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The importance of sedation in patients admitted with COVID-19: a systematic review

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Abstract

Analgesia and sedation are an integral part of the care provided to critically ill patients with COVID-19. These patients experience moderate to severe pain at rest and during standard care procedures. Objectives: The objective of this work is to identify the importance of sedation in patients hospitalized with COVID-19. Method: The Latin American and Caribbean Literature in Health Sciences (LILACS) and National Library of Medicine (MEDLINE) database were used to find scientific articles that were useful in clarifying this study. Results: An analysis and discussion of 5 experimental articles were carried out to fulfill the objective of this study. Conclusion: Regardless of the medications used, it is believed that it is essential that each ICU develop its management schemes for sedation, analgesia, delirium, mobility, and family involvement to achieve a consistent approach in the management of its patients and, thus, improve the clinical results.

Keywords: COVID-19. Patients. Hospitalization. Intensive care unit. Sedation.

Introduction

Coronavirus-2 severe acute respiratory syndrome (SARS-CoV-2) is the pathogen responsible for the 2019 coronavirus disease (COVID-19) pandemic that affected more than 10.5 million people and led to more than 500,000 deaths in June 2020 [1]. The first cases of COVID-19 infection were reported in Wuhan, China, in December 2019 and have since spread around the world, creating a threat to global health. The most common early symptoms of the illness include fever, cough, and myalgia or fatigue. In a subset of patients, the disease can progress to pneumonia and acute respiratory failure, requiring admission to the ICU in up to 26% of patients, with approximately 4 to 33% of patients requiring invasive mechanical ventilation [1].

COVID-19-associated pneumonia can be complicated by the development of acute respiratory distress syndrome (ARDS) in up to 42% of patients. Patients with ARDS may need moderate to deep levels of analgesia and sedation to decrease respiratory drive and optimize respiratory status. In addition, neuromuscular blocking agents in ARDS facilitate ventilator synchrony [2]. The increase in critically ill patients has created an increased demand for these therapies, in addition to the extraordinary doses of sedatives and analgesics that individual COVID-19 patients are demanding, resulting in drug shortages which can significantly impact the quality of care and safety of patients [3].

In this setting, there are 10 sedative and analgesic agents in the FDA and American Society of Health-System Pharmacist shortage databases, including propofol and dexmedetomidine. It is unfortunate, but this shortage is only likely to worsen as the pandemic progresses, making the use of more expensive alternatives and unfamiliar drugs a reality [4].

With any large-scale event, including a pandemic that leads to outbreaks of intensive care patients, the capacity and response of the outbreak are measured based on 3 levels: conventional care, contingency care, and crisis care. Contingency care includes those practices that may be outside of usual care but attempt to maintain usual care, whereas crisis care practices are outside of the standard of care but provide the best possible care when resources are severely limited [4].

The need for unusually high sedation in a large proportion of patients with COVID-19 is noted in current

clinical experience. These high sedation requirements are likely related to the younger age and good health of many patients before the onset of COVID-19, high respiratory drive, and intense inflammatory responses previously associated with tolerance [5].

This translates into the need to administer combinations of multiple agents (eg, propofol, ketamine, hydromorphone, dexmedetomidine, and midazolam), increasing the potential risks of side effects (eg, QT interval prolongation, hypertriglyceridemia, hypotension, and delirium) and requiring surveillance of the personal ICU [5]. When these are administered in combinations, typical requirements to ensure patient comfort and ventilator synchrony in adult patients range from 25 to 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 [5].

Deeper levels of sedation may be needed to facilitate ventilator synchrony in patients with severe acute respiratory distress syndrome (ARDS) and may also be favored by ICU staff to reduce the patient's risk of self-extubation, which is particularly problematic in this case. population gave the emerging need for reintubation and risk of exposure to the coronavirus. Subsequent tolerance to sedatives (eg, dexmedetomidine) from their use early in the disease course and at high doses will also limit the effectiveness of these drugs during weaning from the respirator [6].

Intermittent administration of certain medications (eg narcotics) tailored to each patient's individual needs may not always be feasible in situations of overburdened healthcare systems (eg when a nurse is needed to care for multiple critically ill patients). In these situations, continuous infusions of sedative drugs are favored for practicality, but this practice further increases the risk of side effects [7].

Why are critically ill patients with COVID-19 who require mechanical ventilation an understandable concern for clinicians in the pursuit of educating and challenging to improve the practice of sedation? A significant proportion of patients with COVID-19 require intensive care and mechanical ventilation, requiring sedation and analgesia. These patients tend to require higher doses of medication sedatives and often for long periods [2]. Most commonly used sedative and analgesic agents present unique risks that must be considered within the context of COVID-19's unique pathophysiology, the logistical problems the disease presents, and the continuing shortage of medications [3].

