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CRITICAL CARE ANESTHESIA (BS RASMUSSEN, SECTION EDITOR)

Challenges in Sedation Management in Critically Ill Patients with COVID-19: a Brief Review

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Abstract

Purpose of Review To highlight the challenges associated with providing sedation and analgesia to critically ill patients with coronavirus disease 2019 (COVID-19) and also understand the pathophysiological alterations induced by the disease process as well as the logistical difficulties encountered by providers caring for these patients. We also discuss the rationale and risks associated with the use of common sedative agents specifically within the context of COVID-19 and provide evidence-based management strategies to help manage sedation and analgesia in such patients.

Recent Findings A significant proportion of patients with COVID-19 require intensive care and mechanical ventilation, thus requiring sedation and analgesia. These patients tend to require higher doses of sedative medications and often for long periods of time. Most of the commonly used sedative and analgesic agents carry unique risks that should be considered within the context of the unique pathophysiology of COVID-19, the logistical issues the disease poses, and the ongoing drug shortages.

Summary With little attention being paid to sedation practices specific to patients with COVID-19 in critical care literature and minimal mention in national guidelines, there is a significant gap in knowledge. We review the existing literature to discuss the unique challenges that providers face while providing sedation and analgesia to critically ill patients with COVID-19 and propose evidence-based management strategies.

Keywords COVID-19 · SARS-CoV-2 · Sedation · Analgesia · Critically ill patients

Introduction

A novel strain of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has impacted patients across the world, leading to a pandemic. Patients with SARS-CoV-2 infection develop coronavirus disease 2019 (COVID-19), which can present from asymptomatic or mild illness to hypoxemic respiratory failure and multisystem organ failure, necessitating hospitalization and intensive care unit (ICU) admissions [1•]. Roughly 10–12% of patients who test positive require ICU admission [2•]. The virus binds to the angiotensin-converting enzyme 2 receptor expressed in the lower respiratory tract causing an increased production of angiotensin II, leading to increases in pulmonary vascular permeability and induction of cytokines [3, 4]. The ensuing endothelial injury can lead to a wide variety of complications, ranging from pneumonia to acute respiratory distress syndrome (ARDS). Patients who develop severe acute hypoxic respiratory failure often require invasive mechanical ventilation, thus necessitating effective analgesia and sedation. Appropriate sedation in these patients helps prevent patient-ventilator dys-synchrony, accidental extubations, and circuit disconnections and also facilitates prone ventilation and paralysis in those that develop refractory hypoxic respiratory failure. It has been reported that critically ill patients with COVID-19 tend to require higher doses of sedation and analgesia [5••]. However, providing optimal sedation in patients with COVID-19 poses unique challenges not only due to the pathophysiology of the disease but also due to the ongoing

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drug shortages that have been plaguing the critical care community for years and seem accentuated in the aftermath of the pandemic. There seems to be very little attention to sedation in these patients in the critical care literature, with minimal mention in the Society of Critical Care Medicine's COVID-19 guidelines or clinical reviews [4, 6].

In this article, we discuss the challenges that providers face as they strive to provide sedation and analgesia for critically ill patients impacted by the SARS-CoV-2 pandemic. We review the unique adverse effects of each sedative agent, the physiologic insults imposed by COVID-19 that impacts the choice of sedative agents, and provide a systematic framework to help critical care clinicians manage sedation and analgesia in critically ill patients with COVID-19.

Analgesia and Sedation in Critically Ill Patients with COVID-19

Analgesia and sedation are an integral part of the care provided to critically ill patients. These patients experience moderate-to-severe pain at rest and during standard care procedures [7, 8]. Further, ICU stay provokes anxiety via both physiological and psychological pathways, and more than half of patients admitted to the ICU have remembrance of being in the ICU or being intubated [9]. This pain and anxiety add to the pre-existing sympathetic stress response and lead to increased endogenous catecholamine activity, increased oxygen consumption, tachycardia, hypercoagulability, hypermetabolism, and immunosuppression [10]. Unrelieved pain and anxiety in this setting can also lead to severe agitation and removal of lifesaving medical devices (e.g., endotracheal tubes and intravascular lines), thus placing both the patient and health care providers at risk [11]. This may also contribute to significant physical and psychological stress during the acute event and in future lead to the development of long-term consequences such as posttraumatic stress disorder (PTSD) [12]. Adequate pain control and sedation also play a significant role in preventing ventilator dys-synchrony [13], which can negatively affect patient outcomes by causing ventilator-induced lung injury (VILI) due to increases in peak airway pressures [14].

