Usefulness of Inhaled Sedation in Patients With Severe ARDS Due to COVID-19

Mario Gómez Duque, Ronald Medina, Cesar Enciso, Edgar Beltran, Kevin Hernandez, Daniel Molano Franco, and Joan R Masclans

BACKGROUND: Sedation in intensive care is fundamental for optimizing clinical outcomes. For many years the world has been facing high rates of opioid use, and to combat the increasing opioid addiction plans at both national and international level have been implemented.[1] The COVID-19 pandemic posed a major challenge for health systems and also increased the use of sedatives and opioid analgesia for prolonged periods of time, and at high doses, in a significant proportion of patients. In our institutions, the shortage of many drugs for intravenous (IV) analgosedation forces us to alternatives to replace out-of-stock drugs or to seek sedation goals, which are difficult to obtain with traditional drugs at high doses.[2] METHODS: This was an analytical retrospective cohort study evaluating the follow-up of subjects with inclusion criteria from ICU admission to discharge (alive or dead). Five end points were measured: need for high-dose opioids (≥ 200 μg/h), comparison of inhaled versus IV sedation of opioid analgesic doses, midazolam dose, need for muscle relaxant, and risk of delirium. RESULTS: A total of 283 subjects were included in the study, of whom 230 were administered IV sedation and 53 inhaled sedation. In the inhaled sedation group, the relative risks (RRs) were 0.5 (95% CI 0.4–0.8, $P = .045$) for need of high-dose fentanyl, 0.3 (95% CI 0.20–0.45, $P < .001$) for need of muscle relaxant, and 0.8 (95% CI 0.61–1.15, $P = .25$) for risk of delirium. The median difference of fentanyl dose between the inhaled sedation and IV sedation groups was 61 μg/h or 1,200 μg/d (2.2 ampules/d, $P < .001$), and that of midazolam dose was 5.7 mg/h. CONCLUSIONS: Inhaled sedation was associated with lower doses of opioids, benzodiazepines, and muscle relaxants compared to IV sedation. This therapy should be considered as an alternative in critically ill patients requiring prolonged ventilatory support and where IV sedation is not possible, always under adequate supervision of ICU staff. *Key words: analgesia; sedation; SARS-CoV-2; COVID-19; ARDS; inhaled anesthetics; intravenous sedation; opioids; benzodiazepines; neuromuscular blockade.*
[Respir Care 2023;68(3):293–299.

Introduction

Since March 11, 2020, the world has faced a new pandemic that has not only claimed a large number of lives but has placed an enormous strain on health care systems. SARS-CoV-2 infection has become one of the most important challenges to public health in the last 100 years, since the infectious process it generates in large swaths of the population due to its high contagious capacity brought health systems to a standstill in just a few months and caused a functional emergency.[3-6]

Due to the severity of the presentation of COVID-19, alternative respiratory care strategies were required such as the prolonged use of the prone position, sedatives, opioids, and muscle relaxation, lasting for up to several weeks.[7-13]

Sedation is one of the most frequently used measures in critical care patients undergoing mechanical ventilation. It aims to improve comfort, reduce anxiety and agitation, and help patient-ventilator synchrony.[14] Benzodiazepines (especially midazolam) are among the drugs administered.[15,16] In general, sedation seeks to achieve moderate hypnosis; during the pandemic, however, perhaps due to the severity of these patients, strategies seeking deep and prolonged sedation were used.

The inappropriate use of opioids in COVID[17-20] entails a number of potential risks, especially adverse effects such as diarrhea, hyperalgesia, excitability, tolerance processes, delirium, and dependence. The prolonged use of opioids could be associated with immune system impairment.[21] Additionally, opioid users represent a population at high

risk of developing critical illnesses, especially the post-ICU group, in whom subsequent deprivation is associated with complications that can negatively affect prognosis, such as myocardial infarction, stroke, and infection.[21]

SEE THE RELATED EDITORIAL ON PAGE 437

Neuromuscular blockade is a pharmacologic measure used in patients with severe ARDS.[22] The aim is to improve endurance in the muscles of the rib cage and to abolish intractable effort and work of breathing.[23,24] However, prolonged use of these drugs in critically ill patients has been associated with severe complications such as myopathy,[25] prolonged hospital stay, increased mechanical release time, and muscle atrophy.[26]

In this scenario, inhaled anesthetics are drugs with a long history of use around the world. Although little is known about their mechanism of action and their pharmacologic properties, the use of molecular methods and pharmacologic profiles has shed some light on their characteristics and has expanded their use outside the anesthesia rooms into intensive care.[27-29] These drugs have become a useful tool for providing sedation and analgesia to critically ill patients. The shortage of conventional drugs during the pandemic, and the complexity of pulmonary involvement in some patients, led us to use this alternative at our hospital and to share our experience with the scientific community.

