Original Article

Cukurova Anestezi ve Cerrahi Bilimler Dergisi

Association of Dexmedetomidine Use with Time to Intubation in Critically Ill COVID-19 Patients: A Retrospective Observational Study

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Abstract

Aim/Objective: Dexmedetomidine (DEX), a highly selective α2-adrenoceptor agonist, has sedative, analgesic, anxiolytic, and immunomodulatory properties that may provide benefits in critically ill patients with COVID-19 acute respiratory distress syndrome (ARDS). This study aimed to evaluate the effect of DEX on clinical outcomes in patients with severe COVID-19 treated in the intensive care unit (ICU). **Methods:** We retrospectively analyzed the medical records of patients admitted to the ICUs of Sakarya University Training and Research Hospital with a diagnosis of COVID-19 between October 2020 and February 2021. A total of 134 patients were included, of whom 45 received DEX and 89 did not. DEX infusion was discontinued upon intubation. Patients receiving DEX in addition to standard care were classified as the DEX group, while those receiving other sedatives or no sedative treatment were classified as the non-DEX group. Demographic, clinical, laboratory, and outcome data were compared between groups. **Results:** The median age of the study population was 69.5 years, and 62.7% were male. Age distributions were similar between groups ($p>0.05$). Patients with diabetes mellitus and those receiving insulin therapy were less likely to receive DEX ($p=0.040$ and $p=0.016$, respectively). The median time from ICU admission to intubation was significantly longer in the DEX group than in the non-DEX group (4 vs. 1 day, $p<0.001$). No significant differences were observed between groups regarding laboratory findings, mortality, intubation rates, comorbidities, or other treatments. **Conclusions:** DEX therapy may prolong the time to intubation in patients with severe COVID-19 ARDS but does not appear to reduce mortality.

Keywords: COVID-19; Dexmedetomidine; Intubation; Mortality; SARS-CoV-2; ARDS

1. Introduction

Sedation plays a key role in the management of pain, anxiety, and agitation which are important problems for the patients treated in the ICUs. It becomes very difficult to apply frequently used procedures in the ICUs such as high flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), and continuous intravenous (IV) fluid/drug infusions which require high levels of cooperation to an agitated and anxious patient. Thus, sedative agents are usually applied to render patients calmer, more cooperative, and communicable.[1]

Dexmedetomidine (DEX) is a highly selective α2-adrenoceptor agonist that is increasingly used in the daily practice of intensive care units (ICUs) with its sedative, analgesic, anxiolytic, and immunoprotective effects.[1,2] The sedative effect of DEX might vary from minimal to deep depending on the dose applied to the patient. It is also known for its analgesic potential since it causes a reduction of sympathetic tone. Due to this fact, it can also be used for procedural sedation with high patient and operator satisfaction.[3] DEX can maintain lighter sedation compared to propofol and benzodiazepines (i.e. midazolam and lorazepam) and since the light level of sedation is recommended in ICU when possible, DEX would be preferred over other agents.[1,4] Patients under the DEX effect can be awakened easily when needed, and communicate pain, however, when left undisturbed will fall back into a state very similar to natural sleep.[3,4] Despite these beneficial effects, the common side effect of this agent such as hypotension and bradycardia limits its use, especially for patients with a history of cardiac disease. Still, the unique expedient properties of DEX aroused scientists' interests and were found to be associated with improved outcomes, including a shorter duration of ventilation and a shorter ICU stay in some studies.[5,6]

A novel coronavirus disease caused by SARS-CoV-2 was first identified in China in December 2019 and rapidly evolved into a global pandemic, resulting in millions of deaths worldwide. A considerable proportion of infected individuals develop acute respiratory distress syndrome (ARDS), requiring management in intensive care units (ICUs).[7,8] Emerging evidence indicating high mortality among intubated patients has led clinicians to prioritize delaying or avoiding invasive ventilation whenever feasible. Consequently, non-invasive respiratory support strategies—such as HFNC and CPAP, often combined with prone positioning—have been widely adopted in the management of patients with severe respiratory failure.[9,10] Besides, states of impaired consciousness, including delirium might occur in up to 15% of the patients with severe COVID-19 and are associated with a poorer prognosis.[11] Therefore, considering the high frequency of respiratory failure and delirium in patients with severe COVID-19, it is obvious that proper agents with sedative, analgesic, and anxiolytic effects are highly required in the setting of ICU. At this point, it can be hypothesized that DEX would be an important part of the treatment for COVID-19 due to its aforementioned potential beneficial effects, especially for the patients in ICU. Theoretically, it would increase the compliance of patients to treatments with its sedative effect while decreasing the inflammation with its potential immunomodulatory effect. In this study, we aimed to analyze whether Dexmedetomidine improves the outcomes in patients treated in ICUs.