Analgesia and sedation are an integral part of critical patient care. These patients experience moderate to severe pain at rest and during standard care procedures. Staying in the ICU causes anxiety in physiological and psychological ways, and more than half of the patients admitted to the ICU remember being in the ICU or being intubated. This pain and anxiety increase the response to pre-existing sympathetic stress and lead to increased endogenous activity of catecholamines, increased oxygen consumption, tachycardia, hypercoagulability, hypermetabolism, and immunosuppression [7].

In this scenario, there are still no specific sedation guidelines for this population of patients who require high doses and prolonged administration of medication. Therefore, this study aimed to identify the importance of sedation in patients hospitalized with COVID-19.

Methods

Study Design

The present study followed a systematic review model, following the rules of systematic review - PRISMA (Transparent reporting of systematic review and meta-analysis, access available in: http://www.prisma-statement.org/).

Data Sources

The search strategy was performed in the PubMed, Scielo, Cochrane Library, Web of Science and Scopus, and Google Scholar databases, using scientific articles from 1996 to 2021.

Descriptors (MeSH Terms)

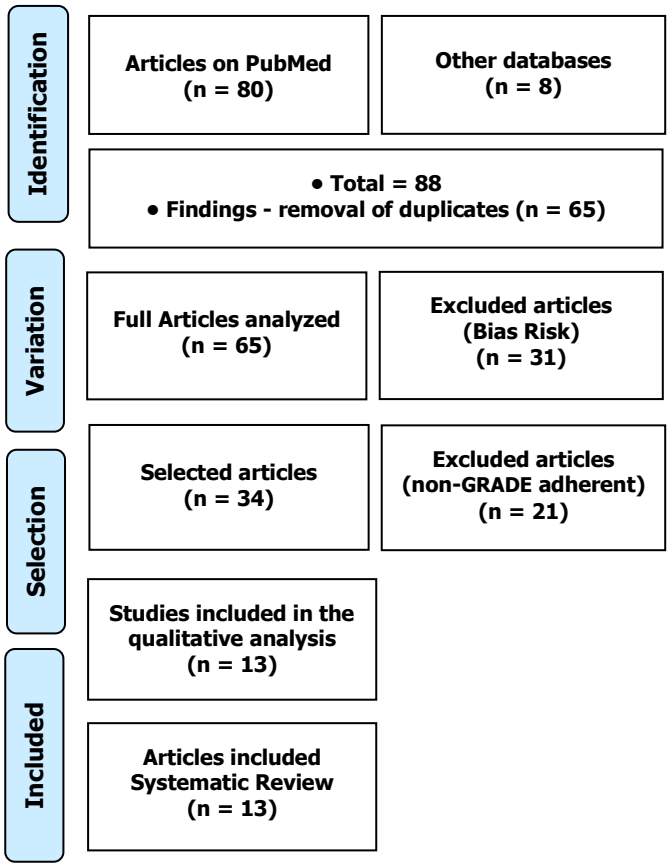
The main MeSH Terms used were "*COVID-19. Patients. Hospitalization. Intensive care unit. Sedation*", following the rules of the word PICOS (Patient; Intervention; Control; Outcomes; Study Design). The Cochrane Instrument was used to assess the risk of bias of the included studies.

Development

Results and Discussion

A total of 88 articles were found involving the importance of sedation in inpatients with covid-19. Initially, the duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, based on the elimination of articles with biases that could compromise the reliability of the results, according to the rules of the Cochrane instrument, as well as articles that presented low quality in their methodologies, according to the GRADE classification (Quality of Studies). A total of 34 articles were fully evaluated and 13 were included in this study (**Figure 1**).

Figure 1. Flowchart showing the article selection process.



After the selection process, the results were presented in the order of the questions that constitute the data collection instrument. For a better analysis of the studies and the reader's understanding, the numerical coding and description of their references were initially carried out.

Thus, in case study number 1, recommendations were agreed upon, and tools were developed to ensure a comprehensive approach to analgesia, sedation, delirium, early mobility, and family involvement for adult patients with acute respiratory distress syndrome due to COVID-19. Given the new order generated in intensive care due to the advance of the COVID-19 pandemic, it was proposed not to set aside the usual good practices, but to adapt them to the particular context generated. The consensus was supported by scientific evidence and national and international experiences and will be an attractive consultation tool in intensive care [8].

