INVITED COMMENTARY

Analgesia and Sedation Strategies in Mechanically Ventilated Adults with COVID-19

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Evidence-based management of analgesia and sedation in COVID-19-associated acute respiratory distress syndrome remains limited. Non-guideline recommended analgesic and sedative medication regimens and deeper sedation targets have been employed for patients with COVID-19 due to exaggerated analgesia and sedation requirements with extended durations of mechanical ventilation. This, coupled with a desire to minimize nurse entry into COVID-19 patient rooms, marked obesity, altered end-organ function, and evolving medication shortages, presents numerous short- and long-term challenges. Alternative analgesic and sedative agents and regimens may pose safety risks and require judicious bedside management for appropriate use. The purpose of this commentary is to provide considerations and solutions for designing safe and effective analgesia and sedation strategies for adult patients with considerable ventilator dyssynchrony and sedation requirements, such as COVID-19.

KEY WORDS analgesia, sedation, COVID-19, pharmacology.

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Coronavirus disease 2019 (COVID-19) is a novel disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). High-quality supportive critical care remains an essential aspect of effective COVID-19 management.[1] There is wide global variability in patient characteristics and outcomes; in New York City, 12.2–33.1% of patients with COVID-19 required mechanical ventilation (MV) with an overall mortality of 10.2–21% (14.6–88.1% in the MV population).[2, 3] Global rates of MV have ranged from 10% to 88% in patients infected with SARS-CoV-2, depending on patient characteristics and practice strategies.[4, 5]

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Non-guideline recommended medication regimens and deeper target sedation strategies have been employed for patients with COVID-19 due to exaggerated analgesia and sedation requirements with extended durations of MV.[6] This, coupled with a desire to minimize nurse entry into COVID-19 patient rooms, marked obesity, altered end-organ function, and evolving medication shortages, presents numerous short- and long-term challenges. Alternative analgesic and sedative agents and regimens may pose safety risks and require judicious bedside management for appropriate use. The purpose of this commentary, rather than a position statement or guideline, is to provide considerations and solutions for designing safe and effective analgesia and sedation strategies for adult patients with considerable ventilator dyssynchrony and sedation requirements, such as COVID-19.

This commentary was informed by articles identified through literature searches (PubMed from inception to June 2020) and the authors' clinical experiences. The primary author developed the initial structure of the commentary outline, then each commentary section was written by one to two authors. Each author critically evaluated subsequent revisions of the commentary to align with their interpretation of available evidence and best clinical practices. Most authors practiced in institutions that experienced a surge prior to or during commentary development, which informed recommendations given studies of analgesia and sedation in COVID-19 are limited.

Overarching Strategies for Mitigating Risk and Improving Efficacy with Sedation and Analgesia

Many evidence-based practices for pain, agitation, delirium, immobilization, and sleep (PADIS) have been challenged during the COVID-19 pandemic.[7] The approach to sedation in mechanically ventilated COVID-19 patients exemplifies a confluence of an incompletely understood disease state, unprecedented constraints on resources, and behavioral changes to minimize exposure risk to health care workers. Promotion of light sedation, sedation interruption, and avoidance of deliriogenic pharmacotherapies has been difficult or, in some cases, impossible to apply.

A strategy of light sedation tends to reduce time to extubation and tracheostomy placement with inconsistently beneficial effects on delirium, mortality, and psychological well-being after discharge.[7, 8] Historically, achieving light sedation has been considered difficult in patients with severe acute respiratory distress syndrome (ARDS); however, recent trials suggest many non-paralyzed patients will tolerate light sedation and experience improved or similar outcomes compared with paralyzed patients.[9] Early anecdotal observations have suggested COVID-19 ARDS patients are difficult to keep comfortable and synchronous with the ventilator, and large sedative exposure is necessary to achieve goals. Concern for unintentional self-extubation appears heightened because of the availability and time needed to don personal protective equipment if emergent room entry is needed. Finally, as many nursing practices during the pandemic have shifted to facilitate minimization of room entry (e.g., placing infusion sets outside of room), dynamic analgesia and sedation assessments have become limited. Despite these hurdles, targeting the lightest level of sedation necessary and using intermittently dosed sedatives and analgesics to support ventilator synchrony should still be attempted.[10, 11] If deep sedation is initially required (e.g., persistent patient-ventilator dyssynchrony, repositioning, proning, or neuromuscular blocking agent (NMBA) use), it should be lightened over time as respiratory mechanics improve.[12, 13]

Given these challenges, daily awakening trials in all patients without contraindications remains imperative, particularly because of the prevalence of deeper sedation utilized in COVID-19.[14] Although similar health care worker exposure concerns related to self-extubation remain with a daily interruption strategy, interruption that considers patient-specific pharmacodynamics remains the best strategy to mitigate drug accumulation. Accumulation of medications with context-sensitive half-lives that increase with prolonged exposure (e.g., fentanyl, hydromorphone, morphine, methadone, benzodiazepines, propofol, and phenobarbital) can be avoided with thoughtful agent selection and diligent monitoring.[15] (Table 1).

