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BRIEF REPORT

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Standard Sedation and Sedation With Isoflurane in Mechanically Ventilated Patients With Coronavirus Disease 2019

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OBJECTIVES: To describe sedative and analgesic drug utilization in a cohort of critically ill patients with coronavirus disease 2019 and compare standard sedation with an alternative approach using inhaled isoflurane.

DESIGN: This was a retrospective cohort study designed to compare doses of sedatives between ICU patients receiving standard IV sedation and patients receiving mixed sedation including inhaled isoflurane. Data were obtained from electronic medical records.

SETTING: ICU at large academic medical center where mechanical ventilation was delivered with Draeger Apollo (Draeger Medical, Telford, PA) anesthesia machines.

PATIENTS: Consecutive adult patients (≥ 18 yr) with confirmed coronavirus disease 2019 admitted to ICU between April 2, 2020, and May 4, 2020.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Thirty-five mechanically ventilated patients were included in the study, with a mean (SD) age of 59.4 (12.8) years. Twenty-three patients (65.7%) were men. Seventeen patients (48.6%) received standard IV sedation, whereas 18 (51.4%) also received isoflurane. The mean duration of mechanical ventilation (SD) was 23.3 (11.6) days in the standard sedation group and 23.8 (12.5) days in the isoflurane group. Mean (SD) duration of isoflurane exposure was 5.61 (2.99) days, representing 29.1% of total sedation time (SD, 20.4). Cumulative opioid exposure did not differ between the standard sedation and isoflurane sedation groups (mean morphine milligram equivalent 6668 [SD, 1,346] vs 6678 [SD, 2,000] mg). However, the initiation of isoflurane in patients was associated with decreased utilization of propofol (mean daily amount 3,656 [SD, 1,635] before vs 950 [SD, 1,804] mg during isoflurane) and hydromorphone (mean daily amount 48 [SD, 30] before vs 23 [SD, 27] mg).

CONCLUSIONS: In the subjects that received isoflurane, its use was associated with significant decreases in propofol and hydromorphone infusions.

KEY WORDS: acute respiratory distress syndrome; coronavirus disease 2019; isoflurane; sedation

Patients with coronavirus disease 2019 (COVID-19)–induced acute respiratory distress syndrome (ARDS) commonly received prolonged invasive mechanical ventilation (1). Deeper levels of

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sedation may be required to facilitate lung-protective ventilation, reduce patient-ventilator dyssynchrony, ensure patients safety in prone position, prevent self-extubations, and ensure amnesia during neuromuscular blockade (2). Continuous infusions of propofol, dexmedetomidine, midazolam, hydromorphone, fentanyl, and ketamine have been administered to patients oftentimes in combinations to achieve these sedation goals (3).

The addition of inhalational anesthetics (e.g., sevoflurane, isoflurane) to sedation regimens has been proposed as a strategy to conserve IV sedative agents in the setting of drug shortages and to limit exposure of patients to propofol, benzodiazepines, and opioids in order to reduce wide array of side effects of these drugs including immunosuppression, delirium, ileus, tolerance, and hyperalgesia (4). Flinspach et al (5) recently documented feasibility of isoflurane sedation in five patients with COVID-19 ARDS. Inhalational halogenated anesthetics are liquids at room temperature and require the use of anesthetic vaporizers. These anesthetics have favorable pharmacokinetics of fast onset and offset, low levels of hepatic metabolism, and limited systemic accumulation, allowing fast emergence from anesthesia and sedation. Furthermore, these anesthetics also have bronchodilatory and possibly lung-protective and anti-inflammatory effects further supporting their use in patients with COVID-19 (4, 6). Clinical experiences from Europe and Canada using these agents for ICU sedation and experiences in the United States with patients treated for refractory status asthmaticus and status epilepticus suggest that prolonged administration of these agents is safe (6–10).

Despite high numbers of ventilated patients with COVID-19 worldwide, there is a paucity of analyses of sedation practices in this population. During the surge of critically ill COVID-19 patients in Massachusetts in 2020, we used anesthesia machines to ventilate patients in one of the ICUs due to the shortage of ICU ventilators. Anesthesia machines also allowed us to deliver isoflurane to a cohort of patients with COVID-19. We hypothesized that addition of inhalational anesthesia to sedation regimen could result in reduced doses of IV sedatives. In the present study, we quantified sedative drug utilization and compared standard sedation with an alternative approach using inhaled isoflurane.