Although there is wide variation in the presentation of patients with COVID-19, those presenting to the emergency department with hypoxia have been noted to deteriorate quickly, ultimately requiring intubation, proning, and paralytics [2•]. Sedation is particularly important in this patient population to allow for paralytic use, preventing unintentional extubations, and to promote ventilator synchrony. A significant proportion of patients with COVID-19 tend to be younger, have fewer comorbidities, have a high respiratory drive, and mount intense inflammatory responses which has previously been linked to increased tolerance to sedative agents [15]. Thus, these patients require unusually high doses of sedatives and often need administration of multiple agents, increasing the potential risks of side effects [5••]. The duration of mechanical ventilation is also longer in these patients, with a median duration of mechanical ventilation ranging from 7 to 12 days [16], thus the need for prolonged duration of sedation. These prolonged periods of sedation may lead to drug accumulation, tolerance and tachyphylaxis, as well as unwarranted side effects of individual drugs.

Deeper sedation levels may be required to facilitate ventilator synchrony and may also be needed to reduce the risk of patient self-extubations. Patient self-extubations and circuit disconnections are particularly problematic in this population, given the need for emergent reintubation and worsening hypoxia and for the caregivers as it exposes them to aerosols, which increase the risk of transmission [17]. Unfortunately, health care workers treating patients with COVID-19 are at increased risk of contracting the illness [18, 19], and appropriate sedation management in mechanically ventilated critically ill patients might help mitigate this risk. Attention must also be paid to the potential interaction between sedative drugs and other agents administered as part of experimental therapy for COVID-19. For instance, significant QT prolongations may result from combinations of hydroxychloroquine and haloperidol, and administration of barbiturates may increase metabolism of hydroxychloroquine. There are currently no sedation guidelines specific for this patient population requiring high doses, prolonged administration, and frequent co-administration of multiple drugs.

Choice of Sedative Agents in Critically Ill COVID-19 Patients

When choosing agents for sedation in these patients, it is imperative that a multidisciplinary team, comprising of critical care providers, caregivers, as well as pharmacists review and decide on the appropriate choice of sedative on a case by case basis, incorporating all aspects of the medication process, including availability. Since protocolized, nurse-controlled sedation has been shown to reduce sedation requirements, duration of mechanical ventilation, and ICU length of stay (LOS) [20], it might be reasonable to start with a protocolized sedation regimen, with a clear understanding that deviation from the protocol and individualized care may be needed. Recent reports indicate that acute kidney injury (AKI) is common in critically ill patients with COVID-19 and the incidence has been reported to be as high as 25% [21, 22].Hence, drug accumulation and associated side effects also dictate the choice of sedative regimen. Prolonged infusions of high doses of sedatives and analgesics in large numbers of these patients have already resulted in drug shortages at hospital, regional, and state levels. From the very beginning of this outbreak, the US Food and Drug Administration (FDA) has been

monitoring the medication supply chain, expecting disruptions due to COVID-19. Disruptions in supply chains from manufacturers, as well as increased demands, have worsened already burdensome drug shortages and introduced new ones. These ongoing critical shortages have impacted the availability of agents that play a vital role in the treatment of COVID-19. Hence, multidisciplinary teams must implement conservation plans which individualize therapy while limiting unnecessary use and waste. Figure 1 highlights the concerns with each of the individual drugs in patients with COVID-19.