One of the pillars of the approach was to first maintain an analgesia strategy, always evaluating the presence of pain and its management, before administering or increasing sedatives. Opioids continued to be the pharmacological group that showed the greatest efficacy and safety in the management of pain in mechanically ventilated patients, with intravenous medication being the preferred option. An important clinical aspect to be emphasized to fentanyl and morphine is its well-documented pharmacological interaction with benzodiazepines (midazolam and lorazepam), dexmedetomidine, and propofol during its hepatic metabolism, potentially resulting in respiratory distress, hypotension, and deep sedation. There was also clinically relevant evidence for interactions between remifentanil and benzodiazepines, dexmedetomidine, and propofol that can lead to episodes of hypoventilation, airway obstruction, desaturation, or apnea. Although this evidence did not contraindicate their joint use, it was always extremely important to adjust the minimum effective doses of sedatives and opioids through a continuous assessment of the personalized goals proposed for the analgesedation of each patient [8].

Patients with severe cases of COVID-19 who enter the ICU have, for the most part, severe hypoxemia and/or ARDS, requiring mechanical ventilation, deep sedation, and sometimes NMB. The challenge was to maintain deep sedation strictly when needed, and at the same time identify the first time when light sedation can begin. It is important to recognize the benefits of avoiding deep and prolonged sedation, along with the benefits of light sedation with active family participation, despite not always being able to implement participation during a pandemic due to the risk of exposure and infection. For example, and despite its proven benefit, applying daily sedation breaks is difficult and potentially risky in these patients. Therefore, special care must be taken, and the protection of the health team must always be prioritized, even if it is harmful to it [8].

Also, in study 2, 7 studies were included, with a total of 892 patients. Intensive care unit mortality was not different between the sedation protocol or daily sedation interruption groups (OR = 0.81; 95% CI 0.60 - 1.10; I2 = 0%). Hospital mortality, duration of mechanical ventilation, and intensive care unit stay were also not different between groups. Sedation protocols were associated with an increase in the number of days off mechanical ventilation (mean difference = 6.70 days; 95% CI 1.09 - 12.31 days; I2 = 87.2%). Sedation protocols were associated with a shorter length of hospital stay (mean difference = -5.05 days; 95% CI -9.98 -0.11 days; I2 = 69%). There were no differences regarding accidental extubation, extubation failure, and the occurrence of delirium [2].

In case 3, midazolam and propofol are the agents of choice only for the short-term treatment (less than 24 hours) of anxiety in adults in intensive care, and the high cost is offset by the quick awakening; Lorazepam is the agent of choice for the prolonged treatment of adult anxiety in intensive care. Lorazepam is not available for parenteral administration, so this option would be feasible for us only in those patients with free oral

intake. A reasonable option is a diazepam, and it should only be remembered that, as it is more lipophilic than lorazepam, it has a greater propensity for accumulation in peripheral tissues after continuous or repeated administration; Haloperidol is the agent of choice for the treatment of delirium in adults in intensive care. Contraindicated drugs for use in adults in intensive care are a) etomidate, an anesthetic inducing agent with a small depressant effect on the cardiovascular system [3].

Often used in intensive care for sedation during short-term procedures, it is not recommended for use not continuous due to its adrenal cortical suppressor effects; b) ketamine can increase blood pressure, heart rate, and intracranial pressure; c) barbiturate agents such as sodium thiopental and pentobarbital, used in intensive care primarily to control intracranial hypertension, are not recommended as sedatives due to the absence of amnestic effects and due to their depressant and vasodilatory properties, with resulting arterial hypotension and tachycardia; d) droperidol and chlorpromazine, due to the lack of sufficient studies to make them recommendable in intensive care. Morphine is the analgesic of choice for critically ill patients, despite the release of histamine and the possibility of causing arterial hypotension; Fentanyl is the analgesic of choice in critically ill patients with hemodynamic instability, for patients with symptoms of histamine release after morphine use, or patients with morphine allergy [3].

Some analgesics have not been recommended for use in critically ill patients: meperidine (due to the active metabolite (normeperidine) with the possibility of causing seizures), agonist-antagonists (such as nalbuphine and buprenorphine due to the risk of reversing the action of other opioids) and NSAIDs (by the risks of gastrointestinal bleeding and renal failure); Pancuronium is the preferred neuromuscular blocker for critically ill patients; Vecuronium is the neuromuscular blocker of choice in patients with heart disease or hemodynamic instability, in which tachycardia episodes can be deleterious [2].