METHODS

Study Population

We retrospectively analyzed a cohort of 35 mechanically ventilated adult patients (age ≥ 18 yr) with polymerase chain reaction confirmed COVID-19 who were admitted to an ICU at Massachusetts General Hospital in Boston, MA, between April 2, 2020, and May 4, 2020. All patients met criteria for ARDS. The final date of the follow-up was July 6, 2020, when all the studied patients were discharged from the hospital. This study was approved by the Partners Healthcare System Institutional Review Board as Protocol number 2020P001048. The Institutional Review Board waived the need for informed consent.

Ventilation With Anesthesia Machines

Mechanical ventilation was delivered with Draeger Apollo (Draeger Medical, Telford, PA) anesthesia machines which were used to expand hospital's capacity to provide ventilatory support during the surge of critically ill COVID-19 patients. Anesthesiology residents supervised by anesthesia-trained intensivists had the direct responsibility for ventilator management. The responsibilities included the following:

- Performance of machine check every 72 hours with one anesthesia clinician dedicated to machine check and one clinician dedicated to ventilation of patient with manual resuscitator and close hemodynamic monitoring.
- Heat and moisture exchanger/high-efficiency particulate air filter filter and breathing circuit exchange every 24 hours or more often in case of excessive accumulation of condensation (e.g., when leading to increased peak airway pressures).
- Inspection of CO_2 absorbers, water traps every 12 hours, and exchange when necessary.
- Adjusting ventilator settings (fresh gas flows, positive end-expiratory pressure, ventilator mode).
- Immediately responding to patient-specific ventilator alarms.

Sedation With Isoflurane

The use of anesthesia machines allowed clinicians to deliver isoflurane for sedation. History of malignant hyperthermia was investigated before isoflurane initiation. The initiation, dosing, and discontinuation of isoflurane were at discretion of attending ICU physicians. The initiation of isoflurane was gradual in 0.2% increments to prevent hemodynamic instability. The use of isoflurane was consistent with "American Society of

Anesthesiologists/Anesthesia Patient Safety Foundation Guidance for Use of Volatile Anesthetic for Sedation of ICU Patients. Emergency Use for the COVID-19 Pandemic." For isoflurane scavenging, the standard active-open scavenger system of Draeger (Draeger Medical) anesthesia machines was used, and machines were connected to the hospital vacuum suction system. Inspired and expired concentrations of isoflurane were recorded by ICU nurses when changes were made.

Standard Sedation With IV and Oral Agents

Institutional recommendations for sedation of COVID-19 ARDS patients were consistent with Society of Critical Care Medicine guidelines. Institutional protocol encouraged to target lighter depth of sedation (RASS –2 to +1) if this level of sedation was tolerated by patients and did not result in respiratory decompensation (e.g., cough, dyssynchrony). In the instances

TABLE 1.
Characteristics of Patients and Main Results

Characteristics	Standard Sedation (*n* = 17)	Isoflurane Sedation (*n* = 18)	*p*
Baseline characteristics			
Age, mean (SD), yr	64 (13.6)	55 (10.4)	0.034
Sex, *n* (%)			
Men	12 (71)	11 (61)	0.725
Women	5 (29)	7 (39)	
BMI			
Mean (SD)	32.7 (5.6)	31.6 (7.3)	0.622
BMI < 30, *n* (%)	7 (41)	8 (44)	> 0.999
BMI ≥ 30, *n* (%)	10 (59)	10 (56)	
Hypertension, *n* (%)	9 (53)	9 (50)	> 0.999
Diabetes, *n* (%)	8 (47)	8 (44)	> 0.999
Congestive heart failure, *n* (%)	3 (18)	0 (0)	0.104
Chronic obstructive pulmonary disease, *n* (%)	1 (6)	1 (6)	> 0.999
Asthma, *n* (%)	4 (24)	1 (6)	0.177
Smoking status, *n* (%)			
Active	2 (12)	0 (0)	0.301
Former	3 (18)	6 (33)	
Never	8 (47)	6 (33)	
Unknown	4 (24)	6 (33)	
ICU outcomes			
Duration of ventilation, mean (SD), d	23.3 (11.6)	23.8 (12.5)	0.903
In-hospital mortality, *n* (%)	5 (29.4)	3 (16.7)	0.443

(*Continued*)

TABLE 1. (*Continued*).
Characteristics of Patients and Main Results

Characteristics	Standard Sedation (*n* = 17)	Isoflurane Sedation (*n* = 18)	*p*
Cumulative sedation exposure, mean (SD)			
Isoflurane sedation			
Duration, d	0	5.61 (2.99)	< 0.001
Day of isoflurane start	NA	14 (5.3)	
Percent of total sedation time	0	29.1 (20.4)	< 0.001
Minimum inspired concentration, %	NA	0.27 (0.09)	
Maximum inspired concentration,%	NA	0.84 (0.29)	
Propofol, mg	52,151 (34,424)	56,520 (40,018)	0.730
Dexmedetomidine, µg	10,797 (20,224)	21,027 (24,179)	0.183
Ketamine, mg	7,846 (14,672)	8,010 (14,334)	0.973
Midazolam, mg	795 (1,372)	285 (439)	0.160
Morphine equivalents, mg	6,668 (1,346)	6,678 (2,000)	0.986
Adjunct antipsychotic use			
Quetiapine, mg	45.58 (53.94)	38.19 (40.96)	0.645
Haloperidol, mg	0.43 (1.04)	0.42 (0.69)	0.902

