

## **USE OF SEDATIVE, ANALGESIC AND NEUROMUSCULAR BLOCKING AGENTS IN THE INTENSIVE CARE UNIT DURING THE NOVEL 2019 CORONAVIRUS PANDEMIC- MICHIGAN MEDICINE GUIDELINES**

These guidelines will focus on the use of sedative, analgesic and neuromuscular blocking agents in critically ill patients with COVID-19 infection as required for the management of pain, agitation and delirium, and to optimize ventilator synchrony and gas exchange in the setting of severe hypoxic respiratory failure. This document will not cover the use of procedural sedation or analgesia, which is addressed in the moderate and deep sedation policies of Michigan Medicine.

### **PAIN, AGITATION, AND DELIRIUM**

Critically ill patients with COVID-19 infection often require the use of sedation, analgesia and medications to manage delirium, for the following reasons-

1. Patient comfort during invasive mechanical ventilation.
2. Synchrony with mechanical ventilation, to optimize oxygenation and ventilation in the setting of severe hypoxemic respiratory failure.
3. Prevention of unplanned device removal, especially unplanned extubation.
4. Management of agitated delirium.

### **Specific challenges with management of pain, agitation and delirium in patients with COVID-19 infection.**

1. Early reports and anecdotal experience suggests a high rate of acute encephalopathy and agitated delirium in patients with COVID-19 infection.[2] The presence of acute encephalopathy leads to increased usage of sedative and analgesic agents to prevent unplanned device removal and improve ventilator synchrony.
2. A significant proportion of COVID-19 patients develop the acute respiratory distress syndrome (ARDS), necessitating measures that require sedation and analgesia, such as low tidal volume ventilation, high positive end expiratory pressure (PEEP) and prone ventilation.
3. *For the above reasons, consumption of sedative and analgesic agents such as Propofol, Midazolam and Fentanyl is high, leading to medication shortages across the United States.*
4. The risk of transmission to healthcare workers requires that room entry by nursing and providers be minimized and tasks consolidated, which impacts the ability to perform frequent re-assessments and medication titration.
5. Anecdotal experience suggests that hypertriglyceridemia may be common in critically ill COVID-19 patients receiving Propofol infusions, including at lower infusion rates.

No specific data exists on the optimal use of sedation, analgesia and agents to control delirium in patients with COVID-19 infection. Recommendations for the use of these agents will therefore be based primarily on consideration of the challenges described above and indirect

evidence from other populations of critically ill patients, reflected in the Society of Critical Care Medicine's 2018 clinical practice guidelines for the prevention and management of pain, agitation/ sedation, delirium, immobility, and sleep disruption in adult patients in the intensive care unit (ICU), accessible at <https://www.sccm.org/ICULiberation/Guidelines>. [3]

### **Depth of sedation**

1. Light sedation, defined as a Richmond Agitation Sedation Score (RASS) of 0 to -2 is an appropriate initial goal for depth of sedation in critically ill, mechanically ventilated adults with COVID-19 infection. A goal of light sedation decreases time to extubation.
2. A low threshold should exist to deepen sedation when any of the following conditions exist-
  - a. The patient is at risk for unplanned device removal despite light sedation and appropriate use of restraints.
  - b. Significant ventilator dys-synchrony exists with evidence of impaired gas-exchange despite light sedation.
  - c. There is evidence of significant patient discomfort despite light sedation.
  - d. Patients who require a high level of ventilator support following intubation may be less likely to tolerate an initial goal of light sedation.
3. Deep sedation (RASS -4 to -5) should be achieved prior to the use of neuromuscular blocking agents. The sedative infusion should subsequently not be weaned down while neuromuscular blockade is in use.

### **Analgo-sedation**

1. The use of analgo-sedation is appropriate as an initial strategy in critically ill, mechanically ventilated patients with COVID-19 infection. Unrecognized pain is a frequent cause of agitation in mechanically ventilated patients, and a strategy of analgo-sedation may decrease time to extubation. This may include-
  - a. Analgesia-first sedation where a potent opioid analgesic infusion such as Fentanyl is used before a sedative to reach the sedative goal
  - b. Analgesia-based sedation where a high-dose infusion of an opioid analgesic such as Fentanyl is used instead of a sedative to reach the sedative goal.
2. Intravenous opioid agents preferred for analgo-sedation include Fentanyl and Hydromorphone. Consult with the clinical pharmacist for updates on drug shortages and medication availability.
3. Consider the use of scheduled enteral opioid agents such as Oxycodone to decrease consumption of intravenous opioids.
4. A low threshold should exist to escalate beyond analgo-sedation to the use of conventional sedative agents (such as Propofol, Dexmedetomidine or Benzodiazepines) when any of the following conditions exist-
  - a. The patient is at risk for unplanned device removal despite the use of analgo-sedation and appropriate use of restraints.
  - b. Significant ventilator dys-synchrony exists with evidence of impaired gas-exchange despite the use of analgo-sedation

- c. There is evidence of significant patient discomfort despite the use of analgo-sedation.
- d. Patients who require a high level of ventilator support following intubation may require the use of conventional sedative infusions (Propofol, Dexmedetomidine or Benzodiazepines) as part of the initial sedation strategy.

