Contents lists available at ScienceDirect

American Journal of Emergency Medicine

Sedation in mechanically ventilated covid-19 patients: A narrative review for emergency medicine providers

Sedatives play an integral role in patients with COVID-19 by acting as induction agents prior to neuromuscular blockade and reducing discomfort during periods of mechanical ventilation. During induction, sedatives facilitate amnesia and cause a blunted sympathetic response, creating favorable intubation conditions [1]. Post-intubation maintenance sedation improves pulmonary compliance, prevents asynchrony, and facilitates adaption to the ventilator; however, in severe cases, additional paralytics are required [2,3]. Although emergency medicine physicians are typically involved in the initial stabilization of patients that require prolonged sedation and mechanical ventilation, limited ICU capacity has created longer boarding times for patients in the ED. As such, ED physicians require a basic understanding regarding management of sedation for these critically ill patients, which will be summarized in this review.

Etomidate is a sedative hypnotic frequently used as an induction agent during rapid sequence intubation (RSI). It has a rapid onset and short duration of action, making it a suitable for unstable patients [4]. Of note, elevations in arterial carbon dioxide are associated with etomidate and can exacerbate hypercarbia and acidosis in COVID-19 patients [4]. Etomidate is associated with reduced plasma cortisol levels that persist for hours after administration; however the significance of this finding is controversial [4]. Although data have been largely extrapolated from non-COVID patients, etomidate is a useful agent in COVID-19 patients due to its ability to maintain hemodynamic stability, short duration of action, and favorable adverse effect profile [5]. (Table 1).

Ketamine is a dissociative anesthetic that is used as an induction agent for RSI, procedural sedation, and analgesia. Due to its ability to elevate blood pressure and heart rate by inhibiting the reuptake of endogenous catecholamines, ketamine is recommended for induction in COVID-19 patients that are hemodynamically unstable [6]. Increased secretions are a well-known adverse effect of ketamine due to preservation of normal pharyngeal and laryngeal reflexes; however, the use of an anti-sialagogue such as atropine can reduce secretions which may reduce aerosolizing the virus [7]. Previous studies found a reduction in the release of inflammatory markers such as IL-6 after the administration of ketamine, which could be useful in stifling the cytokine storm that leads to rapid deterioration in COVID-19 patients [8]. Furthermore, ketamine does not cause significant respiratory depression, which can facilitate weaning COVID-19 patients from mechanical ventilation [9]. While ketamine has been associated with hallucinations and psychological disturbances, there is low concern for these effects in COVID-19 patients due to the deep level of sedation required for mechanical ventilation. More recent studies are examining the role of ketamine in treating neuropsychiatric conditions in COVID-19 patients due to its dual function as an NMDA receptor antagonist and immune modulator [10]. Ketamine's

ability to maintain hemodynamic stability make it an attractive option for sedation.

Propofol is a sedative hypnotic used for induction and maintenance of sedation in mechanically ventilated patients. It is a popular choice for sedation due to its highly predictable pharmacokinetic properties, including rapid onset and short duration of action [11]. The adverse effect profile of propofol makes it suboptimal for sedating critically ill COVID-19 patients. Diminished cardiac output and hypotension are known adverse effects of propofol and these effects are exacerbated in the setting of mechanical ventilation [11]. The use of propofol as an induction or maintenance agent in COVID-19 patients with shock could lead to profound hypotension. Propofol infusion syndrome is a rare, but potentially fatal adverse effect that can occur in the setting of prolonged use. It is characterized by bradycardia, metabolic acidosis, and rhabdomyolysis. Propofol should be discontinued, and sedation changed to another agent(s), such as dexmetatomadine and midazolam, and supportive care for complications initiated [12]. It has been suggested the critical illness myopathy COVID-19 patients experience could be due in part to low-grade myotoxicity associated with prolonged propofol administration [13]. Although limited data exists on the use of propofol in COVID-19 patients, its adverse effect profile limits its use for prolonged sedation.