BMI = body mass index, NA = not applicable.

when patients received paralysis, deep levels of sedation were targeted (RASS –4 to –5). Sedation management of each patient was formally evaluated twice a day during intensivist-led rounds. The multistep approach to sedation prioritizes analgesia, and hypnotics are added as needed. IV infusions of propofol, midazolam, ketamine, dexmedetomidine, hydromorphone, and fentanyl were used in the patient cohort. Oral agents included oxycodone, methadone, quetiapine, and haloperidol. The use of oral agents was encouraged by institutional protocol to wean IV sedatives and prevent withdrawal.

Statistical Analysis

The primary outcome was the cumulative dose of IV sedative agents (propofol, dexmedetomidine, ketamine, midazolam, hydromorphone) in standard sedation and isoflurane cohort. In the isoflurane cohort, the doses of sedation before, during, and after initiation of isoflurane were compared. The secondary outcomes were duration of mechanical ventilation and in-hospital mortality rates. Data were collected from the electronic medical records, and the use of all sedatives and opioids was quantified. The exact inspired concentrations of isoflurane were available from 16 of 18 patients that received isoflurane. Descriptive statistics were used to summarize demographics and clinical data. *p* values were calculated using chi-square test or Fisher exact test in categorical variables and Student *t* test or repeated measure analysis of variance test in continuous variables.

RESULTS

Thirty-five mechanically ventilated patients were included in the study, with a mean (SD) age of 59.4 (12.8) years. Twenty-three patients (65.7%) were men. Seventeen patients (48.6%) received standard IV sedation, whereas 18 (51.4%) also received isoflurane

TABLE 2.
Sedation Doses in Relation to Administration of Isoflurane

Sedation Doses	Before Isoflurane	During Isoflurane	After Isoflurane	*p*
Duration, mean (SD), d	13 (5.1)	5 (2.6)	8 (16.1)	0.066
Continuous infusion				
Propofol, mean (SD), mg				
Cumulative	47,562 (32,930)	38,797 (5,080)	51,178 (13,476)	< 0.001
Daily	3,656 (1,635)	950 (1,804)	591 (861)	< 0.001
Daily/kg	42.04 (16.78)	9.62 (14.10)	7.11 (11.31)	< 0.001
Patients receiving infusion	18	13	6	< 0.001
Midazolam, mean (SD), mg				
Cumulative	211 (423)	3 (11)	72 (210)	0.119
Daily	13 (24)	1 (6)	3 (11)	0.105
Daily/Kg	0.14 (0.23)	0.01 (0.04)	0.76 (2.38)	0.241
Patients receiving infusion	8	1	1	0.004
Dexmedetomidine, mean (SD), µg				
Cumulative	7,466 (8,145)	4,641 (5,553)	8,920 (21,078)	0.519
Daily	583 (609)	1,079 (1,331)	979 (814)	0.183
Daily/Kg	6.90 (7.58)	12.04 (12.11)	11.93 (10.73)	0.121
Patients receiving infusion	15	15	14	> 0.999
Ketamine, mean (SD), mg				
Cumulative	5,420 (9,164)	818 (1,920)	1,771 (5,851)	0.044
Daily	389 (648)	250 (800)	50 (140)	0.105
Daily/Kg	3.90 (6.38)	1.99 (5.92)	0.52 (1.55)	0.070
Patients receiving infusion	9	3	2	0.022
Hydromorphone, mean (SD), mg				
Cumulative	685 (507)	126 (143)	55 (130)	< 0.001
Daily	48 (30)	23 (27)	4 (6)	< 0.001
Daily/Kg	0.57 (0.38)	0.23 (0.23)	0.05 (0.07)	< 0.001
Patients receiving infusion	17	13	18	0.038
Fentanyl, mean (SD), µg				
Cumulative	1,102 (3,308)	0 (0)	0 (0)	0.175
Daily	103 (286)	0 (0)	0 (0)	0.143
Daily/Kg	1.14 (2.78)	0 (0)	0 (0)	0.135
Patients receiving infusion	2	0	0	< 0.001

(*Continued*)

TABLE 2. (*Continued*).
Sedation Doses in Relation to Administration of Isoflurane