Managing Shortages

Already challenging sedation and analgesia requirements have been exacerbated by medication shortages arising secondary to increased use and stockpiling by institutions. For example, analgosedation with a favored opioid analgesic may have been substituted to a different agent with dissimilar pharmacokinetics, side effect

Table 1. Properties and Dosing for Analgesic and Sedative Medications in Patients with COVID-19

Opioids	Equivalent Dose	Bolus Dose	CI Dose	Onset (min)	Metabolism	Active Metabolite	Elimination Half-life (h)	ADRs/ Considerations
Fentanyl	0.1	0.35–0.5 mcg/kg Q0.5–1 hr	0.7–10 mcg/kg/hr	1–2	Hepatic	No	2–4[b]	Accumulation with hepatic impairment and obesity
Hydromorphone	1.5	0.2–0.6 mg Q1–2 hrs	0.25–6 mg/hr	5–15	Hepatic	No	2–3[b]	Accumulation with hepatic/renal impairment
Morphine	10	2–4 mg Q1–2 hrs	0.5–15 mg/hr	5–10	Hepatic; active metabolite (renal)	Yes	3–4[b]	Accumulation with hepatic/renal impairment; histamine release
Remifentanil	~0.1	1.5 mcg/kg[a]	0.5–15 mcg/kg/hr	1–3	Hydrolysis by plasma esterases	No	3–10 min	Ultra short half-life, rebound pain; use IBW if ABW> 130% IBW
Sufentanil	0.01	0.05 mcg/kg[a]	0.05 mcg/kg/hr	1–3	Hepatic	No	2.7 min	Ultra short half-life, rebound pain; use IBW if ABW> 120% IBW
Alfentanil	0.75	5–7.5 mcg/kg[a]	0.1–0.2 mcg/kg/min	≤5	Hepatic	No	1.5–1.85 min	Ultra short half-life, rebound pain; use IBW
Methadone	N/A	2.5–10 mg Q6–12 hrs	N/A	10–20	Hepatic	No	15–60[b]	QTc prolongation, unpredictable PK
Benzodiazepines	**Equivalent Dose**	**Bolus Dose**	**CI Dose**	**Onset (min)**	**Metabolism**	**Active Metabolite**	**Elimination Half-life (h)**	**ADRs/Considerations**
Midazolam	2	0.01–0.05 mg/kg	0.02–0.1 mg/kg/hr	2–5	Hepatic	Yes	3–11[b]	Respiratory depression, CNS depression, hypotension
Lorazepam	1	0.02–0.06 mg/kg Q2–6 hrs	0.01–0.1 mg/kg/hr	15–20	Hepatic	No	8–15[b]	Respiratory depression, CNS depression, hypotension, propylene glycol toxicity
Diazepam	5	5–10 mg, 0.03–0.1 mg/kg Q0.5–6 hrs	N/A	2–5	Hepatic	Yes	20–120[b]	Respiratory depression, CNS depression, hypotension, propylene glycol toxicity
Other Sedatives	**Mechanism**	**Bolus Dose**	**CI Dose**	**Onset (min)**	**Metabolism**	**Active Metabolite**	**Elimination Half-life (h)**	**ADRs/Considerations**
Propofol	GABA agonist, weak NMDA antagonist	N/A	5–80 mcg/kg/min	1–2	Hepatic	No	3–12[b]	Hypotension, respiratory depression, hypertriglyceridemia, acute pancreatitis, propofol-related infusion syndrome
Dexmedetomidine	Alpha-2	1 mcg/kg	0.2–1.5 mcg/kg/hr	5–10	Hepatic	No	1.8–3.1	Bradycardia, hypotension
Ketamine	NMDA antagonist	0.5–1 mg/kg	1–5 mg/kg/hr	5–15	Hepatic	Yes	2–3	Excess secretions, emergence phenomenon, sympathetic surge, hypertension
Phenobarbital	GABA agonist	5–10 mg/kg load, 1–2 mg/kg/day in 2–4 divided doses, 65–130 mg	N/A	5	Hepatic	No	80[b]	Hypotension, propylene glycol toxicity, drug interactions (CYP3A4 inducer)

ABW = actual body weight; ADR = adverse drug reaction; CI = continuous infusion; CNS = central nervous system; GABA = gamma aminobutyric acid; IBW = ideal body weight; IV = intravenous; NMDA = N-methyl-D-aspartate; PK = pharmacokinetics; Q = every (e.g., Q1h: every 1 hr).