Dexmedetomidine, a presynaptic α_2 adrenergic agonist, can be used for light sedation or in conjunction with other sedatives if deeper sedation is required for effective mechanical ventilation [14]. Prolonged use of dexmedetomidine in the ICU setting has been studied extensively and it has been shown to reduce sepsis-related lung injury and ischemia-reperfusion injury in the heart, kidney, and brain [15]. The most common adverse effects include hypotension and bradycardia within a few hours of initiation and the drug is contraindicated in patients with bradydysrhythmias [16]. It is hypothesized that the use of dexmedetomidine as part of the sedation strategy in COVID-19 patients may improve oxygenation by reducing hypoxic pulmonary vasoconstriction and ventilation-perfusion mismatch [17]. Furthermore, dexmedetomidine has been shown to modulate several immune pathways that may be advantageous to COVID-19 patients [17]. Currently, there are ongoing trials to assess the role of dexmedetomidine in COVID-19 patients. The results of these studies will be instrumental in providing definitive data regarding the use of dexmedetomidine; however, in the interim clinicians can continue to use this drug to maintain sedation in mechanically ventilated patients.

Benzodiazepines are sedative hypnotics that are most commonly used for continuous sedation in the setting of anxiety and agitation in the ICU [18]. Although they are efficacious, there are several studies that indicate worse outcomes with the use of benzodiazepines compared to non-benzodiazepine sedatives in ventilated patients who require longer periods of sedation [19,20]. These include longer time spent on the ventilator, risk of hemodynamic instability due to decreased respiratory drive and hypotension, as well as an increased risk for delirium [19,20]. A recent study comparing the use of

Table 1
Sedatives considered in mechanically ventilated COVID-19 patients.

Sedatives	Current use	Potential benefits in COVID-19	Potential adverse effects	Any COVID-19 study	Findings related to COVID-19	Recommendation
Etomidate	Induction agent	- Hemodynamic stability - Minimal respiratory depression - Reduced risk of histamine release	- Adrenocortical suppression - Hypercarbia - Cardiovascular instability in elderly patients with HTN	No	N/A	May be used for induction in young patients
Ketamine	- Induction agent - Maintenance at low doses - Analgesia in ICU	- Reduces inflammatory markers such as IL-6 - Minimal respiratory depression	- Hallucinations	Yes	- Potential for immune modulation - Neuropsychiatric benefits	Primary choice for induction of sedation of COVID patients, particularly those that are hemodynamically unstable
Propofol	- Induction agent - Maintenance at low doses	- Rapid onset, rapid recovery - Anti-inflammatory/immunomodulatory effects	- Diminished cardiac output, hypotension - Propofol infusion syndrome	Yes	- Myotoxicity - Propofol infusion syndrome	Should not be used for prolonged deep sedation
Dexmedetomidine	Light sedation in mechanically ventilated patients	- Minimal risk of delirium - Hemodynamic stability - Reduced time requiring ventilation - Reduced peri-intubation agitation (lower risk of aerosolizing particles)	- Bradycardia and hypotension with initial bolus - Withdrawal when used in high doses >24 h	Yes	- Combination of Dexmedetomidine and midazolam is effective dual therapy for long term sedation with limited side effects	Primary choice for long-term sedation when used in conjunction with benzodiazepines
Benzodiazepines	Continuous sedation in the setting of anxiety and agitation	- Treatment of acute agitation - Short-term breakthrough sedation	- Hypotension - Reduced respiratory drive - Longer ventilator times - delirium	Yes		Should not be used as monotherapy for long term sedation due to increased risk of aspiration causing refractory hypoxemia and longer ventilation times
Inhalational Volatile Sedatives	- Pediatric patients - Ambulatory surgeries	- Reduced need for hemodynamic support - Reduced need for opioids - Shorter ventilation times	- Malignant hyperthermia	No	N/A	Use for prolonged sedation is experimental and not FDA approved

dexmedetomidine and midazolam in 35 patients with severe COVID-19 requiring non-invasive ventilation, found greater effectiveness and fewer adverse events in the patients sedated using dexmedetomidine [21]. The adverse events in the benzodiazepine group were related to excess sedation resulting in aspiration or intubation and intubation due to refractory hypoxemia [21]. Still, benzodiazepines may be a viable option if the preferred sedatives are contraindicated or in patients that develop propofol-related infusion syndrome [22]. They may also be beneficial for the treatment of acute agitation and as an adjunctive therapy to maintain deep sedation in mechanically ventilated patients with COVID-19. Of note, some benzodiazepines such as lorazepam, have large amounts of propylene glycol diluent, which causes metabolic acidosis; therefore, midazolam is the preferred choice for prolonged or repeated use.

