been shown to improve clinical outcomes[1–5].

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Optimal analgosedation is critical in patients on ECMO support. The main goals for analgosedation during ECMO support are pain control, agitation prevention and treatment, ventilator synchrony, optimization of ECMO flows, lowering metabolic demand, as well as facilitation of patient communication and neurological examination, early liberation, and optimization of long-term functional outcomes. Both inadequate and excessive analgosedation may lead to potential harm and worsen short- and long-term functional and cognitive outcomes[6].

Several clinical guidelines have been published for analgosedation in acute respiratory distress syndrome and severe cardiogenic shock patients[7,8]. Although the principles of analgosedation are likely similar for all critically ill patients, no specific guidelines exist for patients receiving ECMO support, and deviations from current international guidelines are not unexpected in this complex population. ECMO circuitry can alter the pharmacokinetics of analgosedation medications[9,10]. In addition, ECMO initiation and maintenance require adequate pain, agitation, and movement control to optimize ventilatory support and gas exchange in VV-ECMO, lower metabolic demand of VA-ECMO patients, and prevent potential harm[11–14]. Therefore, ECMO patients commonly receive higher doses of analgesic and sedative medications than patients with similar disease severity who are not receiving ECMO support[15]. Lack of evidence-based practice guidelines is more conspicuous during increased demand and medication shortage, as experienced in the ongoing COVID-19 pandemic. This article reviews analgosedation in critically ill adults receiving ECMO support.

Pharmacological Considerations

The analgosedation choice varies based on clinical goals and patient-specific factors such as hemodynamics and renal and hepatic function. In addition, the ECMO circuit alters medication pharmacokinetics and pharmacodynamics[16] depending on the physicochemical properties of the drug, such as lipophilicity, protein binding, molecular size, and ionization degree[17]. Pharmacokinetic properties of commonly used analgesic and sedative agents with considerations in ECMO are summarized in Table 1. Of note, practitioners must be cautious when interpreting this data as much of the available literature is extrapolated from *ex vivo* and neonatal studies with limited evidence regarding clinical outcomes as well as the differences in body composition and immature renal and hepatic function in the neonatal population[17].

Alterations in Volume of Distribution

ECMO can increase the volume of distribution (V_d) and decrease serum levels of certain medications[17] that can significantly increase the analgosedation requirement. Components of the ECMO circuit, such as the membrane oxygenator and polyvinyl chloride (PVC) tubing, increase the surface area for drug sequestration and adsorption, although the oxygenator contribution to sequestration is minimal[17,18]. The degree of sequestration typically depends on the medication lipophilicity and protein binding[19], but the effects of molecular size and ionization degree are not well-characterized[18]. Lipophilic medications with a higher positive n-octanol/water partition coefficient (typically with a log P of ≥2)

have a higher risk of sequestration than hydrophilic medications due to solubility in organic materials, such as PVC tubing[16,17,20]. Sequestration is also higher with highly protein-bound medications, likely due to the binding of blood or the priming solution proteins to the circuit[16]. Critical illness may also alter plasma concentrations of highly protein-bound medications due to decreased albumin and increased α_1-acid glycoprotein concentrations[20]. However, less medication may be necessary over time after the binding sites on circuit surfaces become saturated[17]. Conversely, increased drug dosing may be required when circuit components are exchanged[18]. The circuit acts as a reservoir and slowly releases sequestered drugs after medication discontinuation resulting in a prolonged duration of action[17,18]. The V_d for hydrophilic medications also increases in ECMO from hemodilution due to priming solutions or volume resuscitation or by inducing a systemic inflammatory response with leaky capillaries[17,20]. Hemodilution can reduce concentrations of plasma proteins leading to higher free concentrations of highly protein-bound medications and toxicity[20]. Liberation from ECMO will decrease the V_d necessitating a significant empiric reduction in medication dosing to avoid toxicity[20].

Alterations in Medication Clearance

Medication clearance is typically reduced in patients receiving ECMO due to renal and hepatic hypoperfusion or insufficiency, resulting in the accumulation of medications and metabolites[17]. However, clearance may initially increase due to augmented cardiac output from volume resuscitation, inotropic support, and cardiac support with VA-ECMO[17,20].