[a]Not recommended as bolus alone due to ultra-short half-life

[b]Context-sensitive half-life.

profiles, and dosing in many institutions. Nursing and provider unfamiliarity with alternative pharmacotherapies may lead to dosing errors and subsequent under-sedation or over-sedation regardless of patient characteristics. Many institutions may also experience an increase in continuous infusion benzodiazepine use due to propofol shortages, inability to attain adequate sedation with dexmedetomidine alone, or deleterious effects on hemodynamics from propofol, dexmedetomidine, and/or ketamine.[16] Additionally, propofol and dexmedetomidine use may be less frequent in patients who would otherwise qualify for remdesivir if they do not require vasopressor support because vasopressor therapy to mitigate hypotension may exclude patients from qualifying for the antiviral medication.[17–20] Compared to these two agents, benzodiazepines have been associated with an increased risk for delirium and time spent on MV, particularly in the milieu of deeper sedation.[19, 20] The limited availability of many commonly used agents has necessitated the development of unconventional strategies to keep patients with COVID-19 on MV comfortable and synchronous. (Table 2).

Analgesics and Analgosedation

General Principles

Analgosedation consists of managing pain and attempting to achieve sedative goals with an analgesic-first strategy before considering other non-analgesic sedative agents.[7] Implementing strategies to promote usual care as it pertains to analgesic use and analgosedation in the current pandemic should be strongly attempted.[20] Assessment of pain is complex because of the need to consider the temporality (i.e., acute, chronic, or acute-on-chronic); source (i.e., somatic, visceral, or neuropathic); interpatient variability in pain perception and analgesia tolerance; and masking of pain from deeper sedation and neuromuscular blockade.[7] During the H1N1 pandemic in 2009–2010, higher fentanyl requirements were observed in patients with H1N1-associated pneumonia compared with non-H1N1-associated pneumonia or ARDS associated with bacterial pneumonia.[16] Anecdotally, we have observed this phenomenon again with COVID-19.

Because patients will likely develop tachyphylaxis to specific opiate agents and medication shortages are ever-present, transitioning between opiate analgesics may be a necessary and preferential strategy.[21] At usual doses, most opioids exhibit selectivity for μ-receptors, but differences in relative selectivity may result in variable pharmacodynamic responses. Some opioid agents also have mixed μ-, κ-, and/or δ-receptor agonist activity and even mixed agonist/antagonist activity (e.g., buprenorphine). If a patient has escalating requirements, clinicians may consider transitioning to another opioid with a different binding profile.[21] When transitioning, the new opioid dose should be 25–50% lower than the calculated equianalgesic dose though a 50% reduction is appropriate for most critically ill patients receiving higher doses who may have additional risk factors.[21] (Table 1) Safer and more effective transitions may be accomplished by allowing higher dosages and more frequent intravenous bolus administration alongside infusion titration schemas that consider the opiate's onset of action and half-life. The predictability of the effects from agents that undergo organ-dependent metabolism and elimination is reduced in the critically ill and those with end-organ dysfunction. This necessitates monitoring for dose-dependent adverse effects such as over-sedation, constipation, hypotension, and respiratory depression.[21, 22] For these reasons, enteral opioids are not routinely recommended while patients are mechanically ventilated, other than methadone and buprenorphine peri-extubation to mitigate opioid withdrawal syndrome development, unless intravenous opioid shortages necessitate their use because of their risk of accumulation and prolonging time to extubation.[16, 21] Analgesia should be evaluated routinely with attention to whether continuous infusions are still needed and a goal of transitioning to intermittent and as needed administration when possible. The following subsections focus on opioids with potential roles for analgesia and analgosedation in mechanically ventilated COVID-19 patients with attention to agent preference and special considerations for use.

Fentanyl

Fentanyl is a synthetic phenylpiperidine derivative that provides analgesia and sedation through μ-opioid receptor agonism in the central nervous system (CNS). Because of its high lipophilicity (≈580-times greater than morphine), intravenous fentanyl has a rapid onset (<1 minute) and short duration of action (≈30 minutes), making it an ideal agent to

Table 2. Example Analgesia and Sedation Regimens Based on Patient Characteristics and Medication Availability