QUICK LOOK

Current knowledge

New sedation strategies have been published in recent years aiming to reduce delirium and decrease the use of benzodiazepines and opioids. Volatile anesthetics are a suitable and promising alternative to standard intravenous (IV) sedation. During the COVID-19 pandemic, these alternatives were frequently used due to the global shortage of commonly used drugs and the difficulty in achieving sedation goals in this patient population.

What this paper contributes to our knowledge?

These data suggest that in situations where the use of IV sedation is not possible alternatives such as inhaled sedation could be considered. In critically ill patients with ARDS, inhaled sedation was associated with less use of opioids, neuromuscular blockade, and benzodiazepines.

Methods

Design

A retrospective cohort study was conducted including subjects > 18 y of age admitted from July 1, 2020–December 1, 2021, to the ICU of the University Hospital of San José with a diagnosis of ARDS triggered by confirmed COVID-19 and requiring mechanical ventilation under sedation and analgesia.

Convenience sampling was performed. Subjects who met the inclusion criteria were followed from admission to discharge. The data collected were sociodemographic data, comorbidities, chronic treatments, symptoms of disease presentation, vital signs, which sedative and sedative dose, type of sedation (inhaled or intravenous [IV]), type of opioid analgesic used in infusion (only fentanyl was used in infusion), need for analgesia, dose of opioid analgesic, requirement of high or low dose (high dose $\geq$ 200 μg/h and low dose < 200 μg/h) based on the requirement of fentanyl infusion > 200 μg/h since admission and intubation to the ICU or during the stay for a period > 6 h, and need for neuromuscular blockade and type of agent for infusion (only used in non-depolarizing neuromuscular blockade infusion with cisatracurium). Finally, prognostic variables were included, such as days of mechanical ventilation; and presence or absence of delirium based on Confusion Assessment Method for the ICU (CAM-ICU) score was determined by examining the subject for (1) acute or fluctuating changes in mental status, (2) inattention, (3) altered level of consciousness, and (4) disorganized thinking. Subjects were considered delirious if they displayed acute or fluctuating changes in mental status and inattention, plus altered level of consciousness, and/or disorganized thinking on the CAM-ICU, and the result was a positive or negative dichotomous variable for delirium. Finally overall mortality was collected daily from the electronic medical record by the group of COVID-19 researchers from the CIMCA research group during follow-up.

Pressure controlled ventilation was used, and ventilator settings were set at target values of tidal volume 6–8 mL/kg body weight. Inspiratory peak pressures > 30 cm H_2O

Drs Gómez Duque, Hernandez, and Beltran and Messrs Medina and Enciso are affiliated with Service of Intensive Care Medicine, Hospital de San José, Fundación Universitaria de Ciencias de la Salud, Research Group CIMCA, Bogota, Colombia. Mr Franco is affiliated with Service of Intensive Care Medicine, Hospital de San José, Los Cobos Medical Center, Research Group GRIBOS, Bogotá, Colombia. Dr Masclans is affiliated with Service of Intensive Care Medicine, Hospital del Mar de Barcelona, IMIM (GREPAC), Department of Medicine (MELIS), Universitat Pompeu Fabra, Barcelona, Spain.

The authors have disclosed no conflicts of interest.

Correspondence: Dr Daniel Molano Franco, Calle 18 N 10-57, 2 floor Intensive Care Unit, Hospital de San José, Bogotá, Colombia. E-mail: dalemofra@gmail.com.