Analgosedation Medications

Opioids

Clinical practice guidelines for preventing and managing pain, agitation/sedation, delirium, immobility, and sleep disruption in critically ill adults acknowledge that opioids remain the cornerstone for pain management in most settings[20]. These guidelines support an analgesia-first approach to minimize the use of sedatives. Using the lowest effective dose of opioid with careful titration as part of a multimodal analgesia regimen is recommended[21]. Daily sedative interruption and nursing-protocolized targeted sedation can be utilized to maintain light levels of sedation and minimize medication-related adverse effects[21]. The choice of opioid and the frequency of dosing (e.g., intermittent bolus, continuous infusion) depend on goals of care, frequency and severity of pain or agitation, and pharmacokinetic factors.

Fentanyl is commonly utilized in intensive care settings based on its rapid onset and ease of titration; however, its high sequestration level in ECMO circuits makes it a less desirable agent in this population.[10] The anilidopiperidines (such as fentanyl, alfentanil, remifentanil, and sufentanil) are highly lipophilic and highly protein-bound; therefore, extensive binding to components of the ECMO circuit occurs (Table 1)[10]. An *ex vivo* study evaluated fentanyl concentrations in crystalloid- and albumin-primed circuits and demonstrated a significant 97% loss of fentanyl at 24 hours compared to baseline[12]. Another *ex vivo* study compared crystalloid- and blood-primed circuits and showed fentanyl losses of 87% and 100%, respectively, at 24 hours[22]. Based on these findings, high doses of fentanyl would be required to be effective for ECMO patients, and alternative/additional agents may be

considered[18]. A strategy recently described in the literature is to initiate fentanyl as the first-line opioid and convert it to hydromorphone if fentanyl doses reach 400 mcg/hr without achieving adequate analgesia[23]. In a retrospective cohort study of 81 (38 obese and 43 non-obese) patients receiving VV-ECMO, 31 (38%) required a switch to hydromorphone within the first seven days[23].

Hydromorphone may be considered an initial opioid agent in patients requiring ECMO or a second-line agent for patients who have failed alternative agents. The onset of hydromorphone is slightly longer than fentanyl; however, it is hydrophilic and not highly protein-bound, which may be preferable in patients receiving ECMO. An *ex vivo* analysis of a pediatric ECMO circuit demonstrated hydromorphone losses at 12 hours were 23.5% compared to fentanyl losses of 55.4%[24]. A single-center propensity-matched study, comparing ECMO patients who received hydromorphone versus fentanyl, demonstrated significantly lower median (interquartile range; IQR) daily fentanyl equivalents [555 mcg (287–905) vs. 2291 mcg (1053–4023), $p<0.005$], and an increased number of delirium-free and coma-free days (53.2% vs. 42.1%, $p=0.006$) in patients receiving hydromorphone[25].

Morphine is hydrophilic and not highly protein-bound; and, therefore, is not sequestered in the ECMO circuit. An *ex vivo* study of morphine concentrations in ECMO circuits primed with crystalloid, albumin, and fresh whole blood demonstrated no significant loss of morphine at 24 hours compared to baseline (103% vs. 97%)[12]. However, the risk of adverse effects with morphine administration may outweigh the benefits in critically ill patients. Morphine and its active metabolites may accumulate in patients with renal dysfunction, and adverse effects include prolonged sedation, neurotoxicity, and histamine release resulting in hypotension and bronchospasm[16,26].