Sedation target	Recommendation	End-organ dysfunction	Scheduled analgesia and sedation	Intermittent analgesia and sedation
Light (e.g., RASS + 1 to −1)	Primary	None Hepatic Renal	Fentanyl 25–150 mcg/hr + propofol 5–50 mcg/kg/min	Fentanyl 50–75 mcg IVP Q1H PRN + lorazepam 0.5–2 mg IVP Q1H PRN
	Alternative	None Hepatic Renal	Hydromorphone 0.5–2 mg/hr + dexmedetomidine 0.2–1.5 mcg/kg/hr[a]	Hydromorphone 0.25–1 mg IVP Q1H PRN + lorazepam 0.5–2 mg IVP Q1H PRN
Moderate (e.g., RASS −2 to −3)	Primary	None Hepatic Renal	Fentanyl 25–300 mcg/hr + propofol 5–80 mcg/kg/min ± dexmedetomidine 0.2–1.5 mcg/kg/hr[a] ± ketamine 0.5–2.5 mg/kg/hr	Fentanyl 50–100 mcg IVP Q1H PRN + lorazepam 0.5–2 mg IVP Q1H PRN
	Alternative	None Hepatic Renal	Hydromorphone 0.5–4 mg/hr + dexmedetomidine 0.2–1.5 mcg/kg/hr[a] ± ketamine 0.5–2.5 mg/kg/hr	Hydromorphone 0.25–2 mg IVP Q1H PRN ± ketamine 0.5–1 mg/kg IVP Q1H PRN + lorazepam 0.5–2 mg IVP Q1H PRN
Deep (e.g., RASS −4 to −5)	Primary	None Hepatic Renal	Fentanyl 25–300 mcg/hr + propofol 5–80 mcg/kg/min ± dexmedetomidine 0.2–1.5 mcg/kg/hr[a] ± ketamine 0.5–5 mg/kg/hr	Fentanyl 50–100 mcg IVP Q1H PRN + lorazepam 0.5–2 mg IVP Q1H PRN
	Alternative	None Hepatic	Hydromorphone 0.5–6 mg/hr + midazolam 0.5–15 mg/hr OR lorazepam 0.5–8 mg/hr ± dexmedetomidine 0.2–1.5 mcg/kg/hr[a] ± ketamine 0.5–5 mg/kg/hr	Hydromorphone 0.25–2 mg IVP Q1H PRN ± ketamine 0.5–1 mg/kg IVP Q1H PRN + lorazepam 0.5–2 mg IVP Q1H PRN OR midazolam 0.5–4 mg IVP Q1H PRN
		Renal	Hydromorphone 0.5–4 mg/hr + midazolam 0.5–6 mg/hr OR lorazepam 0.5–8 mg/hr ± dexmedetomidine 0.2–1.5 mcg/kg/hr[a] ± ketamine 0.5–5 mg/kg/hr	Hydromorphone 0.25–2 mg IVP Q1H PRN ± ketamine 0.5–1 mg/kg IVP Q1H PRN + lorazepam 0.5–2 mg IVP Q1H PRN OR midazolam 0.5–2 mg IVP Q1H PRN

IVP: intravenous push; Q1H: every 1 hr; RASS: Richmond Agitation Sedation Scale
Alternative regimens consider medication shortages for desired primary analgesics and sedatives; if fentanyl or propofol is available then they may be substituted for agents in alternate regimens
End-organ dysfunction refers to moderate-to-severe degree of impairment
[a]Not recommended for longer than 5–7 days to reduce likelihood of withdrawal syndrome

quickly manage acute uncontrolled pain, although repeat doses may be needed sooner than with other opioids.[23] However, prolonged infusions increase its duration of action by extending its context-sensitive half-life. The lipophilicity of fentanyl can also cause adipose accumulation in obese patients. This can lead to unintended effects when fentanyl is used for an extended period of time, such as over-sedation, respiratory depression, and a depot effect upon discontinuation. Fentanyl undergoes phase 1 hepatic metabolism to norfentanyl, an inactive metabolite, and may accumulate in moderate-to-severe hepatic dysfunction.[23]

In addition to the intravenous dosage form, fentanyl may be administered through various other routes. Though less commonly used in critically ill patients, transdermal fentanyl patches may be considered to reduce intravenous fentanyl requirements in patients receiving a stable fentanyl dosage in cases of considerable intravenous opioid shortage.[7] Fentanyl patches should be avoided when managing acute pain because peak effects will not be achieved until 24 hours after patch application. The extent of absorption from fentanyl patches is also variable and increases in area-under-the-curve and maximum concentration may be observed in patients who sweat and/or exhibit fever, such as COVID-19 with cytokine release syndrome.[3, 24]