Inhalational volatile anesthetics such as isoflurane have many beneficial properties that would make them promising for maintenance sedation; however, their use for this purpose is still experimental and the extensive technology and training that is required to deliver these drugs may be a significant limiting factor.

Another aspect of respiratory support for COVID-19 patients is the use of prone positioning, which has been shown to increase oxygenation and reduce lung damage by decreasing the shunting of blood and improving perfusion. Sedation plays an important role in allowing patients to tolerate longer periods of prone positioning and may improve clinical outcomes [23]. Studies are needed to optimize the care of proned intubated patients, which includes frequent endotracheal suctioning and the logistics of physically turning patients over without compromising the airway and dislodging other catheters or IVs.

Patients with COVID-19 and refractory hypoxemia require long periods of deep sedation and mechanical ventilation; however, limited data exists to guide sedation practices. Although most sedatives come with some risk of hemodynamic instability and other adverse effects especially at higher doses, dual therapy sedation is reasonable for achieving deeper sedation while minimizing the adverse effects of each individual medication. Specifically, a combination of dexmedetomidine and midazolam can provide long-term sedation while simultaneously improving oxygenation in hypoxemic COVID-19 patients.

Although some recommendations can be made for the choice of sedation in mechanically ventilated COVID-19 patients, the ultimate decision will need to be made on an individualized basis depending on the dynamic nature of that patient's clinical condition and on evolving external factors that impact the availability of these medications. Future

studies examining at dual and triple therapy for prolonged sedation in intubated COVID-19 patients will be of the utmost importance in the upcoming months as the pandemic continues.

Financial support

This is a non-funded study, with no compensation or honoraria for conducting the study.

Declaration of competing interest

The authors do not have a financial interest or relationship to disclose regarding this research project.

References

[1] Sivilotti MLA, Filbin MR, Murray HE, Slasor P, Walls RM. On behalf of the NEAR investigators. Does the sedative agent facilitate emergency rapid sequence intubation? Acad Emerg Med. 2008;10(6):612–20. https://doi.org/10.1111/j.1553-2712.2003.tb00044.x.

[2] Payen J-F, Chanques G, Futier E, Velly L, Jaber S, Constantin J. Sedation for critically ill patients with COVID-19: which specificities? One size does not fit all. Anaesth Crit Care Pain Med. 2020;39(3):341–3. https://doi.org/10.1016/j.accpm.2020.04.010.

[3] Salluh JIF, Ramos F, Chiche JD. Delivering evidence-based critical care for mechanically ventilated patients with COVID-19. Lancet Respir Med. 2020;8(8):756–8. https://doi.org/10.1016/S2213-2600(20)30266-6.

[4] Williams LM, Boyd KL, Fitzgerald BM. Etomidate. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 (accessed 18.02.21) https://www.ncbi.nlm.nih.gov/books/NBK535364/.

[5] Chokshi T, Channabasappa S, Vergheese D, Bajwa SS, Gupta B, Mehdiratta L. Re-emergence of TIVA in COVID times. Indian J Anaesth. 2020;64(14):125. https://doi.org/10.4103/ija.IJA_554_20.

[6] Cook TM, El-Boghdadly K, McGuire B, McNarry AF, Patel A, Higgs A. Consensus guidelines for managing the airway in patients with COVID-19: guidelines. Anaesthesia. 2020;75(6):785–99. https://doi.org/10.1111/anae.15054.

[7] Suri A, Sindwani G. Ketamine use in the COVID-19 era: be cautious! Korean J Anesthesiol. 2020;73(6):568–9. https://doi.org/10.4097/kja.20318.

[8] Ortoleva J. Consider adjunctive ketamine in mechanically ventilated coronavirus disease-2019 patients. J Cardiothorac Vasc Anesth. 2020;34(10):2580. https://doi.org/10.1053/j.jvca.2020.04.037.

[9] Rosenbaum S, Gupta V, Palacios J. Ketamine. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 (Accessed 18.02.21) https://www.ncbi.nlm.nih.gov/books/NBK470357/.