Please note: Once a decision has been made to use conventional sedation (with agents such as propofol, benzodiazepines or dexmedetomidine) as the primary strategy, slowly wean down intravenous opioid agents as tolerated to minimize drug consumption and side effects of opioids.

### **Choice of sedative agent**

1. Options for sedative infusions include propofol, midazolam, dexmedetomidine, ketamine and lorazepam. Consult with the clinical pharmacist for updates on drug shortages and medication availability.
2. Propofol is preferred as a first line agent for sedation in critically ill, mechanically ventilated adults with COVID-19 infection. Compared to benzodiazepine infusions, propofol may shorten time to light sedation and extubation.
  - a. Anticipate hemodynamic instability and the need for vasopressor support. Consider transition to an alternate agent such as midazolam and/ or ketamine in the presence of severe hemodynamic instability and vasopressor requirement, such as with septic shock.
  - b. Transition to an alternate agent such as a benzodiazepine in the presence of significant hypertriglyceridemia (>750mg/dL) to minimize the risk of acute pancreatitis.[4] Anecdotal experience suggests that hypertriglyceridemia is common in patients with COVID-19 infections on a propofol infusion, including at lower rates of infusion.
3. A dexmedetomidine infusion is appropriate when the goal is light sedation, however, an alternate agent should be considered when deep sedation is required.
4. Midazolam may cause prolonged sedation if administered over a longer duration, particularly in the presence of hepatic or renal dysfunction.
5. Consider using scheduled high-dose enteral lorazepam when long-term sedation is required, to decrease consumption of intravenous agents.
6. A ketamine infusion may be considered either as an adjunct to other agents, or as an initial agent, particularly in the setting of severe hemodynamic instability with high vasopressor requirements or bronchospasm.
7. Transition to an alternate agent when adverse effects occur with the agent in use.

### **Bolus dosing**

An order for bolus dosing should be entered for most sedative and analgesic agents at the time of initiation. Episodic agitation and discomfort requires the use of bolus doses from the medication infusion bag, particularly when using agents with slower onset, such as benzodiazepines.

## Daily sedation interruption (DSI)

Daily sedation interruption (DSI) should be performed *in conjunction with spontaneous breathing trials (SBT)* in accordance with Michigan Medicine protocol, with due consideration of exclusions based on the required level of ventilator support.

A DSI is defined as a period of time, each day, during which a patient's sedative medication is discontinued and patients can wake up and achieve arousal and/or alertness, defined by objective actions such as opening eyes in response to a voice, following simple commands, and/or having a Sedation-Agitation Scale (SAS) score of 4–7 or a RASS score of –1 to +1. A DSI may be performed in the absence of an SBT if clinically appropriate, however, this should be coordinated in advance between the provider and the bedside nurse.

## Delirium

1. Patients should be assessed for the presence of delirium per Michigan Medicine protocol (UMHS Prevention, Detection and Management of Delirium Guidelines, 62-01-007) using a validated tool such as the Confusion Assessment Method for the ICU (CAM-ICU).
2. Pharmacological prophylaxis should not be used in patients without objective evidence of delirium.
3. A dexmedetomidine infusion is the preferred agent in critically ill COVID-19 patients with objective evidence of agitated delirium, to decrease the risk of unplanned device removal and optimize respiratory function. The use of a continuous infusion permits more consistent control of agitation and may decrease the frequency of required room entry by the bedside nurse.
4. The use of adjunctive agents such as Quetiapine, Olanzapine and Risperidone is appropriate, however, intermittent electrocardiograms (ECG) may be required to assess the QTc interval.
5. Multi-compartment nonpharmacological interventions are appropriate. These include strategies to reduce or shorten delirium (e.g., reorientation, cognitive stimulation, use of clocks); improve sleep (e.g., minimizing light and noise); improve wakefulness (i.e., reduced sedation); reduce immobility (e.g., early rehabilitation/mobilization); and reduce hearing and/or visual impairment (e.g., enable use of devices such as hearing aids or eye glasses).

## NEUROMUSCULAR BLOCKADE

Neuromuscular blockade (NMB) has been studied as an adjunct to treatment of acute respiratory distress syndrome (ARDS) in multi-center randomized controlled trials.