2. Materials and Methods

2.1. Study Design and Patient Selection

The study was conducted retrospectively and included the patients who were treated in the ICUs of Sakarya University Training and Research Hospital with diagnosis of severe COVID-19 between October 2020 and February 2021. Nasopharyngeal swab PCR positivity has been considered the reference standard for confirming the diagnosis of COVID-19. Individuals younger than 18 years and those with a negative PCR test result were excluded from the study. We included 134 patients in the study, 45 of whom the treatment regimen included dexmedetomidine infusion at least for 24 hours during their ICU stay and 89 of whom were treated with other agents for sedation such as haloperidol, quetiapine, and lorazepam or needed no therapy for sedation. Patients treated with DEX at any time during the treatment were defined as the "DEX group", whereas patients without DEX use were defined as the "non-DEX group" and the parameters were compared between these groups. DEX infusion was applied to the patients who were agitated and non-cooperative for HFNC, NIMV, and prone positioning (PP) and had no history of cardiac disease such as congestive heart failure, coronary artery disease, and atrial fibrillation, etc. whereas other agents were applied for these kinds of patients in the non-DEX group. The treatment protocol in our ICU unit did not include DEX for patients with cardiac diseases since this agent is famous for its cardiac side effects such as bradycardia and hypotension. DEX infusion was applied to the patients as the loading dose

of 1 mcg/kg IV over 10 minutes, and once sedation was ensured, the maintenance dose of 0.2-0.7 mcg/kg/hr continuous IV infusion. Patients who progressed to endotracheal intubation were suspended from DEX infusion immediately and other anesthetics such as midazolam and propofol were initiated for deeper sedation. For the standard group; haloperidol was used as a 4x10mg/day IV infusion in 150cc saline for 30 minutes each time, quetiapine was used as 25 or 50 mg/day P.O or through the feeding tube, and lorazepam was used 2x0.5 mg/day P.O or through the feeding tube, or no agent was needed for sedation.

The standard therapy regimen in our institution at the time of the study for patients with severe COVID-19 was favipiravir for 5 to 10 days (2x1600mg as the loading dose, 2x600mg as the maintenance dose) plus dexamethasone 24 mg IV for the first 3 days, 16 mg IV for the second 3 days and 8 mg IV for the third 3 days. After 9 days, tapering the dexamethasone dose day by day to prevent adrenal insufficiency irrespective of the clinical status of the patient was also part of our medical protocol. All individuals included in the study were treated with this protocol. Standard ICU management for these patients included intravenous fluid resuscitation, antibiotic therapy when indicated, and a stepwise approach to oxygen support (ranging from nasal cannula and non-rebreather mask to HFNC, CPAP, and, if necessary, intubation). Prone positioning (PP) was applied for up to 16 hours per day when tolerated. In addition, low-molecular-weight heparin was administered for anticoagulation, and proton pump inhibitors were used for stress ulcer prophylaxis. Demographical data such as age, gender, drug history, and comorbidities were obtained from patients' medical records along with applied treatments during the ICU stay. Lab parameters that were obtained at the time of admission to ICU were used for analysis. Collected data were analyzed in the biostatistical program.

2.2. Ethics Approval

This study was approved by the Sakarya University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Committee Name: Sakarya University Faculty of Medicine Non-Interventional Ethics Committee; Date: 29.05.2021; Decision No: 32203/320). All procedures were conducted in accordance with the ethical standards of the institutional research committee and with the principles of the Declaration of Helsinki (revised 2024). This study was presented as an oral presentation at the "8th International May 19th Congress on Innovative Scientific Approaches" on 22-23 November 2022.

2.3. Statistical Analysis

Descriptive statistics were reported as medians with interquartile ranges (IQR) for variables that did not follow a normal distribution. Group comparisons for these variables were performed using the Mann-Whitney U test. Categorical variables were compared using the chi-square test and are presented as frequencies and percentages. Fisher's Exact Test was utilized for categorical variables when expected cell frequencies were less than 5. A p-value of less than 0.05 was considered statistically significant. All analyses were conducted using SPSS software (version 21).