Opioids

Opioids form the cornerstone of sedation and analgesia management in critically ill patients. Pain is omnipresent in the ICU and is attributed to prolonged immobility, indwelling devices, and exposure to invasive procedures, among other etiologies [8]. Management of pain in critically ill patients is prioritized by consensus guidelines, which recommend treating pain first or utilizing analgosedation (e.g., analgesia-first or analgesia-based) with opioids as the mainstay of pain management [10]. Opioids act upon a variety of different receptors, including the mu-opioid receptor, which is involved in nociception. Opioids may be administered as boluses or an infusion depending on the level of pain a patient may be experiencing [23]. Fentanyl, which has no active metabolites and has a high lipophilicity, is commonly used as a continuous infusion. Morphine and hydromorphone are the other drugs that are used for pain management in ICU patients. Morphine is water-soluble, has active metabolites (morphine-6-glucoronide) that may accumulate in renal failure, and may cause more histamine release than other agents in this class. In addition, the active metabolite of morphine has been shown to be nephrotoxic which can negatively contribute to pre-existing AKI often seen in this patient population. Hydromorphone, a semi-synthetic derivative of morphine, is devoid of most of the adverse effects of morphine and can be administered as intermittent boluses.

Prolonged infusions of opioids that are often required to facilitate strict lung-protective ventilation in critically ill