In the ACURASYS trial (NEJM 2010), inclusion criteria included early, severe ARDS (< 48 hrs of P/F ratio < 150 on PEEP of at least 5, low tidal volume ventilation, and clinical diagnosis of ARDS). Pts were randomized to cisatracurium infusions (37.5 mg/hr for 48 hours) vs. placebo. ARDS Network ARMA protocol was used for mechanical ventilation. There was a significant decrease in 90-day mortality in the cisatracurium group (n =340, HR 0.68, 95% CI 0.48-0.98, p=0.04). Possible mechanisms of clinical benefit include a decrease in patient-ventilator asynchrony, a decrease in inflammation, and a decrease in oxygen consumption.

The more recent ROSE-PETAL trial (NEJM 2019) was modeled after ACURASYS but differed in that it emphasized lighter sedation targets in the control group as well as a higher PEEP/FiO<sub>2</sub> table and conservative fluid management in both groups. Inclusion criteria were similar but specified a P/F ratio < 150 on PEEP of at least 8. Cisatracurium dosing was unchanged. After enrolling 1006 patients, the trial was stopped for futility with 90-day mortality rates of 42.5% and 42.8% in the intervention and control groups.

Based on these trial results, the current Michigan Medicine ARDS algorithm does not recommend routine use of NMB in ARDS but suggests consideration when there is evidence of persistent patient-ventilator asynchrony despite ventilator adjustments and routine sedation.

NMB is often employed simultaneously with prone positioning (> 80% of patients in both arms of the PROSEVA trial, NEJM 2013) as prone positioning has also been linked to decreased mortality in severe ARDS. It is not however necessary that all patients must have NMB in order to undergo proning.

Of note, both large trials of NMB have used a specific agent (cisatracurium) at a high hourly dose. It is unlikely that the benefits of NMB are limited to this agent or dosing scheme.

Train-of-four (TOF) monitoring is routinely used in the operating room to measure depth of, reversibility of, and recovery from NMB. In the ARDS patient in the ICU, the primary goal of neuromuscular blockade is reduction in patient-ventilator asynchrony as opposed to a specific TOF measurement. Selective TOF measurement after NMB has been discontinued can be used to confirm recovery of neuromuscular function and appropriateness of weaning concomitant sedation. During NMB, deep sedation is recommended to minimize the likelihood of patient awareness.

There will be no reliable spontaneous ventilation in a patient receiving NMB in the event of endotracheal tube dislodgement or ventilator malfunction; such situations demand immediate bag-mask ventilation and re-intubation if tube dislodgement and manual bag ventilation via endotracheal tube if ventilator malfunction

## Proposed MM COVID-19 ARDS Protocol for Neuromuscular Blockade (NMB)

- There is no indication for routine use of neuromuscular blockade in ARDS patients regardless of severity
- For patients demonstrating patient-ventilator asynchrony, NMB can be used to maintain oxygenation as well as facilitate lung-protective ventilation and prone positioning
- Goal to limit NMB to 48 hours or fewer
- Deep sedation is required for all patients receiving NMB; this corresponds to a RASS of -4 to -5 in patients prior to receiving NMB; such sedation must be continued during NMB as it is not possible to meaningfully measure RASS after NMB initiation
- If available, first-line neuromuscular blocker is cisatracurium
- The “ICU Neuromuscular Blocking Agents” order set should be used in MiChart which includes loading and infusion doses for cisatracurium, atracurium, and vecuronium
- Given high demand and shortages, consult with ICU pharmacy support regarding alternative agents (i.e. rocuronium, pancuronium) that may be given intermittently
- Q2H TOF monitoring not recommended
- Consider TOF check with cessation of NMB to confirm recovery; this is especially relevant if agents with less predictable pharmacokinetics than cisatracurium are employed
- Alternative ventilator (i.e. self-inflating bag) must be immediately available at all times

## **Strategies to address shortages of sedative, analgesic and neuromuscular blocking agents during the COVID-19 pandemic**

Nationwide shortages of sedative, analgesic and neuromuscular blocking agents have been reported due to a large increase in demand during the COVID-19 pandemic.

1. Consider the use of intermittent dosing of longer-acting agents to minimize the need for agents with limited availability. For example, consider-
  - a. Scheduled high-dose intermittent enteral Lorazepam to minimize the need for propofol or midazolam
  - b. Scheduled enteral Oxycodone to minimize the need for intravenous fentanyl or hydromorphone
  - c. Intermittent doses of IV Rocuronium, Vecuronium or Pancuronium to minimize the need for Cisatracurium.
2. Clinical pharmacists will provide notification to clinical teams of all known and anticipated shortages of these agents. Frequent communication between providers and the clinical pharmacist is essential.
3. When an agent is identified by the clinical pharmacist as being in shortage, an alternative agent should be preferentially used on the unit. For example, Hydromorphone should be used as the preferred agent on the unit when Fentanyl is in shortage.

## REFERENCES

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