3. Results

The median age of all patients was 69.5 whereas it was 67 for the DEX group and 70 for the non-DEX group. There was not any significant difference in terms of median ages between the groups ($p>0.05$). 62.7% of the patients were male and there was no significant difference in gender between the groups ($p>0.05$). Mortality rates were 71.1% for the DEX group, 76.4% for the non-DEX group, and 74.6% for all patients, however, these differences were not significant ($p>0.05$). There was also no significant difference in intubation rates between the groups ($p>0.05$). The median duration of intubation was 3 days for the DEX group while it was 5 days for the non-DEX group, however, the difference was not significant ($p>0.05$). The median duration between ICU admission of the patients and their time of intubation was 4 days for the DEX group whereas it was 1 day for the non-DEX group and the difference was strongly significant ($p<0.001$). Analysis of lab parameters including white blood cell (WBC), hemoglobin (HB), platelet count (PLT), c-reactive protein (CRP),

procalcitonin (PCT), sedimentation rate (sedim), D-dimer, lactate dehydrogenase (LDH), fibrinogen, Troponin-I, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and ferritin revealed a no significant difference between the groups (p>0.05) (Table 1).

Table 1. Comparison of demographical data, clinical courses, and laboratory parameters between the groups

Parameters	DEX Group (n=45)	non-DEX Group (n=89)	All Patients (n=134)	p
Age (years)	67 (63-75)	70 (65-77)	69.5 (64-77)	0.094
Gender (male)	33 (73.3%)	51 (57.3%)	84 (62.7%)	0.07
Gender (female)	12 (26.7%)	38 (42.7%)	50 (37.3%)	0.07
HFNC	6 (13.3%)	6 (6.7%)	12 (9%)	0.217
CPAP	20 (44.4%)	15 (16.9%)	35 (26.1%)	0.001
Intubated	30 (66.7%)	67 (75.3%)	97 (72.4%)	0.292
Duration of intubation (day)	3 (1-8)	5 (1-8)	5 (1-8)	0.521
Duration btw ICU admission and intubation (day)	4 (2-5)	1 (0-3)	2 (0-4)	<0.001
Fatality	32 (71.1%)	68 (76.4%)	100 (74.6%)	0.506
WBC ($10^3/\mu L$)	12.6 (11.4-18.8)	13.8 (9-16.8)	13.1 (9.6-17.5)	0.501
HB (g/dl)	12.5 (11-14.9)	12.4 (11-13.5)	12.4 (11-13.9)	0.276
PLT ($10^3/\mu L$)	207.5 (173.5-248.5)	199 (150-287)	200 (157-272)	0.584
CRP (mg/L)	116 (65-167)	130 (74-177)	128.5 (73-174)	0.9
PCT (ng/ml)	0.5 (0.4-1.2)	0.9 (0.2-4.1)	0.8 (0.2-3.1)	0.677
Sedimentation (mm/h)	64 (38-76)	60 (39-74)	60 (39-74)	0.888
Ferritin (ng/mL)	734 (334-1884)	1136 (489-2495)	1016 (432.5-2287.5)	0.11
D-dimer (ng/mL)	1300 (500-3390)	1880 (853-6230)	1755 (697-5930)	0.119
LDH (U/L)	524 (433-745)	496 (358.5-747.5)	508 (402-745)	0.366
Fibrinogen (mg/dL)	443 (348-483)	412 (315.5-539)	417 (337-493)	0.968
Troponin-I (ng/L)	41.8 (12.9-369)	103 (18.1-392)	90 (16.8-386)	0.328
AST (U/L)	37 (28-57)	40 (26-70)	38 (27-60)	0.492
ALT (U/L)	28 (17-44)	29 (18.5-48)	29 (18-45)	0.757

Data are presented as median (interquartile range, IQR) for continuous variables and n (%) for categorical variables. Comparisons between groups were performed using the Mann-Whitney U test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. Abbreviations: DEX, dexmedetomidine; ICU, intensive care unit; HFNC, high-flow nasal cannula; CPAP, continuous positive airway pressure; WBC, white blood cell count; HB, hemoglobin; PLT, platelet count; CRP, C-reactive protein; PCT, procalcitonin; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