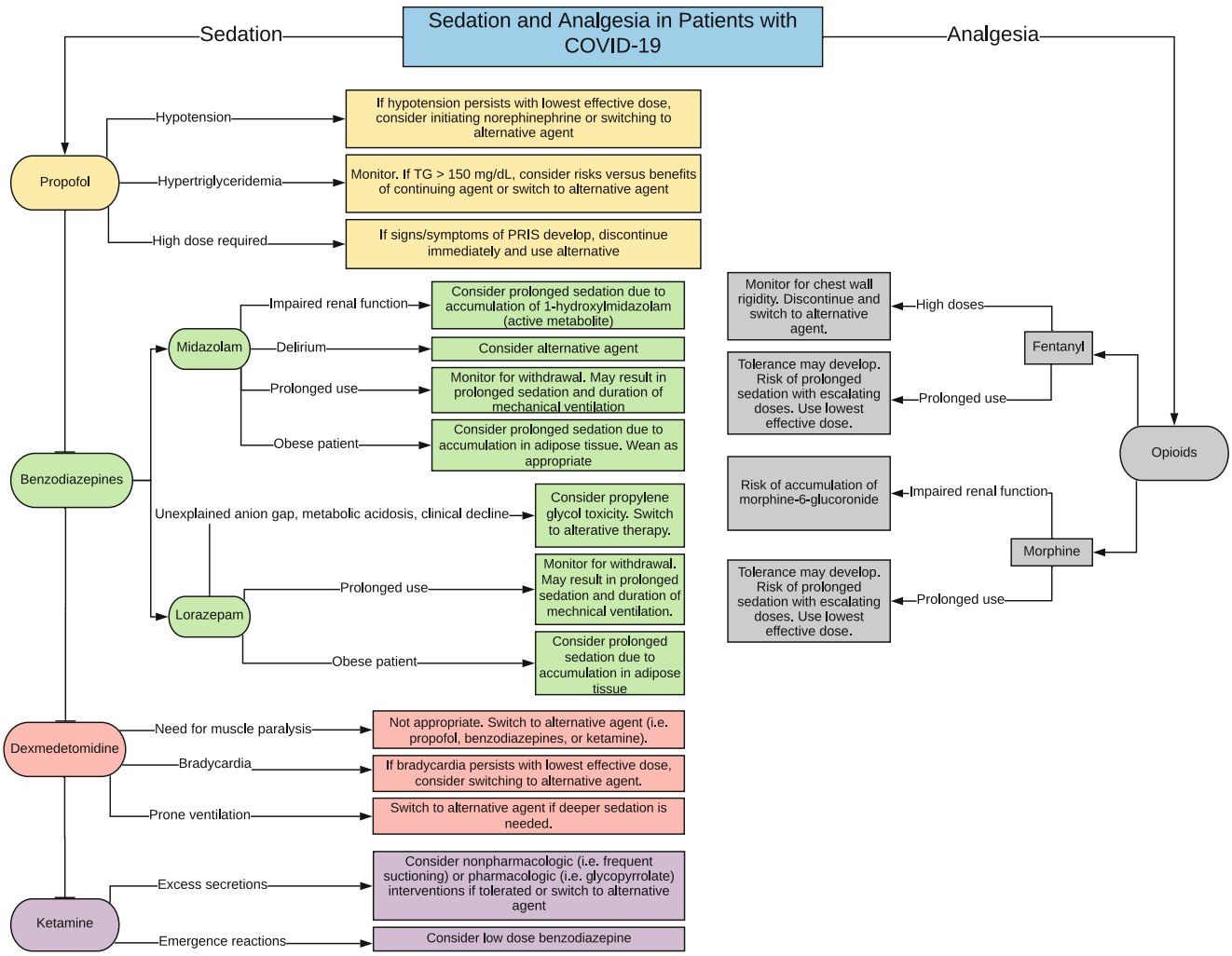

Fig. 1 Medication options for analgesia and sedation in critically ill patients with COVID-19. COVID-19; coronavirus disease 2019; PRIS, propofol infusion syndrome; TG, triglyceride

patients with COVID-19 have undesirable effects. Such infusions are known to result in gut hypomotility, leading to intolerance to feeding, interruptions in feeding, and malnutrition during prolonged ICU stay. The drugs may accumulate in adipose tissue and delay neurologic recovery especially if used for prolonged durations given their long context sensitive half-life. Pre-existing AKI may further contribute to drug accumulation. Abrupt removal of these infusions can precipitate a withdrawal syndrome and make weaning from mechanical ventilation challenging [24]. Prolonged duration of therapy may also lead to development of tolerance and long-term adverse effects including B and T cell-mediated immune dysfunction, opioid-induced hyperalgesia (OIH), and the potential for physiological and psychological addiction [25]. Therefore, risks and benefits of utilizing a continuous infusion, including limiting nurse contact with COVID-19-positive patients, must be weighed on a case by case basis [26]. A rare, yet feared complication is opioid-induced chest wall rigidity, in which patients develop increased thoracic and abdominal muscle tone [27]. Intubated patients who develop chest wall rigidity can develop increased airway pressures and oxygen desaturation [28]. This complication could prove fatal if presenting in a COVID-19 patient with ARDS, on aggressive ventilator settings.

Opioid-based pain management approach should be tailored to the individual patient based on physiological derangements and comorbid conditions. An aggressive bowel regimen must be implemented to prevent an ileus or bowel distention, which can impair ventilation. Fentanyl is the preferred drug of choice in patients with renal dysfunction and should be considered as first-line in COVID-19 patients. Acknowledging the well-known risk of delirium associated with excessive use of sedative-hypnotics, a regimen based on continuous fentanyl infusion should be considered. These infusions should be assessed daily and titrated to maintain the minimal dosage to preserve ventilator synchrony and patient comfort. If feasible, daily sedation holidays should be routinely performed in most patients. In patients with adequate enteral access, transition to oral oxycodone formulations using morphine equivalent unit calculations should be considered to conserve parental products and assist with weaning. Intravenous intermittent-dosed hydromorphone is a useful adjunct to wean continuous opioid infusions in patients without adequate enteral access or ileus.

Although opioids are effective analgesic agents, they have weak sedative properties and do not provide adequate sedation in patients requiring muscle paralysis, with the risk of patient recall. Since they might not be able to provide appropriate sedation by themselves, addition of a sedative agent may be required. Hence, appropriate use of sedatives, in addition to analgesia, can facilitate patient care and contribute to overall patient safety. Various modalities of sedation exist, and the selection of the sedative agent(s) must be individualized. As no individual sedative has been shown to be superior, the risks and benefits of each must be closely reviewed in conjunction with patient specific factors and goals of therapy [29]. Characteristics noted in COVID-19 patients, including elevated triglycerides, end-organ dysfunction, and enhanced clearance of medications must be considered when choosing sedative agents. In addition to patient factors, availability of desired medications must be incorporated into clinical decision making.