[10] Akinosoglou K, Gogos A, Papageorgiou C, Angelopoulos E, Gogos C. Ketamine in COVID-19 patients: thinking out of the box. J Med Virol. 2020. https://doi.org/10.1002/jmv.26681 Published online November 20.

[11] Secor T, Safadi A, Gunderson S. Propofol toxicity. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 (accessed 18.02.21) https://pubmed.ncbi.nlm.nih.gov/31082121/.

[12] Lucchetta V, Bonvicini D, Ballin A, Tiberio I. Propofol infusion syndrome in severe COVID-19. BJA Br J Anaesth. 2020;125(5):e441-e442. https://doi.org/10.1016/j.bja.2020.08.020.

[13] Lönnqvist P-A, Bell M, Karlsson T, Wiklund L, Höglund A-S, Larsson L. Does prolonged propofol sedation of mechanically ventilated COVID-19 patients contribute to critical illness myopathy? Br J Anaesth. 2020;125(3):e334–6. https://doi.org/10.1016/j.bja.2020.05.056.

[14] Adams CD, Altshuler J, Barlow BL, et al. Analgesia and sedation strategies in mechanically ventilated adults with COVID-19. Pharmacother J Hum Pharmacol Drug Ther. 2020;40(12):1180–91. https://doi.org/10.1002/phar.2471.

[15] Flanders CA, Rocke AS, Edwardson SA, Baillie JK, Walsh TS. The effect of dexmedetomidine and clonidine on the inflammatory response in critical illness: a systematic review of animal and human studies. Crit Care. 2019;23(1):402. https://doi.org/10.1186/s13054-019-2690-4.

[16] Ammar MA, Sacha GL, Welch SC, et al. Sedation, analgesia, and paralysis in COVID-19 patients in the setting of drug shortages. J Intensive Care Med. 2021;36(2):157–74. https://doi.org/10.1177/0885066620951426.

[17] Jain A, Lamperti M, Doyle DJ. Dexmedetomidine: another arrow in the quiver to fight COVID-19 in intensive care units. Br J Anaesth. 2021;126(1):e35–8. https://doi.org/10.1016/j.bja.2020.10.010.

[18] Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the Management of Pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263–306. https://doi.org/10.1097/CCM.0b013e3182783b72.

[19] Carson SS, Kress JP, Rodgers JE, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. Crit Care Med. 2006;34(5):1326–32. https://doi.org/10.1097/01.CCM.0000215513.63207.7F.

[20] Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301(5):489–99. https://doi.org/10.1001/jama.2009.56.

[21] Xie W, Zhong Z, Li G, Hou G, Huang K, Yu Z. A comparative study on clinical effects of dexmedetomidine and midazolam on patients with severe coronavirus disease 2019 on non-invasive ventilation. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2020;36(2):677–80.

[22] Stockton J, Kyle-Sidell C. Dexmedetomidine and worsening hypoxemia in the setting of COVID-19: a case report. Am J Emerg Med. 2020;38(10):2247.e1–2247.e2. https://doi.org/10.1016/j.ajem.2020.05.066.

[23] Fox ER, Stolbach AI, Mazer-Amirshahi M. The landscape of prescription drug shortages during the COVID-19 pandemic. J Med Toxicol Off J Am Coll Med Toxicol. 2020;16(3):311–3. https://doi.org/10.1007/s13181-020-00786-4.

Meghana Keswani
Department of Emergency Medicine, George Washington University School of Medicine and Health Sciences, Washington DC, United States

Nikita Mehta
Department of Emergency Medicine, George Washington University School of Medicine and Health Sciences, Washington DC, United States

Maryann Mazer-Amirshahi
Department of Emergency Medicine, MedStar Washington Hospital Center, Washington DC, United States

Quincy K Tran
Department of Emergency Medicine, University of Maryland School of Medicine, Baltimore, MD, United States
Program in Trauma, The R Adams Cowley Shock Trauma Center, University of Maryland School of Medicine, Baltimore, MD, United States

Ali Pourmand
Department of Emergency Medicine, George Washington University School of Medicine and Health Sciences, Washington DC, United States
Corresponding author at: Department of Emergency Medicine, George Washington University, Medical Center, 2120 L St., Washington DC 20037, United States.
E-mail address: pourmand@gwu.edu

31 December 2020