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SEDATION AND ANALGESIC REQUIREMENT AND THEIR EFFECT ON COMA, AND MORTALITY IN ICU MECHANICALLY VENTILATED PATIENTS WITH COVID VS NON-COVID PATIENTS

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Abstract

BACKGROUND

Sedatives and opioids are often used in patients with coronavirus disease 2019–associated acute respiratory distress syndrome, which may enhance their vulnerability to neurologic dysfunction. We tested the hypothesis that patients with coronavirus disease 2019–associated acute respiratory distress syndrome are at higher risk of in-hospital mortality due to prolonged coma compared with other patients with acute respiratory distress syndrome matched for disease severity.

OBJECTIVES:

To study the effect of sedation on mortality and coma-free days in COVID-19 patients admitted to the ICU compared to non – COVID – 19 ICU patients. Also, to investigate the possible causes of coma in ICU patients

DESIGN: Retrospective cohort study using propensity matching score

SETTING: Participants will be recruited from KFSH&RC, a major referral center that provides tertiary and quaternary care.

Intervention: None

Primary endpoint:

•difference in cumulative analgesia and sedation dose 48 hours after ICU admission of patients with non-COVID (ATTAINMENT pilot study cohort) compared to patients with COVID-19. We will compare the groups for differences in types of agents utilized, doses (both average and cumulative) and duration

Secondary endpoint:

We will look also at in – hospital mortality, the percentage of comatose days and the causes of coma in ICU patients.

Keywords: Participants will be recruited from KFSH&RC, a major referral center that provides tertiary and quaternary care.

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Background:

Patients with coronavirus disease 2019 (COVID-19) can have neurologic manifestations, including acute cerebrovascular events and coma (1,4). A coma occurs in approximately 15% of COVID-19 patients admitted to the intensive care unit (ICU) and is typically diagnosed within the second week of hospitalization (2, 3). The etiology and effect of coma in patients with COVID-19 presenting to an ICU to treat acute respiratory distress syndrome (ARDS) remain unclear (5). One study showed that COVID -19 patients experienced a higher percentage of coma which has an indirect effect on mortality. In the same study, a higher percentage of comatose patients received higher doses of sedatives for a longer duration (15). Throughout the 2019 coronavirus disease (COVID19) pandemic, many patients depend on ventilators and require sedation in the intensive care unit (ICU) and other hospital sites. Sedatives and opioids are often used in patients with coronavirus illness 2019–associated acute respiratory distress syndrome, which may enhance their vulnerability to neurologic dysfunction (2). Because of improved short-term outcomes such as length of stay (LOS), mechanical ventilation duration, and delirium, the 2018 PAD guidelines suggest that nonbenzodiazepine sedatives (propofol or dexmedetomidine) are preferable to benzodiazepine sedatives in critically ill, mechanically ventilated adults (6).

Study Rational

During the COVID – 19 pandemic, there were high demands on sedatives and analgesics in mechanically ventilated patients, resulting in a short supply of these medications. Alternatively, other sedatives were used to facilitate mechanical ventilation. Moreover, Little is known about these medications' pharmacological action and side effects in this group of patients. According to anecdotal reports, COVID -19 patients require higher doses of analgesics and sedatives and the requirement for combination therapy than most mechanically ventilated critically ill patients (7). These high sedative needs are likely due to many patient's young age and good health prior to the beginning of COVID-19, as well as high respiratory drive and severe inflammatory reactions previously linked to tolerance. Additionally, there is limited information in the new COVID – 19 guideline regarding the choice of sedative agents in COVID – 19 mechanically ventilated patients (8)

Study Hypothesis

Our working hypothesis is that analgesia and sedation requirements of critically ill patients with COVID-19 are heavier and associated with higher hospital mortality compared to patients with ARDS Non-COVID as a consequence of deep sedation during mechanical ventilation.