Large doses of fentanyl have been associated with chest wall rigidity precipitating insufficient ventilation. This phenomenon is most commonly described in neonatal and pediatric patients. Among adults, it is unlikely to be observed unless bolus doses of 100 mcg are exceeded.[25] Fentanyl and other phenylpiperidines possess slight serotonergic activity, which has been linked to serotonin syndrome development when used with monoamine oxidase inhibitors and other serotonergic medications, although

incidence is low (0.09%).[26] Because fentanyl and its derivatives are the most hemodynamically neutral opioids and do not accumulate in renal dysfunction as seen with hydromorphone and morphine, patients at greatest risk for hemodynamic and renal complications may represent ideal candidates to receive fentanyl rather than another intravenous opioid.[22, 23] Because up to 84% of critically ill COVID-19 patients have exhibited renal dysfunction, fentanyl may be the opioid of choice in these patients.[3]

Fentanyl Derivatives

Although significant literature exists for perioperative use of fentanyl derivatives (i.e., sufentanil, alfentanil, and remifentanil), studies for ICU analgesia and sedation are limited.[27–30] Recent fentanyl shortages have forced some institutions to rely on fentanyl derivatives for ICU analgesia and sedation, which may improve our understanding of their benefits and limitations. Sufentanil, alfentanil, and remifentanil possess more rapid onsets of action than fentanyl though their potency varies.[31–33] (Table 1) Similar to fentanyl, sufentanil and alfentanil are hepatically metabolized to renally excreted inactive metabolites.[31, 32] Remifentanil is metabolized by plasma and tissue cholinesterases, yielding an ultra-short half-life (<5 minutes) independent of infusion duration and end-organ dysfunction.[33] Remifentanil has not been compared to fentanyl in ICU patients though its comparisons to benzodiazepines and morphine have suggested patients who received remifentanil had shorter durations of MV, were optimally sedated a greater percentage of the time, and required less benzodiazepines.[29, 30] These unique characteristics and encouraging data led to remifentanil's recommendation in the most recent PADIS guidelines and make it an appealing fentanyl alternative in patients with hepatic dysfunction, obesity, and/or extensive analgesia and sedation requirements.[7, 34] Infusion titration of remifentanil must be precise and performed vigilantly because bolus doses for uncontrolled pain are short-lasting.[34] Remifentanil infusions may cause acute opioid tolerance after a few hours post-initiation and, conversely, opioid-induced hyperalgesia.[34, 35] Although acute opioid tolerance can be overcome with increasing the infusion dosage, this strategy exacerbates hyperalgesia so differentiating between the complications is necessary.[34, 35]

Hydromorphone

Hydromorphone, a semisynthetic μ-opioid agonist, undergoes phase 2 hepatic metabolism (glucuronidation) to inactive metabolites that are renally eliminated and has a minimally or moderately prolonged half-life in patients with severe hepatic or renal dysfunction.[36] Hydromorphone is less lipophilic than fentanyl and its derivatives, resulting in relatively less distribution into adipose tissue.[37] Because of the disproportionately higher percentage of obese patients with COVID-19 ARDS, hydromorphone may be a reasonable option that provides similar analgesia for an obese patient without hepatic or renal dysfunction if fentanyl is unavailable or its use is being stewarded.[2, 38] Additionally, intravenous hydromorphone has a reliably longer duration of action than fentanyl, which allows for less frequent bolus doses for patients who are being titrated down or transitioned off an infusion. This intermittent dosing strategy can reduce nurse exposure and yield more efficient patient care but risks drug accumulation. Hydromorphone may be provided enterally in patients with a functional gastrointestinal tract whom are receiving a relatively stable intravenous hydromorphone dose and are at lower risk for medication accumulation to preserve intravenous hydromorphone and facilitate opioid weaning.[36]

Morphine

Morphine, the prototypical μ-opioid agonist, exhibits dose-response effects depending on metabolic and excretory function.[39] Morphine undergoes phase 2 hepatic metabolism (glucuronidation) to two active, water-soluble metabolites, morphine-3-glucuronide (80%) and morphine-6-glucuronide (20%), which are renally eliminated. The hepatic and renal injury that develops in up to 89% and 84%, respectively, of mechanically ventilated COVID-19 patients suggests morphine use would predispose many patients to adverse effects.[3] Decreased elimination of morphine-3-glucuronide may potentiate a distinct neurotoxicity syndrome characterized by hallucinations, delirium, allodynia, hyperalgesia, myoclonus, and seizures.[40] Neurological dysfunction, potentially from microthrombi, is being more commonly recognized in patients with COVID-19, and morphine use could obfuscate this clinical picture.[41] Additionally, morphine-associated histamine release and subsequent vasodilation is a well-

established adverse effect that may be exacerbated in patients already receiving intravenous vasopressor therapy and/or experiencing renal dysfunction.[6, 42] Although the histamine release and commonly concurrent pruritus frequently respond to antihistamine medications, these medications often have anticholinergic effects that can increase the risk of a bacterial pneumonia and delirium.[43] Collectively, the unpredictable pharmacokinetics and unfavorable adverse effect profile limits the utility of morphine for mechanically ventilated COVID-19 patients unless other options are unavailable. In situations of significant drug shortage, morphine may be an opioid of last resort and should be used at the lowest continuous infusion rates acceptable for ventilator synchrony and patient comfort to reduce medication accumulation. Adequate morphine bolus doses should be available to reduce over-sedation and hypotension risks while limiting nurse exposure.