Intravenous opioids are recommended first-line in patients with non-neuropathic pain and offer rapid onset and titration advantages without concern for erratic absorption[16,26]. However, enteral opioids and non-opioid analgosedation can also be considered in patients with appropriate gastrointestinal functions[26]. In the setting of intravenous analgesia and sedative shortages, optimization of enteral therapy can reduce the dose requirements of intravenous agents but may also require large and frequent enteral dosing to achieve an equianalgesic effect (Table 1). While the onset of enteral opioid therapy is slower than intravenous medications, hence not appropriate for acute pain, their prolonged duration may benefit certain patients. Enteral treatments such as oxycodone and methadone may be considered, but data is minimal. No data are available regarding the serum concentrations or clinical outcomes in ECMO patients receiving oxycodone; however, due to its hydrophilic nature and lack of high protein-binding, the sequestration in the ECMO circuit is likely limited. Methadone is lipophilic and highly protein-bound; therefore, it is not ideal for patients receiving ECMO. It is also associated with QT prolongation, and the risks may outweigh the benefit in high doses. Two case reports of methadone use in patients receiving ECMO showed decreased intravenous opioid and sedative infusion doses after initiating methadone at doses of 30 mg four times per day and 10 mg three times per day[27]. The authors suggested reserving methadone for patients with high sedative requirements, demonstration of opioid tolerance, and need for long-term support.

Benzodiazepines

Benzodiazepines are lipophilic medications; however, they vary slightly in lipophilicity, onset and duration of action, and metabolism. While benzodiazepines may help manage agitation or facilitate mechanical ventilation, non-benzodiazepine sedatives are preferred to improve short- and long-term outcomes in critically ill patients. However, based on the limitations of pharmacological parameters of analgosedation agents in patients receiving ECMO, the use of benzodiazepine agents may sometimes be necessary when adequate analgosedation cannot be achieved with non-benzodiazepine sedatives or is limited by untoward effects.

Midazolam is lipophilic, highly protein-bound, and binds extensively to the ECMO circuit. An *ex vivo* study demonstrated that midazolam losses at 24 hours were 87%, while another *ex vivo* study showed similar losses of 46% at 30 minutes and 89% at 24 hours ($p=0.01$)[9,12]. Accumulation of midazolam and its active metabolites occurs in patients with renal or hepatic insufficiency or prolonged administration, resulting in protracted sedation. Lorazepam is less lipophilic and protein-bound than midazolam and may be preferable in patients receiving ECMO[16]. An *ex vivo* evaluation determined that lorazepam losses in the ECMO circuit at 48 hours were less than midazolam, 59% vs. 83%[28]. However, propylene glycol may be present in parenteral and enteral solution forms of lorazepam resulting in osmolar gap metabolic acidosis, seizures, respiratory depression, and renal insufficiency[29–32]. Monitoring the osmolal gap and substituting tablet formulations can lower propylene glycol toxicity in patients receiving prolonged therapy or high doses. No data exist regarding the use of clonazepam in ECMO patients; however, it may be a reasonable enteral alternative to lorazepam due to similar lipophilicity and protein-binding characteristics. Diazepam is highly lipophilic and protein-bound with 88% sequestration in the circuit and, therefore, is not a preferred agent in patients with ECMO.

Non-benzodiazepine Sedatives

Alpha-2 Agonists: Dexmedetomidine is commonly utilized as a part of the sedation regimen in the intensive care unit. Dexmedetomidine exerts its action as a selective alpha-2 receptor agonist, allowing the patient to be easily aroused with minimal respiratory depressant effects[26]. There is limited clinical data on the use of dexmedetomidine in patients receiving ECMO. *In vitro* studies have shown significant sequestration of dexmedetomidine in the ECMO circuit. Blood sampling at various time intervals showed continuous drug loss, with more than 80% of the medication lost at 24 hours, without a significant difference between new and old circuits or between the pre-and post-oxygenator samples, suggesting the contribution of PVC tubing to drug loss[33]. However, a more recent *in vitro* study showed that predominant drug extracted by the oxygenator with 41% and 96% recovery at 24 hours with and without the oxygenator, respectively[34]. The *in vitro* studies used bolus rather than continuous dexmedetomidine administration. While dexmedetomidine may be sequestered by the PVC tubing and/or the oxygenator in the ECMO circuit, it is still a practical option when light sedation is desired. In a small study of 26 ECMO patients, dexmedetomidine was used in 92% of patients at a median dose of 0.7 mcg/kg/hr without increasing doses needed for prolonged use[35].