Study Objectives

Our objective is to characterize the difference in cumulative analgesia and sedation dose 48 hours after ICU admission of patients with non-COVID (ATTAINMENT pilot study cohort) compared to patients with COVID-

19. We will compare the groups for differences in types of agents utilized, doses (both average and cumulative), and duration.

Materials And Methods

Study Design:

This retrospective hospital study will include adult mechanically ventilated patients admitted to ICUs in King Faisal Specialty Hospital and Research Center (KFSHRC). This center is a major referral center that provides tertiary and quaternary care. Using clinical data obtained from a hospital registry, we will match 60 patients with coronavirus disease 2019 to 60 patients with non-COVID 2019–related acute respiratory distress syndrome patients based on baseline disease severity. The data for non-COVID patients will be obtained from the ATTAINMENT pilot study cohort which was an IRB approved study and conducted in non-COVID ICUs

Study Population

Inclusion criteria:

All adult patients 14 years of age and older admitted to an adult COVID intensive care unit who require invasive mechanical ventilation will be included if they meet one of the following criteria:
Diagnosed with ARDS
Tested positive for COVID-19
Admitted between January 2020 - December 2022

Exclusion criteria

1) Age < 14 years old.
2) MV < 24-hours
3) Proven neurological injury (traumatic brain injury, ischemic stroke, intracranial hemorrhage, spinal cord injury, anoxic brain injury, brain edema).
4) Patients identified as Do Not Resuscitate (DNR) or those expected to die within 24-hours.
5) Patients on extracorporeal membrane oxygenation (ECMO)
6) Patients with missing baseline characteristics for the propensity matching model were exclude

Primary endpoints :

To characterize the difference in cumulative analgesia and sedation dose at day 1, day 3, and day 5 after ICU admission of patients with non-COVID (ATTAINMENT pilot study cohort) compared to patients with COVID-19. We will compare the groups for differences in types of agents utilized, doses (both average and cumulative), and duration

Secondary endpoints :

mortality and the percentage of comatose days. The Richmond Agitation Sedation(RASS) Scale is the tool to record the level of consciousness. Based on previously published trials, patients with a mean RASS score of –3 to –5 were defined as comatose, regardless of whether the status was caused by disease or sedation (10) The ratio of days in coma during the first 2 days of mechanical ventilation for each patient to be used to calculate the proportion of days spent in coma. we are also going to investigate the possible causes of coma in adult mechanically ventilated patients

Statistical analysis :

Based on the results of a trial showing that the cumulative propofol dose on ICU day 3 was 55% larger in patients with COVID-19 than ARDS (9). We chose a an absolute difference of 25% at an alpha level of 0.05 and Beta of 80% to arrive at our target sample size which is 120 patients (60 in each group). Continuous variables and counts are described using mean ± SD or median (interquartile range [IQR]); categorical variables are reported as percentages. The chi-square test, multivariable logistic regression, negative binomial regression, and mediation analysis will be used to conduct the analyses.. The effects of coma on mortality of patients with sedation-related coma versus neurologic injury-related coma will be compared using a Cox proportional hazards regression analysis.

Data collection and management:

The research team will collect and record study data, as outlined in the data collection system REDCap. On all study documents, specific patient data will be identified with unique study identifiers (coded participant number). Data will be stored in a secured hospital network drive Principles of privacy and confidentiality will be followed, whereby the identity and records of the subjects of the study will be kept confidential, and no details about the subjects that would result in the disclosure of their identities will be revealed. We are assuring that personal

information provided by applicants will be protected, and at no stage will it form any part of the assessment process. The data will be collected and stored securely in REDCap. The access to REDCap data require authentication (username and password) to maintain data secure and will be accessible only to study personnel. Eligible patients and clinical data will be collected through the Integrated Clinical Information System (ICIS – the KFSH&RC electronic health record). The study data will be collected and managed utilizing KFSH&RC's REDCap electronic data capture tools.