Methadone

Methadone is a synthetic opioid that acts in the CNS, demonstrating inhibition of norepinephrine and serotonin reuptake, antagonism at N-methyl-D-aspartate (NMDA) receptors, and agonism at μ-opioid receptors.[44] These mechanisms increase effectiveness in neuropathic pain treatment and remodeling pain pathways that prevent maladaptive acute pain responses.[45] Methadone is hepatically metabolized through multiple cytochrome P450 enzymes to inactive metabolites, which increases the risk of drug-drug interactions. These safety concerns are paramount, particularly when used in combination with other QTc-prolonging or serotonergic medications because of increased risks of torsades de pointes and serotonin syndrome, respectively.[46] Although accumulation in renal and hepatic dysfunction is rarely observed, the half-life increases from 7 hours up to 65 hours with longer durations of use, positioning methadone as an ideal agent to facilitate intravenous opioid tapering to discontinuation while mitigating opioid withdrawal risk and symptoms and shortening MV duration and ICU lengths of stay.[46–50] Because of uncertainties regarding equianalgesic dosing conversions and prolonged duration of action with longer durations of use, methadone should be initiated within a couple of days of expected extubation and likely reserved for patients who are at greatest risk of opioid withdrawal syndrome (e.g., intravenous opioid use> 5–7 days).[48, 51] Additionally, buprenorphine may be considered peri-extubation as well to limit opioid withdrawal syndrome development and effects.[47]

Sedatives

Benzodiazepines

Benzodiazepines are CNS ϒ-aminobutyric acid-A ($GABA_A$) receptor agonists that produce amnestic, anxiolytic, sedative, and anticonvulsant effects.[7] Although continuous infusions of benzodiazepines were used in many patients during the H1N1 epidemic due to propofol shortages, their use for traditional sedation has diminished significantly over the last decade because of associations with increased ICU and hospital lengths of stay, MV duration, and delirium and cognitive dysfunction incidence.[7, 16] The poor outcomes may be a result of deeper sedation depth and delayed emergence from sedation with benzodiazepine infusions compared to non-benzodiazepines.[7, 18, 19] In particular, the odds of delirium development appear to be approximately 4% greater for each 5 mg of midazolam equivalents for a benzodiazepine infusion but are similar to non-benzodiazepines for intermittent bolus dosing benzodiazepines.[52] Consequently, intermittent benzodiazepine doses can play a role for remediating acute agitation in mechanically ventilated patients with COVID-19 ARDS.[52] Because benzodiazepines accumulate in hepatic (e.g., diazepam, lorazepam, midazolam) and renal (e.g., diazepam, midazolam) impairment and with increasing age, every reasonable attempt to avoid continuous infusions should be made.[53] However, select circumstances (e.g., chemical paralysis necessitating deep sedation when propofol is contraindicated or unavailable) may require continuous benzodiazepine administration.[7] Strategies to reduce overall benzodiazepine exposure include spontaneous awakening trials, multimodal sedation, and intermittent bolus dosing.[7, 52]

Midazolam

Midazolam has a quicker onset of action for intravenous benzodiazepines alongside a shorter half-life than lorazepam when used intermittently in patients without renal dysfunction or obesity.[53, 54] In obese patients or those with renal dysfunction receiving continuously infused midazolam, delayed emergence is frequently

observed because of a widely variable half-life due to redistribution into adipose tissue and an active metabolite that is renally eliminated and only partially cleared by renal replacement therapies.[55–57] Midazolam should be avoided or limited to intermittent dosing in these at-risk populations unless no other options exist.[58]

Lorazepam

Intravenous lorazepam has a delayed onset of action and relatively longer half-life compared to midazolam, suggesting intermittent doses may take slightly longer to yield an effect but will persist while other sedation and ventilator settings are adjusted or an intermittent NMBA dose is eliminated.[53, 54] Lorazepam undergoes phase 2 hepatic metabolism (glucuronidation) and elimination, making it the preferred benzodiazepine in severe hepatic dysfunction.[7] Intravenous lorazepam contains the diluent propylene glycol, which may accumulate and cause a wide anion gap metabolic acidosis, typically when infused at> 1 mg/kg/day and/or with an osmol gap of> 10 mOsm/L.[59, 60] Although intermittent dosing of lorazepam may play a vital role in management of acute agitation, continuous infusions of lorazepam should be used very cautiously because of the risk for developing propylene glycol-mediated metabolic acidosis and delayed emergence from sedation with continuous infusion benzodiazepines.[7, 52]