DOI: 10.4187/respcare.10371

were avoided. Tidal volume was calculated according to predicted body weight (predicted body weight [kg] = X + 0.91 × [height, cm] − 152.4 cm; with X male = 50 and X female = 45.5). Ventilator settings were adjusted according to blood gas analysis parameters (P_{aO_2} [60–80 mm Hg], P_{aCO_2} [35–45 mm Hg], $S_{aO_2} \geq$ 88–93%, pH 7.35–7.45). Subjects in the IV sedation cohort were initially sedated with propofol or midazolam, in combination with an opioid analgesic drug (fentanyl or morphine) following our institutional protocol. The Richmond Agitation-Sedation Scale was used to monitor the depth of sedation throughout the ICU stay (target range −5 to −4 during the first days of acute illness and throughout the study period). For pain monitoring, physiological and behavioral indicators such as tachycardia, hypertension, diaphoresis, facial musculature, quietness, muscle tone, verbal responsiveness, and comfort were used, measured objectively using the Campbell scale, with our target score 0–3; the use of opioid analgesics was titrated to achieve this range, with measurements being performed every 4–6 h.

Sevoflurane or isoflurane was administered by a miniature vaporizing device (anesthesia conserving device [AnaConDa], Sedana Medical, Danderyd, Sweden), with anesthetic delivery provided using a modified heat and moisture exchanger (HME), which is incorporated into the breathing circuit between the Y-piece and the subject, instead of the usual HME for capturing exhaled gas for rebreathing. The inhaled gas was applied continuously using a syringe pump. Briefly, the syringe was filled with sevoflurane before connecting the device between the subject and the ventilator. It was filled with a 1.5 mL bolus, and additional 0.1 mL boluses were administered until gas was registered on the anesthetic gas monitor. Inhaled anesthetics were removed by connecting the ventilator exhaust air to an absorbent canister.

The decision to assign inhaled or IV sedation was made by the attending physician and also depended on the availability of the drug. Data were extracted and entered into a data collection instrument that fed an Excel database that served as an interface for subsequent use and analysis with the statistical package Stata 16 (StataCorp, College Station, Texas). The parameters recorded and calculated were described by mean (SD) or median (interquartile range); for categorical data, we calculated absolute and relative frequencies (count and %), and 2-proportion Z test was performed, and the *P* value was calculated. The Shapiro-Wilk test was used to determine the distribution of the data. Measurements before and after the change were compared using the paired Student *t* test for normally distributed data and the Wilcoxon rank-sum test for non-normally distributed data. The indicator of association chosen was relative risk (RR).

The need to obtain informed consent from subjects was waived because of the observational and retrospective nature of the study. All subjects' personal data were anonymized for publication.

Results

From July 1, 2020–December 1, 2021, data were collected from 283 subjects who met the inclusion criteria and who had been assigned to IV ($n = 230$) or inhaled sedation management ($n = 53$). Baseline P_{aO_2}/F_{IO_2} at ICU admission was 101. Demographic characteristics are summarized in Table 1. In the IV sedation group, the mean age was 60.9 (SD 14.5) y; Acute Physiology and Chronic Health Evaluation II (APACHE II) severity score was 15.3 (SD 3.1), and Sequential Organ Failure Assessment (SOFA) score was 6.1 (SD 2.3), whereas in the inhaled sedation group the mean age was 63.1 (SD 10.2); APACHE II severity scale was 11.3 (SD 2.8), and SOFA 5.8 (SD 2.8). The most frequent comorbidities were hypertension (45%), 17 subjects in inhaled sedation group versus 112 for IV group; type 2 diabetes (22%), 15 subjects in inhaled sedation group versus 48 for IV group; and obesity (23%), 11 subjects in inhaled group versus 55 for IV group.

Regarding the requirements of other drugs in sedation analgesia and neuromuscular blockade, in the inhaled sedation group the RR for the need for high-dose fentanyl was 0.5 (95% CI 0.4–0.8, $P < .045$), for the need for muscle relaxant 0.3 (95% CI 0.20–0.45, $P < .001$). There was no evidence of difference in doses in the group using relaxation and inhaled sedation, since a fixed infusion protocol was used for the first 24 h after intubation, and for the risk of delirium 0.8 (95% CI 0.61–1.15, $P = .25$) (Table 2).

The difference in median fentanyl doses between the inhaled and IV sedation groups was 61 μg/h or 1,200 μg/d (2.2 ampoules/d), $P < .001$, and the difference in midazolam dose was 5.7 mg/h. In the inhaled sedation group, the post-intubation loading dose was 0.2 mg/h.