Duration of the study:
The expected total duration of the trial is six months started, from May 2022 to December, 2022

Ethical Considerations:
The study will be conducted following ORA policies and procedures. This is a retrospective study so no need for an informed consent due to the nature of the study as well as considering that this research carries no risk for these patients. There will be no interaction with patients during the collection of the data or following the administration of their therapy. In addition, to ensure security, all data collected will be recorded in RedCap. No potential harm or discomfort is expected due to the nature of the study

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Data Collection Sheet

Demographics and baseline characteristics:	
Age:	Gender Female
Weight (Kg):	Height (Cm):
BMI:	
Which of the following was this patient diagnosed with?	ARDS (non-COVID-19) COVID-19
Which of the following was the primary cause of this patient's lung injury?	Pneumonia COVID - 19 Aspiration Nonpulmonary sepsis Other cause
Please provide other cause	

Which APACHE score was used to calculate the value for this patient?	APACHE I APACHE II APACHE III APACHE IV
What was this patient's primary reason for ICU admission	Medical, COVID-19 Medical, NON-COVID-19 Surgical, emergency Surgical, scheduled/elective
Comorbidities : COPD	YES NO
Comorbidities : mild liver dysfunction	YES NO
Comorbidities : Diabetes	YES NO
Comorbidities : CKD	YES NO
Comorbidities : Solid malignancy	YES NO
Comorbidities : hematological malignancy	YES NO
Comorbidities : Recipient of solid organ transplantation	YES NO
Comorbidities : HSCT	YES NO
Comorbidities : AIDS	YES NO
Comorbidities : Hypertension	YES NO
How many days was this patient's length of stay in the hospital?	
How many days was this patient in the ICU during their hospital admission?	
For how many hours was this patient been on mechanical ventilation during their ICU admission?	
Did this patient require a tracheostomy during their admission?	YES NO
Renal replacement therapy at baseline	YES No
If yes, what type of Renal replacement therapy (RRT)	Intermittent hemodialysis (iHD) Continuous Veno-Venous Hemofiltration (CVVH) Continuous veno-venous hemodialysis (CVVHD) Continuous Veno-Venous Hemodiafiltration (CVVHDF)
Lactate level at baseline (mmol/l)	
Mode of mechanical ventilation (MV)	Volume- Control Assist-Control Ventilation (VCAC) Pressure-Controlled Ventilation (PCV) Pressure Support Ventilation (PSV) Synchronized Intermittent-Mandatory Ventilation (SIMV) Pressure Regulated Volume Control (PRVC) Non-invasive ventilation (Bipap, CPAP)
PH from ABG admission	
PCO2 (K pascal) from ABG admission	
PO2 (K pascal) from ABG admission	
HCO3 (mmol/l) from ABG on admission	
Does the pts have metabolic acidosis ?	YES

	NO
Fio2 at baseline	
PF ratio at baseline (calculated field)	
baseline RASS at study entry	+4 +3 +2 +1 0 -1 -2 -3 -4 -5 Not assessed
Fentanyl at baseline	YES NO
If Yes, infusion vs boluses PRN	Infusion PRN boluses both
what is the cumulative dose (mcg) of fentanyl	
Propofol at baseline	Yes No
If Yes, infusion vs boluses PRN	Yes No
what is the cumulative dose of propofol (mg)	
Midazolam at baseline	Yes No
If Yes, infusion vs boluses PRN	Infusion PRN boluses both
What is the cumulative dose of midazolam (mg)	
Morphine at baseline	Yes No
If Yes, infusion vs boluses PRN	Infusion PRN boluses Both
What is the cumulative dose of morphine(mg)	Yes No
Dexmedetomidine at baseline	Yes No
Ketamine at baseline	Yes No
If Yes, infusion vs boluses PRN	Infusion PRN boluses Both
What is the cumulative dose of ketamine	
Endpoint	
What is the mean RASS score in the first 10 days of sedation	+4 +3 +2 +1 0

	-1
Patient outcome	Death Comatose Discharge
Proportion of days spent in coma in the first 2 days of sedation	