Other Benzodiazepines

Diazepam is a rapid-acting benzodiazepine that is less preferred in the critically ill due to highly variable metabolism, longer half-life (20–120 hr), and prolonged sedative effects in hepatic or renal dysfunction. Diazepam intravenous solution also contains propylene glycol, warranting monitoring of the osmol gap for propylene glycol-related toxicity.[53] Enterally administered benzodiazepines may be considered to reduce withdrawal when weaning a continuous infusion to discontinuation prior to extubation after prolonged use (e.g., >7 days).[53] Enteral benzodiazepines that may be considered include chlordiazepoxide, alprazolam, clonazepam, diazepam, or lorazepam.

Propofol

Propofol is a $GABA_A$ receptor agonist displaying sedative, antiemetic, anticonvulsant, and amnestic effects.[61] It has a rapid onset, ability to achieve all depths of sedation, and short duration of action that is prolonged with continuous use and in obesity because it is formulated in a lipid emulsion. This formulation may result in hypertriglyceridemia with extended use. Hypertriglyceridemia may be exacerbated by the hypertriglyceridemia from a secondary hemophagocytic lymphohistiocytosis-like syndrome observed in many COVID-19 ARDS patients.[62] A more lenient serum triglyceride threshold of 1000 mg/dL has been suggested for propofol discontinuation and implemented in many institutions to balance a relatively low risk of acute pancreatitis (1.9%) with a desire to continue propofol for a longer duration in a greater percentage of patients.[63] Green urine is a common effect from propofol that has not been associated with harm.[64] Propofol-related infusion syndrome is a rare adverse effect (1.1%)that has a mortality rate of 52% and appears to be more common with higher infusion rates (i.e., >80 mcg/kg/min), longer durations of use, and greater critical illness.[65] Patients receiving propofol more commonly develop hypotension (16–34%) within a few hours of initiation, particularly in those having received inadequate fluid resuscitation, and may persist with frequent dosage increases, higher dosages, and/or bolus dosing.[17, 66–68] Consequently, bolus dosing is strongly discouraged for ICU sedation. If deep sedation is being targeted, propofol-associated hypotension may be managed with intravenous vasopressor therapy rather than transitioning to a benzodiazepine continuous infusion.[7] If lighter sedation is being targeted, a lower propofol dosage may be used if dexmedetomidine or ketamine are concomitantly initiated, which can help lower the risk of hemodynamic adverse effects and prolong propofol use.[68, 69] Although propofol is considered a first-line sedative in ARDS, potential immunosuppressive effects in animal studies, such as increases IL-1β, IL-6 and tumor necrosis factor-α, and inflammatory effects from omega-6-polyunsaturated fatty acids in the lipid emulsion, warrant further study in COVID-19 ARDS.[69]

Dexmedetomidine

Dexmedetomidine is an alpha-2-adrenergic agonist with preferential CNS activity that provides anxiolysis, sedation, and possible neuroprotection through its unique mechanism of action.[70–72] Its light sedative properties and

predictable pharmacokinetics make dexmedetomidine an attractive monotherapy sedative for patients tolerating MV while remaining more arousable. Dexmedetomidine may potentially play a role as an adjuvant sedative to reduce dosages of other sedatives and analgesics while lessening their adverse effects when deeper sedation is necessary.[7, 67, 68, 73] Patients receiving dexmedetomidine are at risk for hypotension and more commonly bradycardia within a few hours of initiation, particularly if an initial bolus dose is provided, and with dosage escalations more frequently than every 30 minutes, due to medication accumulation because of its relatively longer half-life and time to peak effects.[18, 66, 74] Patients may also benefit from dexmedetomidine initiation in the days leading up to extubation when spontaneous awakening trials and lighter sedation are better tolerated and COVID-19 ARDS sequelae are resolving. Dexmedetomidine use may minimize MV duration and development of delirium and secondary respiratory infections, although prolonged use can contribute to dexmedetomidine withdrawal, which may increase hemodynamics and agitation.[68, 73, 75, 76] Patients may be extubated on dexmedetomidine if sedation without respiratory depression is required, particularly because dexmedetomidine may reduce cough and aerosolization risk of the virus.[75, 77]