Propofol: Propofol is a gamma-aminobutyric acid -agonist with sedative, hypnotic, and anxiolytic properties. Propofol is highly lipophilic with a short duration of action, making it another commonly used sedative in the intensive care unit[26]. Concerns for oxygenator failure with the use of propofol have been raised since it is a lipid emulsion. In a study of 43 patients on ECMO, nearly 40% received propofol for a median duration of four days with no difference in the rate of oxygenator exchange in those receiving propofol versus those who did not.[36] In addition, benzodiazepine and opioid use were significantly lower in the propofol group, suggesting propofol's efficacy as a sedative[37]. Another study evaluated 122 patients with a propofol-based sedation strategy, compared to midazolam, and found no difference in oxygenator duration between the strategies. Propofol sequestration in the ECMO circuit has also been reported. In an *ex vivo* circuit, propofol concentrations decreased by 70% only 30 minutes after administration, where the control sample of propofol in polypropylene tubes had a negligible loss at the same time. This study also demonstrated that higher oxygen concentrations led to further propofol degradation[9]. Since much of propofol is sequestered, patients will likely need higher doses to achieve their sedation targets. Similarly, with the discontinuation of ECMO, a dose reduction is probably warranted. One case report described the development of propofol infusion syndrome upon cessation of ECMO without empiric propofol weaning[38].

Ketamine: Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist which may reduce hyperalgesia and opioid tolerance. Ketamine is lipophilic but not highly protein-bound, so it is unclear whether high doses are necessary to achieve adequate sedation and reduce opioid requirements in patients receiving ECMO. A retrospective, single-center cohort study of 26 ECMO patients reported the median starting dose of ketamine at 50 mg/hr (range 6–150), leading to a reduction in sedative and opioid infusions within two hours of ketamine initiation in more than a third of the patients without a significant difference in sedation 24 hours after initiation[39]. A randomized trial of 20 VV-ECMO patients receiving standard sedation versus low-dose ketamine plus standard sedation did not find a difference in opioid or sedative requirement. However, the findings may be attributed to the deep level of sedation, lack of standardized sedation protocol, and possible inadequate ketamine dosing. Data supporting alterations in ketamine pharmacokinetic parameters during ECMO is limited to case reports. One case showed reduced sedative use in a VV-ECMO patient receiving ketamine infusion, initiated at 0.06 mg/kg/hr and titrated to 0.6 mg/kg/hr[40]. In a VV-ECMO patient who had been started on ketamine infusion at 0.22 mg/kg/hr and titrated to 0.625 mg/kg/hr for mild sedation, the mean ketamine level at the maximum dose was 402 ng/mL, lower than a reference range of 500–6500 ng/mL for non-ECMO patients[41]. Another case report evaluated ketamine pharmacokinetics at high doses (initiated at 0.5 mg/kg/hr and escalated to 2 mg/kg/hr) in a VV-ECMO patient and found the mean steady-state concentration at 1018.7 ng/mL with an estimated V_d of 14.2 L/kg. This level is almost seven times greater than healthy adults but similar to non-ECMO critically ill patients[42]. Patients with lighter sedation levels need to be monitored for side effects such as hallucination.

Adjunctive agents

Adjunctive agents such as gabapentin may be helpful in the management of neuropathic pain. Gabapentin is recommended as an adjunct pain medication after cardiac surgery[21]. Despite the lack of clinical data, it may also be a reasonable adjunct drug during ECMO given its favorable pharmacokinetics with negligible protein-binding and low lipophilicity[43]. Although not part of the standard sedation practices in the intensive care unit, both typical (such as haloperidol) and atypical (such as quetiapine) anti-psychotics, may also be helpful to control severe agitation and delirium, when necessary, in ECMO patients[21].

Analgosedation Protocols

Analgosedation monitoring is required to ensure the adequacy of treatment and minimize medication use. It is critical to define, measure, document, and daily reassess the analgosedation goal, and make adjustments based on the patient's individual needs at various stages of critical illness. Analgosedation monitoring in critically ill patients has been reviewed extensively. Clinical monitoring includes subjective bedside assessment and objective evaluations using standard and validated scoring systems such as Richmond Agitation/Sedation Scale (RASS). Electrophysiological techniques using electroencephalography, electromyography, and evoked potential signals are commonly employed where clinical monitoring is unreliable or insufficient in non-communicating, deeply sedated, and paralyzed patients[44,45]. Advanced processing of electroencephalography signals, such as frequency, power, or burst-suppression analysis, provides objective and continuous monitoring of brain function and sedation. However, additional studies are required to prove their validity and reliability in ECMO patients. The proposed analgosedation protocol, summarized in Figure 1, applies the abovementioned principles and pharmacological considerations.