Total time of mechanical ventilation was 10.5 d in the inhaled sedation group versus 12.7 d in the IV group, with a mean difference of −4.71 to −0.23. Total ICU length of stay was 13.1 d in the inhaled group versus 15.1 d in the IV group, with a mean difference of −3.71 to −0.28. Overall ICU mortality at 28 d was 55%.

Discussion

Our study, carried out with a large cohort with severe ARDS due to COVID-19 managed at 2 university hospitals in Colombia, corroborated the results of studies in other countries, namely that the use of inhaled sedation is a potential alternative in the management of critically ill

Table 1. Demographic Data for Inhaled Versus Intravenous Sedation Groups

Characteristics	Inhaled Sedation ($n = 53$)	Intravenous Sedation ($n = 230$)	Mean Difference	*P*
Age, y	63.1 (± 10.2)	60.9 (± 14.5)	−1.125 to 5.525	NA
Sex				
Male	20	88	NA	.55
Female	33	142		
APACHE II	11.3 (2.8)	15.03 (3.10)	−4.58 to −2.87	NA
SOFA	5.8 (2.8)	6.1 (2.3)	−1.51 to 0.11	NA
Comorbidities				
Arterial hypertension	17 (32)	112 (48)	NA	.62
Type 2 diabetes	15 (28)	48 (20)	NA	.71
Overweight, BMI > 27	11 (20)	55 (23)	NA	.62
Days of mechanical ventilation, d*	10.5 (6.2)	12.7 (8.1)	−4.71 to −0.23	NA
ICU length of stay, d*	13.1 (5.2)	15.1 (7.2)	−3.71 to −0.28	NA

Data are presented as n (%) or mean (SD).
* Difference of means with statistical significance.
APACHE II = Acute Physiology and Chronic Health Evaluation II
SOFA = Sequential Organ Failure Assessment
BMI = body mass index

Table 2. Comparison of Use of Other Drugs Between Inhaled Versus Intravenous Sedation

	Inhaled Sedation ($n = 53$)	Intravenous Sedation ($n = 230$)	*P*	RR
Exposure to high-dose opioids > 200 μg/h	19 (35)	140 (60)	.045*	RR 0.58 (95% CI 0.4–0.8)
Delirium, yes	24 (45)	124 (53)	.25	RR 0.83 (95% CI 0.6–1.1)
Neuromuscular relaxant, yes	16 (30)	230 (100)	< .001*	RR 0.30 (95% CI 0.20–0.45)

Data are presented as n (%).
* Difference of means with statistical significance.
RR = relative risk

subjects, able to reduce the use of opioids, muscle relaxants, and benzodiazepines.

COVID-19 pneumonia constituted a worldwide health crisis given that the massive and concomitant presentation of the disease saturated health care systems for long periods of time.[27] During the pandemic, clinicians were confronted with shortages of drugs for daily use. In ICUs, the lack of resources for the most critically ill patients might have led to adverse and even fatal results,[30] and so physicians were obliged to resort to unconventional sedation strategies. Initial reports demonstrate that the use of inhaled isoflurane was able to achieve the required deep sedation and reduced the need for IV sedation.[31]

Due to this concern, non-conventional alternatives emerged in intensive care such as inhaled sedation, which is frequently used in operating rooms. There are few reports on its routine use in critically ill patients; some beneficial effects in pain modulation have been reported and perhaps a reduction in analgesia requirement, particularly opioids. In Europe, this type of inhaled anesthetics has been used for approximately 12 years, which simplifies the role of the vaporizer and ensures safe use with conventional ventilators. Recently, the use of volatile anesthetics for ICU sedation has been authorized in several European countries and has been included in national guidelines.[32,33]

Data on the clinical benefit of inhaled anesthetics had already been reported prior to the COVID pandemic, especially with regard to the reduction of ventilation time in the ICU,[34] which was close to 2 days in our study. Statistically significant differences were found both in length of stay and in duration of ventilation. There has also been evidence of a reduction in the use of neuromuscular blockade and a non-significant reduction in short- and long-term mortality, possibly due to the cardioprotective effects attributed to this

therapy. Taking into account that many individual factors must be considered risks, the benefits of undergoing general anesthesia merit consideration on a case-by-case basis.[34,35]

In 2021, Meiser et al[36] published their experience in 20 subjects diagnosed with ARDS due to COVID-19 comparing inhaled sedation with sevoflorane against propofol and the requirements of opioid doses (morphine) and the need for neuromuscular blockade. In our series with 283 subjects, the 53 with inhaled sedation received a lower fentanyl neuromuscular blockade; the contrast with Meiser et al study is even more striking: 0% versus 11%.

