The Use of Analgesia and Sedation in Mechanically Ventilated Patients With COVID-19 Acute Respiratory Distress Syndrome

To the Editor

We read with great interest in the article by Hanidziar and Bittner. We have observed high sedation requirements in our coronavirus disease 2019 (COVID-19) patient population and sought to quantify the administered doses to characterize sedation needs in these patients with critical illness. We compared the quantity of sedation used in this population to the quantity of sedation described in a prior study of patients with acute respiratory distress syndrome (ARDS).

METHODS

We included the first 24 adult patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) admitted to the Johns Hopkins Hospital (JHH) Medical Intensive Care Unit (MICU) between March 15 and March 28, 2020. Nineteen patients required mechanical ventilation. All sedation management decisions were made by ICU physicians, and dosing titrated by staff using the Richmond Agitation and Sedation Scale (RASS). Practice guidelines for mechanically ventilated patients at the JHH MICU include the use of analgesia first with intermittent boluses of sedatives followed by continuous drips as warranted. Doses of analgesic and sedative medications were collected from the medical record, summed into daily totals for each patient, and converted into oral morphine and midazolam equivalents via established conversions.

RESULTS

Baseline Characteristics

The study sample included 24 patients, 19 of which were intubated, and included 15 men (63%), with a median age of 56 years (range: 31–80 years). Before ICU admission, 1 patient had preexisting liver disease and another had end-stage renal disease. Before being hospitalized, 2 patients had opiate use and 1 patient had benzodiazepine use.
**Letters to the Editor**

### Analgesia/Sedation

The Figure depicts daily dosages of opiates and benzodiazepines administered to mechanically ventilated patients. Day 1 dosages were significantly lower, likely related to the variability in hours during the first day of mechanical ventilation. All 19 patients required continuous intravenous opioid and midazolam infusions. From day 2 to 7, when most patients remained intubated, the median daily dose of oral morphine equivalents was 775 mg (interquartile range [IQR], 648.4–899.7 mg) and for oral midazolam equivalents was 270.9 mg (IQR, 201.3–304.4 mg).

Of the patients who underwent neuromuscular blockade, the median daily dose of opiates (in oral morphine equivalents) and benzodiazepines (in oral midazolam equivalents) was 937.2 mg (IQR, 667.7–1683 mg) and 224.7 mg (IQR, 56.56–610 mg), respectively. For patients who did not receive neuromuscular blockade, the median daily dosage of opiates (in oral morphine equivalents) and benzodiazepines (in oral midazolam equivalents) was 623.8 mg (IQR, 176.3–726.9 mg) and 135 mg (IQR, 40.63–203.8 mg), respectively.

Propofol (16 of 19 patients, 84%), dexmedetomidine (10 of 19, 53%), and ketamine (2 of 19, 11%) were also used at the discretion of the ICU providers. The highest use of propofol was administered at time of intubation and occurred on day 1 of mechanical ventilation. Dexmedetomidine was used as an adjunctive sedative. Fourteen patients (74%) received antipsychotics, typically to facilitate extubation.

**Therapies and Outcomes**

Of the 19 patients requiring mechanical ventilation, 13 (68%) underwent prone positioning and 10 (53%) received neuromuscular blockade. Five patients died during their ICU stay (21%). Duration of endotracheal intubation was a median of 11 days, with a range of 3–37 days. Three patients received a tracheostomy.

**Discussion**

High analgesic and sedative medication requirements were observed in a cohort of patients with COVID-19–related ARDS, with doses exceeding those previously documented in the literature for patients with ARDS. Notably, the opioid doses in our cohort were more than 3 times higher, and our midazolam doses were also higher than historical cohorts. Participants in the OSCILLATE trial had median fentanyl doses of 2980 µg (IQR, 1258–4800 µg) which converted to a median of 289 mg (IQR, 125.8–480 mg) oral morphine equivalents. Participants in OSCILLATE had median midazolam doses of 199 mg (IQR, 100–382). While not perfectly matched, the cohorts had a similar length of intubation and similar P:F ratios at the time of intubation. The average APACHE II score was lower in our cohort—19.6 vs 29.

There are a number of factors that likely contributed to higher doses of analgesic and sedative medications in this setting. First, the majority of patients required neuromuscular blockade which is accompanied by deep sedation targets, frequently requiring high doses of analgesia and sedation. Second, most patients in this cohort and broadly speaking with COVID-19 have high fevers, increasing ventilatory drive and possibly leading to more ventilator dyssynchrony, necessitating additional sedation. Interestingly, patients received disproportionately higher amounts of opiates than benzodiazepines, likely to reduce respiratory drive. Third, challenges to entering patient rooms frequently in the setting of personal protective equipment requirements may have resulted in reduced downward titrations of continuous infusions. Fourth, concerns over patient harm (ie, self-extubation)
may have led to higher medication doses. Finally, our cohort had a median age of 56 years and minimal liver or kidney dysfunction, potentially promoting faster metabolism of medications compared to cohorts of older patients with multiorgan dysfunction, though the OSCILLATE cohort had a mean age of 54–55. While large dosages of analgesic and sedative medications are typically associated with longer duration of mechanical ventilation, the experience in this cohort showed a median duration of 11 days of mechanical ventilation, which is similar to other trials of ARDS.

Although this report represents a limited sample size at a single center, it provides initial insight into analgesia and sedative use among mechanically ventilated patients with COVID-19. The current pandemic has proven to be a unique challenge to continue established sedation protocols and practices aimed to reduce analgesia and sedative medications. The impact of large doses of sedation in patients with COVID-19 remains to be seen. A previous study has described an increased incidence of delirium with high levels of sedation, as well as long-term cognitive impairment. While further study focused on the physical and cognitive impact is needed, focus on methods to safely minimize analgesia and sedative dosages is also warranted.

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In Response

The challenges related to sedation of mechanically ventilated patients with coronavirus disease 2019 (COVID-19) that we outlined during the early pandemic have since been studied by Kapp et al. In a single-center cohort study, the authors found that the median daily dose of opioids administered in their mechanically ventilated COVID-19 patients (n = 19) was 3 times greater than the cohort of patients with acute respiratory distress syndrome (ARDS) that received high-frequency oscillatory ventilation (n = 275) in the 2013 Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) trial. Interestingly, patients receiving neuromuscular blocking agents (n = 10) in the study by Kapp et al were administered higher doses of opioids when compared to patients (n = 9) who were not paralyzed. Despite its limitations (small single-center study, comparison with a historic ARDS trial cohort), this retrospective study supports the findings of increased sedation requirements in mechanically ventilated patients with COVID-19 compared to non-COVID critically ill patients. Furthermore, the study highlights several important barriers to improving sedation practices in critically ill patients receiving mechanical ventilation including those with COVID-19:

1. There has been wide variation in reporting of the types and quantities of sedatives administered to patients enrolled in major ARDS clinical trials (Table). These inconsistencies in reporting sedation may hamper ARDS research given that there are well-known associations between depth of sedation, sedative side effects and key outcomes, including length of mechanical ventilation and mortality. It seems reasonable to propose that detailed data on sedation administration and sedation depth should be considered when effects of ARDS interventions (eg, ventilator management, antiviral and immunomodulatory therapies) are evaluated in multicenter clinical trials, or when outcomes are reported in smaller cohort studies.

2. Although prioritizing pain control before adding sedatives in mechanically ventilated patients is recommended by Society of Critical Care Medicine guidelines, liberal use of intravenous opioids in conditions that are not associated with significant pain (eg, COVID-19 pneumonia, influenza...