We compared the DEX and the non-DEX group in terms of comorbidities and drug usage history. Diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), asthma, chronic renal failure (CRF), neurological disorders (ND), and atrial fibrillation (AF) were included in the analysis as comorbidities. Among comorbidities, as expected due to our treatment protocol, the patients with DM, CAD and, CHF were significantly less treated with DEX (p=0.04, p=0.000, and p=0.001 respectively). No association was found between the other comorbidities and the study groups. Regular usage of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), ibuprofen, other non-steroidal anti-inflammatory drugs (NSAIDs), steroids, acetylsalicylic acid (ASA), metformin, other oral antidiabetics (OADs), insulin, proton pump inhibitors/histamine-h2 receptor blockers (PPI/H2RB), clopidogrel, immunosuppressive agents (IS), diuretics, inhaler treatments (IT), warfarin and antidepressants (AD) were included in the analysis. Among these, only the patients with a history of insulin use were significantly less treated with DEX (p=0.016). There was no other significant difference regarding the history of drug use between the groups (Table 2).

Table 2. Comparison of comorbidities and history of drug use between the groups

Comorbidities	DEX Group (n=45)	non-DEX Group (n=89)	All Patients (n=134)	p
DM	12 (26.7%)	40 (44.9%)	52 (38.8%)	0.04
HT	25 (55.6%)	57 (64%)	82 (61.2%)	0.341
CAD	0 (0%)	24 (27%)	24 (18%)	<0.001
CHF	0 (0%)	16 (18%)	16 (12%)	0.001
COPD	8 (17.8%)	6 (6.7%)	14 (10.4%)	0.071
Asthma	2 (4.4%)	2 (2.2%)	4 (3%)	0.602
CRF	3 (6.7%)	14 (15.7%)	17 (12.7%)	0.137
ND	8 (17.8%)	19 (21.3%)	27 (20.1%)	0.627
AF	0 (0%)	2 (2.2%)	2 (1.5%)	0.251
Drug Use				
ACEI	14 (31.1%)	20 (22.5%)	34 (25.4%)	0.278
ARB	7 (15.6%)	20 (22.5%)	27 (20.1%)	0.346
Ibuprofen	3 (6.7%)	2 (2.2%)	5 (3.7%)	0.202
Other NSAIDs	6 (13.3%)	16 (18%)	22 (16.4%)	0.493
Steroid	4 (8.9%)	3 (3.4%)	7 (5.2%)	0.224
ASA	16 (35.6%)	33 (37.1%)	49 (36.6%)	0.863
Metformin	3 (6.7%)	11 (12.4%)	14 (10.4%)	0.383
Other OADs	7 (15.6%)	14 (15.7%)	21 (15.7%)	0.979
Insulin	3 (6.7%)	21 (23.6%)	24 (17.9%)	0.016
PPI/H2RB	15 (33.3%)	27 (30.3%)	42 (31.3%)	0.724
Clopidogrel	5 (11.1%)	11 (12.4%)	16 (11.9%)	0.833
IS	5 (11.1%)	3 (3.4%)	8 (6%)	0.118
Diuretics	12 (26.7%)	29 (32.6%)	41 (30.6%)	0.483
Inhalers	9 (20%)	8 (9%)	17 (12.7%)	0.07
Warfarin	0 (0%)	6 (6.7%)	6 (4.5%)	0.097
Antidepressants	2 (4.4%)	6 (6.7%)	8 (6.7%)	0.596

Data are presented as n (%). Comparisons between groups were performed using the Chi-square test or Fisher's exact test, as appropriate. Statistically significant p values (<0.05) are shown in bold. Abbreviations: DEX, dexmedetomidine; DM, diabetes mellitus; HT, hypertension; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; ND, neurological disease; AF, atrial fibrillation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAID, non-steroidal anti-inflammatory drug; ASA, acetylsalicylic acid; OAD, oral antidiabetic drug; PPI, proton pump inhibitor; H2RB, histamine-2 receptor blocker; IS., immunosuppressive therapy.

4. Discussion

First of all, we would like to evaluate whether our analysis was consistent and reliable. At this point, lab parameters that are known as "mortality/severity indicators" such as WBC, PLT, CRP, PCT, sedim, D-dimer, LDH, Fibrinogen, Troponin, ALT, AST, and Ferritin were compared between the DEX and the non-DEX group.[12,13] The comparison analysis revealed no significant difference regarding either of these parameters and we consider that this result is a reliable indicator for the comparability of DEX between these groups. As for the effects of applied treatments on mortality rates, all of the patients received standard therapies that were recommended by the guidelines of the Ministry of Health in our country at that time. This reduces the effect of treatment modalities on the outcomes of the patients. There was also no significant difference in median ages, gender distribution, place of treatment (all patients were treated in the ICUs), and intubation rates between the groups. Therefore, without the effect of these parameters and applied treatments except DEX, the comparison of DEX treatment and its effects on the outcomes in our study group is reliable.