During the COVID-19 pandemic, the use of benzodiazepines increased, frequently at high doses with longer infusions than those previously used in daily practice. This practice has been related to a greater number of days of mechanical ventilation and episodes of delirium in ICU patients.[37,38] Several hypotheses associated with the neurotropism of the virus due to episodes of hyperexcitation and agitation have been proposed,[39] which explains the need for deep sedation in patients in the initial phases of ARDS in order to achieve protective ventilation goals. In our study we found a median dose difference between approaches of 5.7 mg/h, which compared with those who received inhaled sedation, who did not require benzodiazepines, suggests a possible decrease in these complications described; however, the reduction we found was not statistically significant in the inhaled sedation group, RR 0.8 (95% CI 0.61–1.15, $P = .25$).

Although in our study we did not evaluate other possible benefits of inhaled therapy, other effects that have been mentioned include physiological effects with a decrease in the systemic accumulation of the inhaled isoflurane and a lower risk for hepatic toxicity, which leads to a faster recovery from the anesthetic effects.[40] Bronchodilation represents another potential benefit in patients with severe bronchospasm.[41] Immunological phenomena have also been suggested, based on animal studies, regarding the effect on γ-aminobutyric acid type A receptors and via a modulation in the secretion of proinflammatory substances such as tumor necrosis factor-α, interleukin (IL)-6, and IL-1β, among others.

Our study has several limitations, above all its retrospective nature, the incompleteness of the records due to the limitations imposed by the pandemic, and the overload of the health system. In addition, titration of sedative doses inhalational anesthetics, were performed within a institutional protocol executed by the group of adjunct intensivists, most of them with additional training as anesthesiologists, however the care staff such as nursing, respiratory therapy and residents in training, lack such training and experience in handling this type of medication. The high mortality associated with viral pathology and related comorbidities should be considered in the interpretation of these results and in their extrapolation to other types of critically ill patients, especially those without COVID-19 infection.

Further studies are needed to demonstrate the usefulness of these drugs as an effective alternative. Sedation is commonly delivered using IV medications such as propofol, benzodiazepines, and analgesia with opioids. Data are from a local retrospective study, with which we do not intend to inform changes in the protocols and current clinical practices or replace IV sedation medications regularly used in critically ill patients. There are many considerations that must be taken into account before considering the use of this therapy, such as the training of ICU health personnel, safety studies of this therapy, cost-effectiveness, and define the doses and indications in patients without ARDS in whom the duration of mechanical ventilation is expected to be longer than 72 h.

This study shows the results of the use of this therapy at a specific moment of the COVID-19 pandemic, with a specific population, where we are forced to use alternatives to the medications that we traditionally use in our patients and that we believe should continue to study its benefits. Benefits and problems with the development of prospective studies that resolves the doubts that still revolve around inhaled sedation in ICU patients.

Conclusions

In conclusion, the sedation of patients with COVID-19 ARDS is a challenge for ICU staff. In situations where IV sedation is not available or demonstrates complications for its use, alternatives, including inhalation sedation, may be considered, especially for the management of sedation in critically ill patients requiring mechanical ventilation for a prolonged duration. Beneficial effects include reduced requirements for opioid analgesics and neuromuscular blockade.

ACKNOWLEDGMENTS

We thank the residents and all the health care personnel of the critical medicine and intensive care program at Hospital San José for their dedication and commitment in the management of nearly 1,200 patients attended at our institution.

REFERENCES

1. Guy GP, Jr., Zhang K, Bohm MK, Losby J, Lewis B, Young R, et al. Vital signs: changes in opioid prescribing in the United States, 2006–2015. MMWR Morb Mortal Wkly Rep 2017;66 (26):697-704.
2. Dubey MJ, Ghosh R, Chatterjee S, Biswas P, Chatterjee S, Dubey S. COVID-19 and addiction. Diabetes Metab Syndr 2020;14 (5):817-823.