In case 4, midazolam and fentanyl were recommended as initial sedative analgesia, as these drugs were effective, with lower cost and less need for replacements during the day, minimizing the exposure of the nursing staff to the virus. Continuous ketamine infusion was used as second-line therapy to optimize agitation and control pain. The recommended sedative for the mild to moderate sedation phase was low-dose propofol. Dexmedetomidine can be used in patients with agitation close to extubation or as a second option in patients in the mild to moderate sedation phase to control agitation. For those patients with agitation or hyperactive delirium, neuroleptics such as quetiapine or risperidone were started by nasoenteral tube [10].

In case of impaired pulmonary compliance, severe ventilatory asynchrony, or a PaO2/FiO2 ratio below 150, even with the use of optimal doses of sedatives and optimization of ventilatory adjustments, the use of neuromuscular blockers was indicated. Cisatracurium was the neuromuscular blocker of choice when necessary, as it is the most studied drug in patients with acute respiratory distress syndrome. However, its use was not recommended for more than 48 hours due to the high risk of weakness and diaphragmatic dysfunction in critically ill patients. Continuous administration was preferred over intermittent to minimize staff exposure, although this strategy can result in increased costs. The use of neuromuscular transmission monitoring was indicated for patients using neuromuscular relaxation drugs. In addition, for patients under neuromuscular blockade, processed EEG monitoring was included to achieve adequate levels of sedation [10].

The depth of sedation was also monitored for those patients who are not under neuromuscular blockade but require higher doses of sedatives to minimize agitation. In study 5, most patients with COVID-19 had mild to moderate respiratory symptoms; however, some develop severe pneumonia and hypoxemia is a frequent cause of death. Severely ill patients with COVID-19 often require endotracheal intubation and mechanical ventilation. The choice of drugs to sedate these patients differs widely, depending on drug availability and clinical experience. We suggest that healthcare professionals with appropriate clinical experience consider the use of inhaled anesthetics, such as sevoflurane and isoflurane, for the following reasons [11].

In this context, intensivists and anesthesiologists are coming together to treat the sickest patients with COVID-19. They reported that ventilated patients with COVID-19 often required high doses of intravenous sedative drugs such as propofol, midazolam, ketamine, and dexmedetomidine. Not surprisingly, there is a growing shortage of these drugs. Furthermore, studies of patients with severe lung injury from causes other than COVID-19 have shown that inhaled anesthetics improve oxygenation and reduce mortality when compared with propofol or midazolam. The severity of lung injury in patients with COVID-19 correlates with cytokine levels and viral load. Convincing preclinical data from others and we have shown that inhaled anesthetic drugs attenuate lung inflammation and widen the airways. These effects are mediated by γ-aminobutyric acid type A (GABA A) receptors, which are expressed in different types of cells in the lung. Stimulation of GABA A receptors on lung epithelial cells reduces the production of pro-inflammatory cytokines; while

activation of GABA A receptors on airway smooth muscle cells stimulates bronchodilation and improves oxygenation [12].

Also, caregivers should exercise caution and consult anesthesiologists when treating COVID-19 patients with inhalation anesthetics due to adverse drug effects. They are contraindicated in patients with malignant hyperthermia and can cause cardiovascular instability and respiratory depression. It is not yet known whether long-term adverse effects result from long-term drug treatment. Finally, to mitigate adverse effects, the Anesthesia Patient Safety Foundation (APSF) developed guidelines to sedate COVID-19 patients with inhaled anesthetic drugs and recommendations for reusing anesthetic gas machines as ICU ventilators [13].

Conclusion

Given the new reality in ICUs created by the ongoing COVID-19 pandemic, we must not abandon the usual "good practices", but adapt them. This crisis should be used as an opportunity to implement a systematic approach based on the best available evidence, prioritizing targeted strategies with adequate pain control and progressive reduction of sedation and its adverse effects in the short and medium-term. Likewise, it will allow us to adapt the system in the event of a shortage of health resources as a result of the pandemic. The work of the multidisciplinary team inside and outside the ICU and its ability to identify, evaluate and adapt protocols based on the best available evidence, even before authorities at the regional or national level can incorporate changes in general protocols, are examples of versatility and commitment of this change. Therefore, it is considered appropriate to divide disease progression into different stages to plan the management of these sedated patients. Regardless of the medications used, it is believed that it is essential that each ICU develop its management regimens for sedation, analgesia, delirium, mobility, and family involvement to achieve a consistent approach in the management of their patients and thus improve clinical outcomes.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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