Propofol

One of the most commonly used sedative agents in the ICU is propofol, a short acting, lipophilic phenol derivative. Propofol modulates the function of γ-aminobutyric acid (GABA) receptor, ultimately leading to hyperpolarization and inhibition of neurotransmission. Propofol exhibits a rapid onset of action making it a desirable sedative in many situations. In addition, propofol exhibits bi-phasic kinetics with a relatively short initial half-life and a terminal half-life of 4 to 7 h [30]. Unfortunately, this terminal half-life may be extended following long courses of therapy due to accumulation in the body tissues. Despite its benefits, propofol has well-documented, predictable adverse effects, which may be problematic in critically ill patients with COVID-19. Propofol causes a dose-dependent decrease in the systemic vascular resistance and myocardial contractility [31], which may worsen the pre-existing hypotension in COVID-19 patients with septic shock. This hypotension can lead to decreased end-organ perfusion, which may lead to, or compound, multi-organ failure. Patients with COVID-19 have also been known to develop myocardial injury, viral myocarditis, and stress cardiomyopathy [32•], and propofol-induced decrease in myocardial contractility may not be well tolerated in these patients. Other less common side effects of propofol include hypertriglyceridemia and pancreatitis. Outside of COVID-19, hypertriglyceridemia as well as hypertriglyceridemia-associated pancreatitis can be seen in ICU patients receiving propofol. These side effects appear to be exaggerated in patients with COVID-19. In some cases, the presentation of COVID-19 patients is similar to those with hemophagocytic lymphohistiocytosis (HLH) [33]. HLH is an umbrella term for a wide variety of life-threatening disorders caused by an uncontrolled hyperinflammatory response; secondary HLH, of note, is most commonly triggered by a viral infection [34]. Some of the clinical and laboratory findings used to diagnose HLH include fever, cytopenias, hypertriglyceridemia, elevated ferritin, elevated lactate dehydrogenase (LDH), and elevated liver function enzymes. For reasons likely including cytokine storming, a subset of COVID-19 patients have presented with similar laboratory markers as those stated above, including hypertriglyceridemia [35•]. Hypertriglyceridemia, defined as a blood level >150 mg/dL, is independently associated with increased risk of cardiovascular events [36], leading providers to choose sedatives