Ketamine

Ketamine, an NMDA receptor antagonist, interferes with ion channel opening and neuron depolarization to produce sedative and analgesic effects.[78] Additional sedation from functional and electrophysiological dissociation of thalamoneocortical and limbic systems and analgesia, comparable to morphine, from μ- and κ-receptor agonism aid in ketamine's variable and evolving role in COVID-19 ARDS management.[79, 80] Whereas analgesia may be producible at lower ketamine doses (i.e., <0.5 mg/kg/h), dissociative sedation requires higher doses (i.e., 1–5 mg/kg/h). Deeper sedation and burst suppression may be attained with doses> 5 mg/kg/hour.[81] Observational studies of ketamine have suggested reductions in opioid and sedative requirements with neutral or increased time within goal analgesia and sedation targets and similar time and proportion of patients with delirium.[82–86] Ketamine may be initiated with a bolus dose (0.5–1 mg/kg) and initial infusion rate (1–5 mg/kg/hr), depending on the desired analgesia and/or sedative effects.[7, 83] Ketamine typically produces dose-related increases in cardiac index by enhancing sympathomimetic outflow and decreasing catecholamine reuptake; however, critically ill patients replete of endogenous catecholamines may infrequently experience hypotension rather than blood pressure-neutral or hypertensive effects.[87, 88] Similarly, the potential for negative sequelae in patients with COVID-19-associated cardiomyopathy who receive ketamine exists though this requires further evaluation.[86–88] Ketamine may be a valuable adjuvant in COVID-19 ARDS patients requiring moderate-to-deep sedation and may be considered for monotherapy in those tolerating light sedation and analgesia needs. Additionally, ketamine is not associated with significant respiratory depression and actually relaxes smooth muscle in the respiratory tract, supporting its role in peri-extubation agitation management; however, low rates of hypersalivation, laryngospasm, emesis, and emergence phenomenon suggest it should be considered in patients unable to tolerate dexmedetomidine for this purpose.[87]

Miscellaneous

Phenobarbital

Phenobarbital, a barbiturate sedative hypnotic, produces sedation through $GABA_A$ receptor agonism.[89] Prolonged use of phenobarbital may induce cytochrome P450 2C and 3A enzymes, increasing metabolism of enzymatic substrates (e.g., fentanyl, midazolam).[90] Its long half-life (≈80 hrs in adults) precludes safe dose titration and limits utility for acute agitation in COVID-19 ARDS patients synchronous with MV at light or moderate depths of sedation.[89] However, because of critical shortages for common sedatives used to elicit deep sedation (i.e., benzodiazepines, propofol), adjunctive intermittent or scheduled doses of enteral or intravenous phenobarbital (e.g., 5–10 mg/kg loading doses followed by 1–2 mg/kg/day in two to four divided doses and 65–130 mg bolus doses as needed) may be necessary in these patients.[91, 92] Intravenous phenobarbital is dissolved in propylene glycol, which may necessitate osmol gap monitoring.[60]

Antipsychotics

Although routine antipsychotic use is not recommended for ICU delirium prevention or

treatment, short-term intermittent or scheduled doses may facilitate agitation management and/or planned extubation in the hyperactive delirium or agitated patient with COVID-19 at risk for self-extubation or experiencing ventilator dyssynchrony.[7, 93] Each antipsychotic has activity at a variety of receptors, resulting in heterogeneous responses among patients, so their use should be limited to patients not responding to safer, titratable alternatives.[93] Monitoring for QTc interval prolongation and discontinuing the agent if ineffective or the desired outcome (e.g., extubation) has been achieved are best practices.[7, 94]

Valproate

Reducing exposure to psychoactive agents utilized for sedation may be considered, especially as respiratory mechanics improve. Administration of agents that have been used in critical care for agitation, such as valproate, may reduce concomitant psychoactive medication use, although further investigation is required.[95, 96]

Melatonin

Melatonin, an endogenous hormone that regulates sleep-wake cycles primarily through MT1 and MT2 melatonin receptors, has additional anti-inflammatory, anti-oxidation, and immunomodulation effects that may theoretically be beneficial in COVID-19-related cytokine release syndrome.[97] Efficacy and dosing remain areas of future study though 3–20 mg nightly may be reasonable to consider in select patients.[98]

Conclusions

Evidence-based management of analgesia and sedation in COVID-19-associated ARDS remains limited. Although recommendations from PADIS and ARDS guidelines should help guide decision-making, the severity of ARDS and ventilator dyssynchrony coupled with medication shortages require clinicians to explore non-traditional strategies for analgesia and sedation in patients with COVID-19. High-quality care and decision-making at the bedside that considers insights from all health care team members and evolves with patient needs and emerging data are paramount to yielding individualized analgesia and sedation plans that afford patients with COVID-19 their best opportunity to achieve treatment goals.

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