A large number of patients will already be deeply sedated and often paralyzed at the time of ECMO consideration due to the severity of their cardiopulmonary disease. While fentanyl, midazolam, and propofol are the most common analgosedation agents used in the critical care setting, they are not optimal during ECMO support due to their high sequestration.

Intermittent as-needed analgesic and sedative medications are preferred over intermittent scheduled or continuous infusion medications to minimize sedative use. The protocol suggests analgesia-first with hydromorphone infusion as the first line; if a continuous infusion is required, we recommend a starting dose of 1 mg/hr. The alternative opioids are shown in Figure 1. We also recommend prioritizing non-benzodiazepine sedatives, such as ketamine infusion, before initiation of benzodiazepines administered either as a continuous infusion or intermittently as needed. Ketamine infusion can be initiated at 0.5 mg/kg/hr. For patients requiring light sedation, dexmedetomidine is preferred, whereas propofol can achieve deep sedation. In patients with intolerance to non-benzodiazepine sedatives or inadequate sedation, a benzodiazepine may be required; we recommend clonazepam as the first-line agent, to start at 3 mg enteral twice daily (roughly equivalent to lorazepam 1mg/hr). Although lorazepam sequestration is lower than midazolam (30 versus 87%), it is not recommended as a first-line agent due to the associated propylene glycol.

Deeper levels of sedation, frequently with neuromuscular blockade, are often required during the first 24–48 hours of ECMO cannulation to optimize ECMO support. Sedation can be lightened once a steady-state has been achieved and recovery from neuromuscular blockade has been demonstrated. The overall goal should be the maintenance of analgosedation as light as tolerated to enable accurate neurologic assessments and decrease potential side effects. The patient should be awakened when possible, particularly when early mobilization and rehabilitation are desired, such as a bridge to transplant. In such cases, ketamine or low-dose hydromorphone infusion is preferred. The addition of enteral opiates (such as oxycodone) and benzodiazepines (such as clonazepam) can be considered to reduce the total infusion requirements in patients with adequate gastrointestinal absorption. Enteral and second-line intravenous analgosedative agents can also be considered in case of medication shortage. Of note, enteral analgosedation agents may have limited utility in patients with high intravenous analgosedation requirements depending on the pill burden associated with an equivalent enteral dose.

Not uncommonly, weaning analgosedation is delayed due to pain and agitation. Administration of the first-line agents is often titrated to prevent self-injury and interference with the ECMO flows. Adjunct agents, such as dexmedetomidine and quetiapine, are often added to improve delirium and agitation control. At times, agents with higher sequestration, such as propofol, may be required. After a period of analgosedation maintenance, a slower step-wise weaning approach may be more feasible than traditional waking trials when clinical improvement is detected. Weaning the opioid and ketamine doses on alternating days with benzodiazepine doses may effectively reduce sedation without increasing agitation. Complete liberation from all analgosedation medications is often not feasible or necessary. A low dose of dexmedetomidine or other agents in the regimen can be continued through clinical improvement and the ECMO weaning process. Once the patient is decannulated, analgosedation medications shall be carefully adjusted. A more traditional weaning protocol can be adopted without the circuit effects with the administration of agents like fentanyl and midazolam. Adherence to established principles of analgosedation induction, maintenance, and weaning/liberation in critically-ill patients is essential.

