Sedation of Mechanically Ventilated COVID-19 Patients: Challenges and Special Considerations

To the Editor

Management of patient sedation and analgesia to alleviate anxiety and pain and facilitate mechanical ventilation is one of the key roles of every intensivist. During the Coronavirus Disease 2019 (COVID-19) pandemic, unprecedented numbers of patients require sedation in intensive care units (ICUs) and other hospital locations due to their ventilator dependence. However, pharmacologic sedation in mechanically ventilated patients with COVID-19 has thus far received very little attention in the critical care literature, with minimal mention in the Society of Critical Care Medicine's COVID-19 guidelines or clinical reviews.[1,2] We propose that sedation of mechanically ventilated patients with COVID-19 poses unique challenges and has multiple important implications that we would like to briefly outline:

Unusually high sedation requirements in a large proportion of COVID-19 patients are observed in current clinical experience. These high sedation requirements are likely related to younger age and good health of many patients before the onset of COVID-19, high respiratory drive, and intense inflammatory responses previously linked to tolerance.[3] This translates into the need to administer combinations of multiple agents (eg, propofol, ketamine, hydromorphone, dexmedetomidine, and midazolam), increasing potential risks of side effects (eg, QT interval prolongation, hypertriglyceridemia, hypotension, and delirium) and requiring vigilance of the ICU staff. When these are administered in combinations, the typical requirements to ensure patient comfort and ventilator synchrony in adult patients range between 25 and 50 μg/kg/min for propofol, 10 and 20 μg/kg/min for ketamine, 2 and 4 mg/h for hydromorphone, and 2 and 5 mg/h for midazolam. There are currently no sedation guidelines specific for this patient population requiring high doses and prolonged drug administrations.

Deeper sedation levels may be required to facilitate ventilator synchrony in patients with severe acute respiratory distress syndrome (ARDS) and may also be favored by ICU staff to reduce risk of patient self-extubation, which is particularly problematic in this population given the need for emergent reintubation and risk of exposure to coronavirus. Subsequent tolerance to sedatives (eg, dexmedetomidine) from their use early in the course of illness and high doses will also limit the effectiveness of these drugs during ventilator weaning.

Intermittent administration of certain drugs (eg, narcotics) tailored to individual needs of each patient may not always be feasible in situations of overwhelmed health care systems (eg, when one nurse is required to attend to multiple critically ill patients). In these situations, continuous infusions of sedative drugs are favored for their practicality, but this practice further increases the risks of side effects.

A subset of patients with severe ARDS is likely to require prolonged sedation (often >2 weeks)[4] to facilitate lung-protective mechanical ventilation or extracorporeal membrane oxygenation (ECMO) therapy and subsequent weaning. These prolonged periods of time may lead to drug accumulation (midazolam), tolerance and tachyphylaxis (dexmedetomidine), hypertriglyceridemia (propofol), QT interval prolongation (haloperidol), psychomimetic effects (ketamine), hyperalgesia or opioid dependence (fentanyl and/or hydromorphone), and delirium (midazolam).

Increased precision in monitoring the depth of sedation (eg, processed electroencephalogram [EEG]) is required in patients with high sedation requirements who also require neuromuscular blockade to improve respiratory system compliance. While these neuromonitoring technologies exist,[5] they may not be widely available given the number of patients who would benefit. Patient awareness under these conditions (eg, paralysis or prone position) may result in significant psychological trauma.

Prolonged infusions of opioids that are often required to facilitate strict lung-protective ventilation are known to result in gut hypomotility, leading to intolerance to feeding, interruptions in feeding, and malnutrition during prolonged ICU stay. These gastrointestinal side effects of opioids may also result in abdominal distension, which can impair ventilation and/or contribute to nausea/vomiting, increasing the risk of aspiration.

High doses of opioids, sometimes required to facilitate lung-protective ventilation in patients with ventilator dyssynchrony, may paradoxically complicate ventilation management by inducing breathing patterns with large tidal volumes that may further injure lungs.

Prolonged infusions of high doses of sedatives and analgesics in large numbers of patients have already resulted in drug shortages at hospital, regional, and state levels. In these situations, providing sedation with less commonly used agents (barbiturates, methadone, clonidine, chlorpromazine, and propranolol)

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may need to be considered. The use of inhalational anesthetics (eg, isoflurane), at least in locations with appropriately designed scavenging systems, such as operating rooms converted to ICUs, may be a rational alternative that is also supported by anti-inflammatory and lung-protective effects of inhalational anesthetics.[6]

Attention must be paid to the potential interaction between sedative drugs and other agents administered as part of clinical trials (there are >300 clinical COVID-19 trials currently ongoing worldwide). For instance, significant QT prolongations may result from combinations of hydroxychloroquine and haloperidol. Administration of barbiturates may increase metabolism of hydroxychloroquine. In patients with high fevers, dexmedetomidine may need to be discontinued to help delineate the cause of the fever.

In summary, management of sedation in ICU patients with COVID-19 needs to reflect individual properties and side effect profiles of agents, unique patient characteristics (prolonged intubation and virus shedding), and health care system limitations (large numbers of patients, ICU patients in emergency rooms and operating rooms, and drug shortages). Potential for interactions with investigational drugs used in clinical trials (some blinded to ICU staff) needs to be considered. The collective clinical experience from the United States and from other highly affected areas around the world should be quickly leveraged to formulate recommendations and guidelines to increase patient safety and provider awareness of these unique challenges.

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