3. Velikova T, Georgiev T. SARS-CoV-2 vaccines and autoimmune diseases amidst the COVID-19 crisis. Rheumatol Int 2021;41(3):509-518.
4. Ahn D-G, Shin H-J, Kim M-H, Lee S, Kim H-S, Myoung J, et al. Current status of epidemiology, diagnosis, therapeutics, and vaccines for novel coronavirus disease 2019 (COVID-19). J Microbiol Biotechnol 2020;30(3):313-324.
5. Meyer NJ, Gattinoni L, Calfee CS. Acute respiratory distress syndrome. Lancet 2021;398(10300):622-637.
6. Wang F, Kream RM, Stefano GB. Long-term respiratory and neurological sequelae of COVID-19. Med Sci Monit 2020;26: e928996.
7. Huppert LA, Matthay MA, Ware LB. Pathogenesis of acute respiratory distress syndrome. Semin Respir Crit Care Med 2019;40(1): 31-39.
8. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307(23):2526-2533.
9. Gibson PG, Qin L, Puah SH. COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS. Med J Aust 2020;213(2):54-56.e1.
10. Navas-Blanco JR, Dudaryk R. Management of respiratory distress syndrome due to COVID-19 infection. BMC Anesthesiol 2020;20 (1):177.
11. Gautret P, Million M, Jarrot PA, Camoin-Jau L, Colson P, Fenollar F, et al. Natural history of COVID-19 and therapeutic options. Expert Rev Clin Immunol 2020;16(12):1159-1184.
12. Pfortmueller CA, Spinetti T, Urman RD, Luedi MM, Schefold JC. COVID-19–associated acute respiratory distress syndrome (CARDS): current knowledge on pathophysiology and ICU treatment - A narrative review. Best Pract Res Clin Anaesthesiol 2021;35(3):351-368.
13. Chanques G, Constantin JM, Devlin JW, Ely EW, Fraser GL, Gélinas C, et al. Analgesia and sedation in patients with ARDS. Intensive Care Med 2020;46(12):2342-2356.
14. Pearson SD, Patel BK. Evolving targets for sedation during mechanical ventilation. Curr Opin Crit Care 2020;26(1):47-52.
15. Celis-Rodríguez E, Birchenall C, de la Cal M, Castorena Arellano G, Hernández A, Ceraso D, et al; Federación Panamericana e Ibérica de Sociedades de Medicina Crítica y Terapia Intensiva. Clinical practice guidelines for evidence-based management of sedoanalgesia in critically ill adult patients. Med Intensiva 2013;37 (8):519-574.
16. Celis-Rodríguez E, Díaz Cortés JC, Cárdenas Bolívar YR, Carrizosa González JA, Pinilla DI, Ferrer Záccaro LE, et al. Evidence-based clinical practice guidelines for the management of sedoanalgesia and delirium in critically ill adult patients. Med Intensiva (Engl Ed) 2020;44 (3):171-184.
17. Chisholm-Burns MA, Spivey CA, Sherwin E, Wheeler J, Hohmeier K. The opioid crisis: origins, trends, policies, and the roles of pharmacists. Am J Health Syst Pharm 2019;76(7):424-435.
18. Shipton EA, Shipton EE, Shipton AJ. A review of the opioid epidemic: what do we do about it? Pain Ther 2018;7(1):23-36.
19. Durkin E. US drug overdose deaths rose to record 72,000 last year. The Guardian: August 16, 2018. Available at: https://www.theguardian.com/us-news/2018/aug/16/us-drug-overdose-deaths-opioids-fentanyl-cdc.
20. Mallet J, Dubertret C, Le Strat Y. Addictions in the COVID-19 era: current evidence, future perspectives a comprehensive review. Prog Neuropsychopharmacol Biol Psychiatry 2021;106:110070.
21. Palamim CVC, Boschiero MN, Faria AG, Valencise FE, Marson FAL. Opioids in COVID-19: two sides of a coin. Front Pharmacol 2021;12: 758637.
22. Hraiech S, Yoshida T, Annane D, Duggal A, Fanelli V, Gacouin A, et al. Myorelaxants in ARDS patients. Intensive Care Med 2020;46 (12):2357-2372.
23. Yoshida T, Nakahashi S, Nakamura MAM, Koyama Y, Roldan R, Torsani V, et al. Volume controlled ventilation does not prevent injurious inflation during spontaneous effort. Am J Respir Crit Care Med 2017;196(5):590-601.