Nowadays, it is very well known that advanced age, male gender, and comorbidities are risk factors for advanced disease in COVID-19.[14] Concurrently, in our study group which consists of patients with severe COVID-19, the median age was 69.5. While the median age was higher in the non-DEX group (70) than in the DEX group (67), this difference did not reach a significant level. Male predominance was seen in both groups as expected. In a prospective observational study in

which 63 of 89 patients with severe COVID-19 were treated with DEX, HFNC and long periods of PP, the mean age was 67 ± 12, and 74% of the treatment group consisted of males.[15] These results are very similar to our study.

When we did a literature search regarding the articles studying the therapeutic value of DEX in patients with COVID-19, we could not find any prospective randomized controlled trials conducted with large patient populations. Except for three retrospective studies,[15-17] a few case reports, case series, and letters to the editor constitute all studies about this issue.[18-23] In the study Taboada et al. conducted, the clinical characteristics of 63 patients treated with long PP, DEX, and HFNC, 20 of whom failed therapy and 43 of whom experienced successful therapy were compared. 20.6% of the patients either died or remained in the ICU while 30.2% of the patients required endotracheal intubation.[15] A recent study investigating the hemodynamic and respiratory effects of dexmedetomidine sedation in 39 critically ill Covid-19 patients revealed that DEX administration was associated with improvement of partial oxygen pressure of arterial blood/fraction of inspired oxygen-ratio PF-ratio and with a decrease of Richmond Agitation and Sedation Score (RASS).[16] The most recent retrospective study on the DEX effect on 214 severe COVID-19 patients reported reduced mortality in their DEX group. However, in that study, all patients were intubated and patients started to receive DEX after the intubation in contrast to the general approach. In addition, dexamethasone use was significantly higher in the DEX group which might have affected this result.[17] Similarly, in a case series in which 11 patients were treated with helmet CPAP in the prone position with DEX infusion, 3 of the patients required invasive ventilatory support and among these 2 of them died (27% and 18% respectively).[19] However, in our study, the intubation rate was 72.4% and the mortality rate was 74.6% for all patients. This huge difference might have been caused by a few factors. Firstly, COVID-19 daily cases were very high in our country at the time our study was conducted.[24] Therefore, even some patients with SpO2<90% and/or respiratory rate (RR)>20/min had to be treated in the ward since the ICUs were full of patients with severe COVID-19. This situation might have caused a delay in the transfer of the patients from emergency rooms or wards to the ICUs. And this unavoidable delayed start of ventilatory support and DEX infusion might have caused these high mortality and intubation rates in our study group. However, in the beforementioned studies, Hamilton et al., Paternoster et al., and Taboada et al. reported that they dedicated special beds called high dependency units (HDU) for the patients requiring helmet CPAP and as soon as the SpO2 of the patients dropped to below 90% or PaO2/FiO2 dropped to below 200, they transferred them to ICUs. This rapid transfer process and easy access to intensive care resources might have been the reason for their lower mortality and intubation rates. Secondly, the known side effects of DEX infusion are mostly cardiac such as bradycardia and hypotension.[25] Although we could not reach the data regarding the withdrawal rate of DEX during the treatment from the medical files of the patients, as ICU doctors, we had to withdraw DEX infusion on several occasions especially due to bradycardia (HR<50 beat/min) after a few days of continuous infusion. If the intolerance rate had been higher in our study group, this could have caused shorter durations of DEX infusion and NIMV therapies and thus, higher mortality and intubation rates.

Except for one,[17] none of the studies mentioned above compared the parameters of the patients who received DEX therapy versus patients who received therapy without DEX in severe COVID-19. Although mortality and intubation rates were lower numerically in our DEX group, the difference was not statistically significant. Although there was no significant difference in the duration of intubation between the groups, the time between ICU admission and intubation was found to be significantly longer in the DEX group. This might be the most important result of our analyses in this study since treatments to avoid intubation or prolong the time before intubation are of vital importance and potentially life-saving due to high mortality rates reported for intubated patients with severe COVID-19.[12,13] Accordingly, the median time between ICU admission and intubation was found as 3 days in a similar study in which all 63 patients received long PP periods and HFNC treatment.[15] This gained time might help us to apply the potential treatments for severe COVID-19

such as dexamethasone, remdesivir, and tocilizumab for longer periods before intubation and thus, obtain better results.