Sedation Doses	Before Isoflurane	During Isoflurane	After Isoflurane	*p*
IV bolus, mean (SD)				
Propofol, mg	132 (254)	35 (49)	77 (206)	0.180
Hydromorphone, mg	20 (21)	5 (11)	2 (5)	0.036
Fentanyl, µg	3 (12)	0	0	0.332
Oral agents, mean (SD)				
Methadone, mg	25 (37)	53 (65)	37 (100)	0.433
Oxycodone, mg	4 (11)	69 (147)	90 (202)	0.091
Lorazepam, mg	2 (10)	2 (8)	3 (6)	0.870

in addition to IV drugs, with inspired concentrations titrated at the discretion of treating physicians. Patients in whom isoflurane was added to the sedation regimen were significantly younger with mean age of 55 (SD, 10.4) versus 64 (SD, 13.6) years (p = 0.034). Mean (SD) duration of isoflurane exposure was 5.61 (2.99) days, which represented 29.1% of total sedation time (SD, 20.4). The mean duration of mechanical ventilation (SD) was 23.3 (11.6) days in the standard sedation group and 23.8 (12.5) days in the isoflurane group (**Table 1**).

When comparing cumulative opioid exposure (IV hydromorphone, IV fentanyl, oral oxycodone, and oral methadone), we found no significant difference between the standard sedation and isoflurane sedation groups (mean morphine milligram equivalent 6,668 [SD, 1,346] vs 6,678 [SD, 2,000] mg). However, the initiation of isoflurane in patients was associated with decreased utilization of propofol (mean daily amount 3,656 [SD, 1635] before isoflurane vs 950 [SD, 1,804] mg during isoflurane) and hydromorphone (mean daily amount 48 [SD, 30] before isoflurane vs 23 [SD, 27] mg during isoflurane). Furthermore, numbers of patients receiving propofol, midazolam, and fentanyl infusions for at least 12 hours were significantly reduced during the period when isoflurane was administered (**Table 2**).

DISCUSSION

We compared sedative drug utilization between mechanically ventilated patients with COVID-19 who received standard IV sedation and those who also received isoflurane. No significant differences were found in cumulative doses of opioids and IV sedatives. The pattern of isoflurane utilization may explain these statistical findings. Isoflurane was initiated, titrated, and discontinued at a discretion of ICU physicians, resulting in mean duration of isoflurane administration of only 29.1% of total sedation time. Isoflurane was also started at relatively late time points of mechanical ventilation (day 14 on average) when some patients were already undergoing sedation and ventilator weaning (e.g., receiving pressure support ventilation). We suspect that protocolized isoflurane sedation and its use for more substantial periods would result in decreases in cumulative sedation doses.

Upon review of medical records, we found that in six patients, isoflurane was used as a primary sedative/anesthetic during neuromuscular blockade. In 12 patients, it was used as an "adjunct" to multiple IV agents, with the goal to improve ventilator tolerance and avoid further escalation of IV agents, or to allow discontinuation of some agents (e.g., propofol due to hypertriglyceridemia). Our analysis demonstrates that the initiation of isoflurane was in fact associated with decreases in propofol and hydromorphone infusions and also significantly reduced the number of patients receiving certain infusions (propofol, midazolam, fentanyl). That propofol and hydromorphone infusions continued to decrease after cessation of isoflurane is most likely the result of active sedation weaning. Institutional recommendations for weaning analgesia

and sedation encouraged the use of oral opioids (oxycodone, methadone) in patients transitioning to or on pressure support ventilation and to prevent opioid withdrawal.

We found no specific patient characteristics associated with the use of isoflurane other than patient age. Patients treated with isoflurane were younger, but the impact of age on the choice of sedatives remains to be investigated in future studies.

We are unable to draw conclusions about the effects of isoflurane on respiratory mechanics or gas exchange given small numbers of patients and various modes of ventilation when isoflurane was administered (e.g., pressure support, volume controlled with paralysis, volume controlled without paralysis). Future studies are warranted to assess the physiologic effects on these respiratory variables.

Safety of long-term use also needs to be studied further, although the organ toxicity of volatile anesthetics is rare and has been associated with earlier anesthetics that are now rarely being used, such as hepatotoxicity with halothane and nephrotoxicity with methoxyflurane and enflurane. In our cohort, there were no cases of malignant hyperthermia or other complications that could be attributed to isoflurane.

Finally, we show that the use of isoflurane delivered via anesthesia machines in a surge COVID-19 ICU was feasible but required continuous presence and vigilance of anesthesia-trained personnel.

CONCLUSIONS

The initiation of isoflurane in critically ill patients with COVID-19 was associated with significant decreases in propofol and hydromorphone infusions.

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