24. Guervilly C, Bisbal M, Forel JM, Mechati M, Lehingue S, Bourenne J, et al. Effects of neuromuscular blockers on transpulmonary pressures in moderate to severe acute respiratory distress syndrome. Intensive Care Med 2017;43(3):408-418.
25. Testelmans D, Maes K, Wouters P, Powers SK, Decramer M, Gayan-Ramirez G. Infusions of rocuronium and cisatracurium exert different effects on rat diaphragm function. Intensive Care Med 2007;33 (5):872-879.
26. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363 (12):1107-1116.
27. Pollard CA, Morran MP, Nestor-Kalinoski AL. The COVID-19 pandemic: a global health crisis. Physiol Genomics 2020;52(11):549-557.
28. Farrell R, Oomen G, Carey P. A technical review of the history, development, and performance of the anesthetic conserving device "AnaConDa" for delivering volatile anesthetic in intensive and post-operative critical care. J Clin Monit Comput 2018;32(4):595-604.
29. Laferriere-Langlois P, d'Aragon AF, Manzanares W. Halogenated volatile anesthetics in the intensive care unit: current knowledge on an upcoming practice. Minerva Anestesiol 2017;83(7):737-748.
30. Mallah SI, Ghorab OK, Al-Salmi S, Abdellatif OS, Tharmaratnam T, Iskandar MA, et al. COVID-19: breaking down a global health crisis. Ann Clin Microbiol Antimicrob 2021;20(1):35.
31. Flinspach AN, Zacharowski K, Ioanna D, Adam EH. Volatile isoflurane in critically ill coronavirus disease 2019 patients-a case series and systematic review. Crit Care Explor 2020;2(10):e0256.
32. Wolf A, Mörgeli R, Müller A, Weiss B, Spies C. Delirium, analgesia, and sedation in intensive care medicine: development of a protocol-based management approach. Med Klin Intensivmed Notfmed 2017;112(1): 65-74.
33. Sanitarios. Agencia Francesa para la Seguridad de los Productos Sanitarios. Available at: https://www.emergobyul.com/resources/asnm-agencia-francesa-seguridad-productos-sanitarios. Noviembre de 2021.
34. Landoni G, Pasin L, Cabrini L, Scandroglio AM, Baiardo Redaelli M, Votta CD, et al. Volatile agents in medical and surgical intensive care units: a meta-analysis of randomized clinical trials. J Cardiothorac Vasc Anesth 2016;30(4):1005-1014.
35. Delgado-Herrera L, Ostroff RD, Rogers SA. Sevoflurance: approaching the ideal inhalational anesthetic. A pharmacologic, pharmacoeconomic, and clinical review. CNS Drug Rev 2001;7 (1):48-120.
36. Meiser A, Volk T, Wallenborn J, Guenther U, Becher T, Bracht H, et al; Sedaconda study group. Inhaled isoflurane via the anesthetic conserving device versus propofol for sedation of invasively ventilated patients in intensive care units in Germany and Slovenia: an open-label, phase 3, randomized controlled, non-inferiority trial. Lancet Respir Med 2021;9(11):1231-1240.
37. Edalatkhah A, Kazemi MR, Samadi Khorshidi F, Akhoundimeybodi Z, Seyedhosseini SM, Rostami S, et al. Comparison of the effects of etomidate, ketamine, sodium thiopental, and midazolam on the mortality of patients with COVID-19 requiring intubation. Med J Islam Repub Iran 2021;35:49.

38. Krewulak KD, Stelfox HT, Ely EW, Fiest KM. Risk factors and outcomes among delirium subtypes in adult ICUs: a systematic review. J Crit Care 2020;56:257-264.
39. Smeets TJL, Valkenburg AJ, van der Jagt M, Koch BCP, Endeman H, Gommers D, et al. Hyperinflammation reduces midazolam metabolism in critically ill adults with COVID-19. Clin Pharmacokinet 2022;61(7):973-983.
40. Turner GB, O'Rourke D, Scott GO, Beringer TR. Fatal hepatotoxicity after re-exposure to isoflurane: a case report and review of the literature. Eur J Gastroenterol Hepatol 2000;12(8):955-959.
41. Stollings LM, Jia LJ, Tang P, Dou H, Lu B, Xu Y. Immune modulation by volatile anesthetics. Anesthesiology 2016;125(2):399-411.