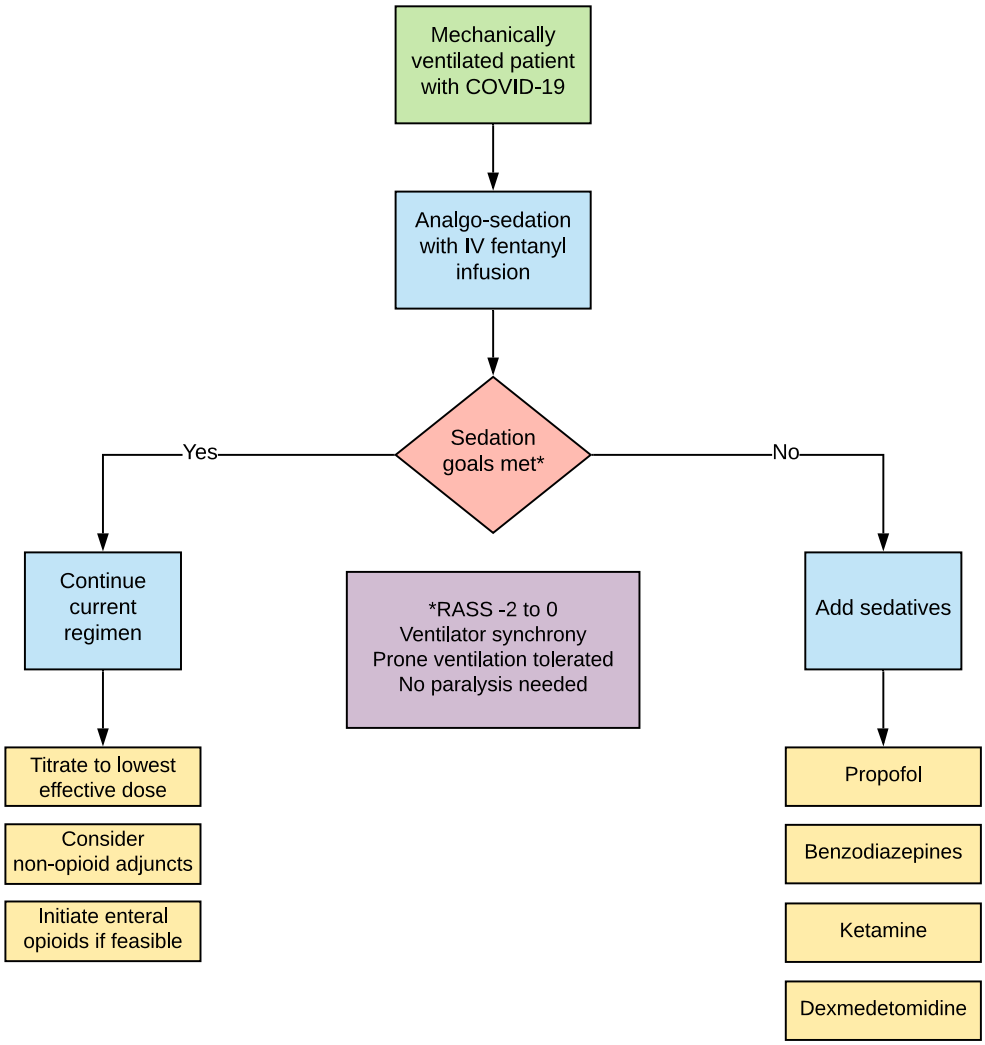

Fig. 2 Overview of sedation management in a critically ill mechanically ventilated patient with COVID-19. COVID-19, coronavirus disease 2019; RASS, Richmond Agitation Sedation Score

other than propofol for sedation in these patients. In addition, since patients with COVID-19 tend to require higher levels of sedation than other critically ill patients due to their hypermetabolic state, long durations of high-dose propofol infusions can independently lead to elevated levels of triglycerides, ultimately leading to pancreatitis if not monitored closely. Another concern that stems from higher doses of propofol is propofol infusion syndrome (PRIS). PRIS is a rare, albeit fatal, condition that may occur with long-term (>48 h) and high-dose (> 4–5 mg kg^{-1} h^{-1}) propofol infusions [37–40]. It is characterized by refractory bradycardia leading to asystole, metabolic acidosis, rhabdomyolysis, hyperlipidemia, enlarged liver, hyperkalemia, and each component's downstream physiologic effects. This avoidable complication should be immediately treated by discontinuing the infusion and providing supportive measures, such as hemodynamic support, hemodialysis, or extracorporeal membrane oxygenation in severe cases. Inability to discontinue or lower the dose of propofol while maintaining adequate sedation proves problematic in certain patients presenting with COVID-19. In addition to clinical concerns, propofol, which has been monitored as a drug shortage since 2018, has seen a spike in use during the COVID-19 pandemic. Increased utilization has led to worsening shortages, ultimately forcing some hospitals to ration supplies and others to go without. Therefore, the question of whether to use propofol, at which dose, and for how long depends on the overall clinical context, patient specific factors, as well as availability.

Benzodiazepines

When propofol is not an option, either due to patient specific factors or lack of resources, benzodiazepines continue to provide an alternative option for sedation. This class of medication, by facilitating the action of GABA, exerts numerous effects, notably sedation, anxiolysis, anterograde amnesia, anticonvulsant properties, and muscle relaxation. The two most commonly used benzodiazepines for ICU sedation are midazolam and lorazepam. Midazolam is one of the shortest acting, water-soluble drugs in its class. It has a short context