Special Considerations and Future Directions

Renal Replacement Therapy

Acute kidney injury is prevalent in ECMO patients due to multiple factors, including predisposing comorbidities, hemodynamic lability, coagulation alterations, systemic inflammation, multi-organ failure, and administration of nephrotoxic agents[46–49]. Acute kidney injury is also associated with worsened clinical outcomes of ECMO patients[48–55]. Accordingly, renal replacement therapy is commonly indicated to treat ECMO patients with acute kidney injury, metabolic derangements, and volume overload[51–53,56–59]. Renal replacement therapy during ECMO is safe, feasible, and life-saving and facilitates weaning ECMO support; however, it is unclear whether it improves survival[56]. However, the addition of renal replacement therapy can further complicate medication pharmacokinetics, especially considering variations in the renal replacement techniques[10]. Various renal replacement modalities can be used, including integration into the ECMO circuit or a separate

circuit[56,60]. Continuous renal replacement therapy is more commonly applied due to hemodynamic instability of ECMO patients[61–63]. In the absence of clinical and population pharmacokinetics studies, close monitoring of analgesic and sedative medications' clinical effects, adverse events, and therapeutic levels, when possible, is recommended.

Therapeutic hypothermia

Induced therapeutic hypothermia and targeted temperature management are commonly employed after cardiac arrest to improve cardiac and neurological recovery. The increasing use of extracorporeal cardiopulmonary resuscitation (E-CPR) has led to increased concomitant hypothermia in ECMO patients, although its impact on neurological outcome is understudied and unclear at this time[64]. Hypothermia can further affect several aspects of pharmacokinetics by decreasing medication metabolism and excretion and absorption and distribution[65]. Therefore, parenteral, short-acting, and rapid-onset analgosedation administration is reasonable during hypothermia[65].

Obesity

ECMO support is feasible and effective in obese patients[66,67]. However, achieving optimal analgosedation during ECMO support can be more challenging in obese patients. As described above, the chemical properties, particularly lipophilic and protein-binding characteristics, can significantly affect medical sequestration. Obesity can further affect medication pharmacokinetics by several mechanisms. Fat tissue in obese patients increases the volume of distribution for lipophilic agents[68,69]. Increased kidney and liver mass and blood flow, as well as decreased expression of hepatic and intestinal cytochrome P450 in critically-ill obese patients, may also enhance drug clearance[70,71]. Together these mechanisms can result in higher analgosedation requirements[9,19,33,72,73]. However, the findings of previous reports have been inconsistent. While some studies suggested an increased need for lipophilic agents such as fentanyl and midazolam during ECMO support, the relationship is not linear with the body mass and was only observed earlier during medication administration[23,68]. Other studies did not find a significant change in midazolam requirement in obese ECMO patients[23].

Medication Shortage

Medication shortage at times of crisis due to decreased production, impaired delivery, or increased consumption can further complicate optimal analgosedation in ECMO patients. For instance, during the COVID-19 pandemic, a surge in mechanical ventilation and ECMO usage was accompanied by a worldwide medication shortage, including analgesics, sedatives, and paralytics[74–77]. A better understanding of medication pharmacodynamics, pharmacokinetics, and safety profile, as reviewed above, provides the opportunity to use alternative medications despite the lack of previous studies and even despite existing clinical guidelines. During the COVID-19 pandemic, some institutions opted to use intravenous benzodiazepines more frequently for deep sedation or administer more available but otherwise less commonly used agents such as oral opiates, benzodiazepines, and alpha-2 agonist (clonidine) as well as volatile agents (such as isoflurane, sevoflurane, and desflurane) and oral and/or intravenous barbiturates (such as phenobarbital and pentobarbital), non-steroidal anti-inflammatory agents (such as ibuprofen and ketorolac),

anti-psychotics, and anti-seizure medications (such as gabapentin, pregabalin, and carbamazepine) with sedative properties[74,75]. Similar strategies may be adopted in future crises.