Our non-DEX group contained significantly more patients with DM, CAD, and CHF than the DEX group. The DEX group did not include any patients with a history of cardiac disease as a result of our treatment protocol as we mentioned before. In the study of Hamilton et al., HT and CAD were more frequently found as comorbidities in the DEX group.[17] HT-hyperlipidemia[15] and HT-COPD[19] were the two most common comorbidities in similar studies whereas HT and DM were the two most common comorbidities in our study group. The predominance of the patients with DM in our non-DEX group might be caused by their fulminant course since DM is a well-known risk factor for higher mortality in COVID-19.[26,27] We hypothesize that their more rapid progression to endotracheal intubation and death as soon as they were transferred to ICUs might prevent them from receiving DEX treatment. Congruently, significantly less requirement of the patients under regular insulin therapy for DEX infusion may also be explained by this hypothesis. Our second hypothesis for the patients under insulin treatment is that they might be more familiar with the ICU setting and thus less agitated/anxious since these patients might have been frequently admitted to ICUs because of diabetic ketoacidosis or nonketotic coma. In a similar study, no significant difference was found between successful and failed therapy groups regarding home treatments, however, they included only ACEIs, anticoagulants, corticosteroids, and statins in the analysis.[15]

CPAP therapy was significantly associated with DEX infusion. Since one of the most important indications of DEX infusion is maintaining cooperation with NIMV techniques, it was not surprising for us to see more patients receiving CPAP in the DEX group. However, what is surprising was not seeing more patients receiving HFNC in the DEX group. Possible reasons for this condition might include the lack of equipment and presentation of the patient to the ICUs at the end stages of ARDS and thus directly applying CPAP or intubation by skipping the first step (HFNC). What should not be overlooked at this point is that patients receiving NIMV support constituted only 26 of the 45 patients treated with DEX which means 19 of the patients received DEX with the indication of either PP without NIMV support and/or solely delirium. This number was more than what we expected before the analysis.

Generally, the studies we mentioned above report that DEX can be a beneficial option in patients with severe COVID-19 especially to increase the patients' tolerance to NIMV support and long periods of PP. However, one letter to the editor drew attention to DEX-associated hyperpyrexia as a side effect and the dosage of infusion as a concern for the withdrawal phenomenon.[22] The author recommends using DEX with caution because of this potential side effect and narrow therapeutic index. In our study, no apparent beneficial effect of DEX has been shown on mortality and intubation rates, however, there are limitations of our study such as being retrospective single center, the missing data regarding withdrawal rates, unknown duration of infusion, and having a standardised sedation treatment protocol excluding some patients with cardiac comorbidities and a small sample size. Moreover, systematic data regarding hemodynamics-related infusion discontinuation (e.g., incidence of severe bradycardia or hypotension requiring treatment) were not fully retrievable from retrospective electronic records, which represents another limitation of our study.

5. Conclusion

In our study, although no apparent contribution of DEX to reducing mortality and intubation rates has been demonstrated, a significantly longer time before intubation was determined for the patients treated with this agent. Given the retrospective observational design and baseline differences between the study groups, the observed longer time to intubation should be interpreted as an association rather than evidence of a causal effect of dexmedetomidine. We think that this association might be a promising result for DEX in terms of its therapeutic value even if not as a mortality and intubation rate reducer, but as a time prolonger before intubation. Maybe this prolongation effect before intubation would rebound in future trials regarding the effect of DEX treatment in severe COVID-19 with large sample sizes as decreased intubation and mortality rates.

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Informed Consent Statement: This study was conducted using retrospectively collected, anonymized data. As no direct patient contact or intervention was involved and all data were analyzed anonymously, informed consent was waived by the Ethics Committee in accordance with national regulations and institutional policies.

genAI: No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by all authors.

Conflict of Interest: The authors declare that they have no conflict of interest.

Data Availability Statement: Due to institutional privacy policies, the datasets generated and/or analyzed during the current study are not publicly available, but they are available from the corresponding author upon reasonable request.

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