sensitive half-time, rendering it to be administered as a continuous infusion [41]. Midazolam rapidly undergoes hepatic metabolism via the cytochrome P450 system to the active metabolite, 1-hydroxymidazolam, which is eventually excreted by the kidneys. This active metabolite can accumulate during long-term infusions and in patients who have renal dysfunction [42]. It is necessary to use caution when administering midazolam for prolonged periods of time in patients with baseline end-stage renal disease (ESRD) or AKI due to the accumulation of the parent drug, as well as its active metabolite [43]. In a case series that included 26 patients on midazolam, 13 patients had detectable serum levels of parent drug and/or the active metabolite for a median duration of 67 h after midazolam was discontinued [44]. It is also important to know that all agents in this class are lipophilic and will accumulate in adipose tissue. Ensuring daily sedation vacations, if appropriate, and utilizing the lowest effective dose will aid in limiting accumulation. As an alternative, lorazepam infusions may also be used for sedation. Lorazepam has a longer duration of action when compared to midazolam. It is also metabolized through the hepatic system to inactive metabolites, which are excreted by the kidneys [45]. Due to the lack of an active metabolite, there may be less accumulation in patients with renal dysfunction, and therefore, this agent may be preferred in patients who are on continuous renal replacement therapy (CRRT) or hemodialysis (HD). Unfortunately, the longer half-life of lorazepam may independently contribute to delays in extubations [43]. Another concern with the use of lorazepam infusions is the risk of propylene glycol toxicity [46]. Propylene glycol (1,2-propanediol) is the solvent used to deliver multiple agents, including intravenous lorazepam. Propylene glycol has been associated with toxicity in high-dose and/or longer-term therapy. Clinical manifestations of propylene glycol toxicity include cardiac arrhythmia, seizures, lactic acidosis, hypotension, and agitation. Propylene glycol toxicity should be considered whenever a patient has an unexplained anion gap, metabolic acidosis, or clinical decline. Although no specific dose cutoff exists, there is evidence to suggest that osmolar gaps of 12 or greater may be predictive of clinical changes related to propylene glycol toxicity [47]. With increasing doses required to adequately sedate COVID-19 patients, the likelihood of toxicity increases and should be monitored closely.

Another challenge provider's face when using benzodiazepines, especially in this patient population, is the risk of withdrawal. Patients with ARDS are more likely to receive higher doses of medications and are at increased risk of withdrawal and prolonged mechanical ventilation [24]. Similarly, patients with COVID-19 associated respiratory failure may need mechanical ventilation for extended periods of time and may require higher doses of sedative agents to achieve adequate levels of sedation; therefore, risks and benefits of long-term therapy should be routinely discussed on interdisciplinary rounds. In general, the use of benzodiazepines for ICU sedation is limited due to the heightened risk of delirium [48–51], which is even more pronounced in older patients [52]. Hence, when possible, intermittent dosing of benzodiazepines should be utilized to limit accumulation, and they should be considered as alternative agents in patients who are not able to tolerate propofol or other sedatives.

Dexmedetomidine

Dexmedetomidine is an α_2-adrenergic agonist commonly used for sedation in the ICU. It binds to central and peripheral α_2-receptors, leading to decreased sympathetic outflow and suppressed norepinephrine release. By providing sedation, anxiolysis, and analgesia, dexmedetomidine is an ideal agent for ICU sedation, procedural sedation, and awake fiberoptic intubations. Dexmedetomidine has an established role in decreasing opioid requirements and reducing the rates of delirium [53, 54]. Unlike other sedatives, dexmedetomidine has minimal effect on the respiratory drive, thus making it the preferred agent when weaning patients from mechanical ventilation. Side effects that limit the universal use of this agent include bradycardia, hypotension, and heart block [55]. These effects can be exaggerated in critically ill COVID-19 patients with whom cardiac complications are still being elucidated.