Awake ECMO and Spontaneous Breathing

Recently, there has been a growing interest in ECMO in spontaneously breathing and awake patients. Awake ECMO enables the initiation and maintenance of ECMO support in non-intubated patients and is even an alternative to mechanical ventilation[78,79]. Awake ECMO requires lighter analgosedation, and at least in theory, can reduce delirium, duration of mechanical ventilation, hospital/ICU length of stay, and short- and long-term adverse effects of prolonged analgosedation and mechanical ventilation[80,81]. It can also enhance neurological assessment, patient communication, early rehabilitation, and even improve mortality[82,83]. However, close monitoring with adequate analgosedation is essential to avoid pain, discomfort, and self-harm. Accumulating evidence supports safety, feasibility, and favorable outcomes of awake ECMO in VV-ECMO for ARDS and patients with cardiogenic shock on VA-ECMO support. A study of 12 patients with severe ARDS extubated after a median of 10.2 days of ECMO showed no increased mortality associated with awake ECMO while awaiting native lung recovery[84]. Several studies have shown that awake ECMO as a bridge to lung transplantation is safe and can improve the duration of mechanical ventilation, respiratory distress, rehabilitation, and survival[85–88]. Similarly, in a series of 231 VA-ECMO patients, 39% of the patients underwent awake ECMO (i.e., invasive mechanical ventilation used in ≤50% of the VA-ECMO duration) that was associated with significantly lower rates of analgosedation use, tracheostomy, pneumonia, and antibiotic use, renal replacement therapy, and mortality[89,90]. Awake ECMO can also facilitate a bridge to left ventricular assist device implantation with improved mortality[91].

Conclusions

Critically ill patients often have significant variability in pharmacokinetics and pharmacodynamics with altered hemodynamics and physiology. The addition of the ECMO circuit poses special challenges in understanding drug metabolism, clearance, and distribution. We provided a comprehensive review of available literature on the pharmacokinetics of commonly used analgosedative medications in ECMO patients. We also provided recommendations on the preferred analgosedative regimen, although the optimal analgosedation medication choice, dosing, duration, and weaning strategy are unknown due to limited data. Also, there are no studies comparing outcomes among different analgosedation strategies. Further research is warranted to understand better the effectiveness of analgosedative medications in ECMO patients and their impact on overall outcomes.

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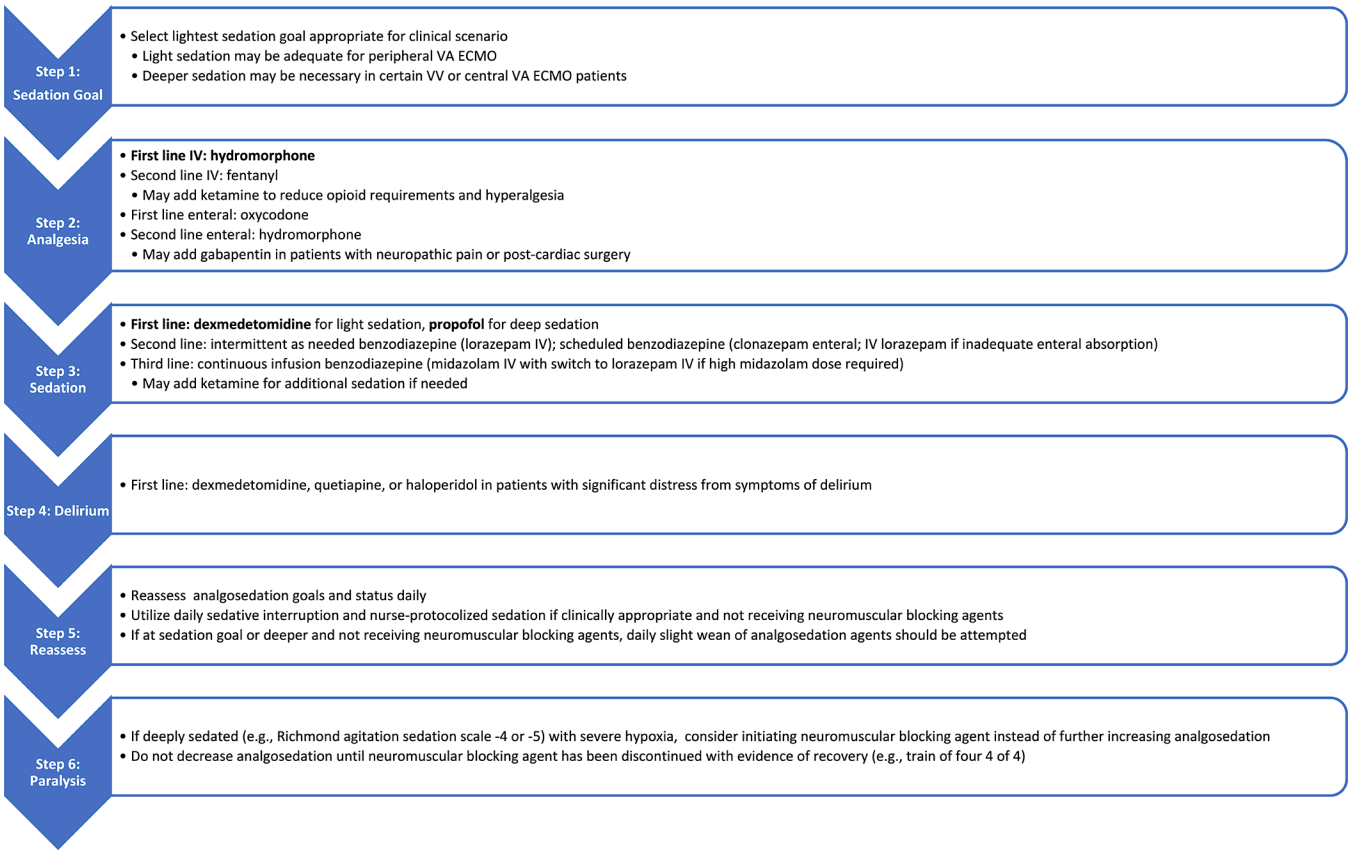