Dexmedetomidine is known to achieve lighter levels of sedation when used as monotherapy. A recent randomized controlled trial revealed an ancillary finding that mechanically ventilated ICU patients, who are sedated with dexmedetomidine as the primary sedative, often require supplemental sedative agents to achieve the desired level of sedation [56]. In patients with COVID-19, who continue to show signs of ventilator dyssynchrony or require proning, dexmedetomidine alone may not be sufficient to obtain desired levels of sedation. In addition, prolonged infusions may also lead to development of tolerance [57]. Clonidine, another alpha-2 adrenergic agonist, that has a similar mechanism of action, is available both as an enteral and transdermal formulation. Although there is insufficient data to recommend its use as a sedative in mechanically ventilated patients, clonidine may have a role in decreasing the duration of dexmedetomidine administration due to its similar mechanism of action, low cost, and excellent bioavailability [58]. A retrospective analysis that included 26 ICU patients showed the enteral clonidine is a safe and effective choice when transitioning patients off dexmedetomidine [59]. In addition, Gagnon et al. reported that transitioning adult ICU patients from dexmedetomidine to clonidine led to significantly lower doses of fentanyl [60]. This transition should be discussed in patients requiring prolonged infusions of dexmedetomidine as a means to limit its utilization, considering its short supply. Careful attention should be paid to formulating a weaning plan for clonidine and medication reconciliation at ICU, and hospital

discharge should be completed to prevent inappropriate continuation.

Ketamine

Ketamine is a N-methyl-D-aspartate (NMDA) receptor antagonist that is used as an analgesic and a sedative-hypnotic agent in the ICU. Ketamine acts as a noncompetitive inhibitor of NMDA receptors, blocking transmission of the excitatory amino acid glutamate. It is increasingly being used for both postoperative analgesia and acute pain management in critically ill trauma patients [25] and has been shown to reduce opioid use in such patients [61]. At sub-anesthetic doses, ketamine has effective analgesic properties while significantly reducing total opioid requirements [62]. In a recent study, adjunctive continuous infusion of ketamine was shown to have analgesic and sedative dose-sparing effects in mechanically ventilated patients while improving time spent within the goal sedation range [63]. The use of ketamine has historically been limited due to its psychotomimetic effects and its tendency to cause delirium. These psychotomimetic effects are however dose-dependent and may be reduced by the concomitant administration of low-doses benzodiazepines [64]. High doses of ketamine may induce myocardial depression in catecholamine-depleted patients based on pre-clinical studies; [65] however, at smaller dosages ketamine demonstrates a sympathomimetic effect without myocardial depression [66]. Ketamine can increase tracheobronchial secretions, which may be detrimental in patients with COVID-19 where excess mucus plugging from respiratory inflammation and injury is common. Ketamine does have bronchodilatory effects, both due to increased catecholamine release as well as inhibition of vagal pathways [67], and may prove beneficial in patients presenting with a history of asthma. Hence, ketamine can be used as an adjunct to other sedatives to limit their dose and duration and may be considered as an alternative agent in specific COVID-19 patients, including asthmatics, or when other sedatives are unavailable or cannot be used. None the less, a thorough risk-benefit analysis should be considered prior to initiation [68].

Figure 2 provides a brief overview of sedation management in a critically ill mechanically ventilated patient with COVID-19.

Conclusion

The burgeoning crisis of COVID-19 disease in the aftermath of the ongoing SARS-CoV-2 pandemic has led to a significant proportion of patients requiring intensive care and mechanical ventilation. Although optimal analgesia and sedation are essential to help improve outcomes in these patients, the need for higher doses as well as longer duration of sedation creates challenges and requires a multidisciplinary approach towards sedation management. Management of sedation in such patients should take into account individual properties and side effect profiles of various agents, unique patient characteristics and health care system limitations, as well as local and national drug shortages. Multimodal sedation regimens with early enteral transitions might be indicated and can help minimize side effects of individual drugs, development of tolerance, and limitations imposed by the supply chain. Formulation of recommendations and guidelines by leveraging the collective clinical experience from around the world may help increase provider awareness of these unique challenges and improve patient safety and outcomes.

Availability of Data and Material Not applicable.

Code Availability Not applicable.

Author Contribution KK conceptualized and edited the manuscript; RD, PM, and JP drafted the manuscript; all authors participated in literature review and revisions; KK and AQ edited the final manuscript; and KK takes responsibility for the final draft.

Compliance with Ethical Standards

Conflict of Interest None of the authors has any potential conflicts of interest to disclose.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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