Figure 1:
Suggested Analgosedation Protocol during ECMO Support. Refer to Table 1 for important considerations regarding each medication listed in the Figure.

Table 1:

Pharmacokinetic properties of analgesic and sedative agents and considerations for use in ECMO.

Class	Medication	Protein Binding	Lipophilicity (logP)*	Sequestration in ECMO Circuit	Considerations for Use in ECMO
Opioid	Hydromorphone	8–19%	1.1	Limited (<25%) sequestration	Standard dosing or slightly increased dosing is likely sufficient
	Fentanyl	80–85%	4.1	Highly sequestered (up to 97%)	May require high doses
	Oxycodone	45%	0.7	Unlikely to be sequestered but no PK data	Requires adequate gastrointestinal absorption May reduce IV opioid requirements but limited utility in patients with high opioid requirements
	Morphine	35%	0.9	Not sequestered	Not preferred due to adverse effects and accumulation in renal dysfunction
	Methadone	85–90%	3.9	Likely sequestered, but no PK data	Requires QTc monitoring Unpredictable sequestration and long half-life may lead to adverse effects
Non-benzodiazepine sedative	Dexmedetomidine	94%	2.8	Likely sequestered	Increased dosing may be necessary to achieve sedation goals but maximum 1.5 mcg/kg/hr still recommended due to the risk of bradycardia and hypotension
	Propofol	95–99%	3.8	Highly sequestered	Increased dosing may be necessary to achieve sedation goals but avoid prolonged high doses Risk of propofol-related infusion syndrome, especially with ECMO decannulation
	Ketamine	54%	2.2	Likely sequestered	Avoid if presence or risk of myocardial ischemia, decompensated heart failure, catecholamine depletion, tachycardia, or arrhythmias
Benzodiazepine	Clonazepam	82–86%	2.4	Likely moderately sequestered, but no PK data	Requires adequate gastrointestinal absorption Slightly higher doses may be required to achieve sedation goals
	Lorazepam	85%	2.4	Moderately sequestered (59%)	Monitor for signs and symptoms of propylene glycol toxicity, including osmolal gap, especially in patients receiving prolonged or high doses
	Midazolam	97%	4.3	Highly sequestered (87%)	May require high doses to achieve sedation goals
	Diazepam	98–99%	2.8	Highly sequestered (88%)	Not recommended due to long half-life and high sequestration
Adjunctive agent	Gabapentin	<3%	1.3	Unlikely to be sequestered but no PK data	Standard dosing is likely sufficient
	Quetiapine	83%	2.8	Likely moderately sequestered but no PK data	No data guiding use; dose to clinical effects with QTc monitoring
	Haloperidol	~90%	4.3	Likely moderately sequestered but no PK data	No data guiding use; dose to clinical effects with QTc monitoring

PK= pharmacokinetic

*LogP: log of the octanol/water partition coefficient, which measures lipophilicity. High positive values indicate lipophilic compounds.