

DOES THE USE OF DEXMEDETOMIDINE AFFECT THE OUTCOMES IN PATIENTS WITH SEVERE COVID-19?

Kubilay İşsever¹, Ahmed Cihad Genç¹, Deniz Çekiç², Ahmed Bilal Genc³, Selcuk Yaylaci⁴, and AHMET NALBANT⁵

¹Sakarya Training and Research Hospital

²Sakarya Universitesi Tip Fakultesi

³Sakarya Universitesi

⁴Sakarya University

⁵Sakarya University Faculty of Medicine

July 23, 2021

Abstract

Objective: Dexmedetomidine (DEX) is a highly selective α_2 -adrenoceptor agonist that is increasingly used in the daily practice of intensive care units (ICUs) with its sedative, analgesic, anxiolytic, and immunoprotective effects. In this study, we aimed to analyze whether Dexmedetomidine improves the outcomes in patients treated in ICU. **Design:** A retrospective study **Place and Duration of Study:** Intensive care units (ICU) of Sakarya University Training and Research Hospital, Sakarya, Turkey, from October 2020 to February 2021 **Methodology:** The medical records of the patients were analyzed retrospectively. We included 134 patients in the study, in 45 of whom the treatment regimen included dexmedetomidine and 89 of whom were not treated with dexmedetomidine. Patients treated with DEX were defined as the “patient group”, whereas patients not treated with DEX were defined as “control group” and the parameters were compared between these groups. Obtained data were analyzed in the biostatistical program. **Results:** The median age of all patients was 64 and 62.7% of them were male. No significant difference was found between the groups in terms of median ages ($p>0.05$). The patients with diabetes mellitus (DM), congestive heart failure (CHF), and undergoing insulin treatment were significantly less treated with DEX ($p=0.04$, $p=0.03$, and $p=0.016$ respectively) whereas intravenous immunoglobulin (IVIG) therapy was found to be more frequently applied to the patient group ($p=0.043$). The median duration between ICU admission and the time of intubation was 4 days for the control group whereas it was 1 day for the patient group and the difference was strongly significant ($p=0.000$, $p<0.001$). The other analyses concerning lab parameters, mortality rates, intubation rates and durations, applied treatments, and comorbidities revealed no significant difference between the groups. **Conclusion:** Our study revealed that DEX therapy can help us to gain time before intubation however can not reduce mortality rates in severe COVID-19.

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 (2).

Providing effective sedation is of vital importance not only in the setting of ICU but also in surgical procedures since perioperative stress and inflammation might contribute to postoperative complications (1). Surgical

trauma induces a variety of stress responses including the release of stress hormones such as catecholamines and cortisol and inflammatory mediators such as interleukins and tumor necrosis factor- α . It may also cause immune dysfunction via CD4 T cells and all of these factors might contribute to increased risk of delayed wound healing, postoperative infections, morbidity, and mortality (1). Therefore, discovering multimodal therapies containing anxiolytic, analgesic, anesthetic, sedative, and immunomodulatory effects at the same time, is extremely important to resolve the aforementioned problems in the setting of ICU and surgery (3).

Dexmedetomidine (DEX) is a highly selective α_2 -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 potential 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 (4). 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 (2) (5). 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 (4) (5). These unique properties 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 (6).

A novel Coronavirus disease caused by SARS-CoV-2 was first detected in China in December 2019 and has become a pandemic causing the fatality of millions of people so far. A relevant part of the infected patients might present with acute respiratory distress syndrome (ARDS) and must be treated in ICUs (7) (8). Since evolving data reported high mortality rates for intubated patients, delaying or avoiding intubation as much as possible with non-invasive mechanical ventilation (NIMV) methods such as HFNC and CPAP especially with prone positioning has been the management of choice for a long time for 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 is 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 in COVID-19 due to its beforementioned 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 ICU.

METHODOLOGY

The medical records of the patients who were admitted to the ICUs of Sakarya University Training and Research Hospital with the diagnosis of COVID-19 between October 2020-February 2021 were analyzed retrospectively. Nasopharyngeal swab PCR test positivity was accepted as the gold standard for the diagnosis of COVID-19. Patients who were below the age of 18 and had a negative PCR test result were excluded from the study. We included 134 patients in the study, in 45 of whom the treatment regimen included dexmedetomidine and 89 of whom were not treated with dexmedetomidine. Patients treated with dexmedetomidine at any time during the treatment were defined as the "patient group", whereas patients without dexmedetomidine use were defined as "control group" and the parameters were compared between these groups. DEX infusion was applied to the patients who were agitated and non-cooperative for NIMV and prone positioning (PP). Patients who were progressed to endotracheal intubation were suspended from DEX infusion and started other anesthetics such as midazolam and propofol for deeper sedation. 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.

Descriptive analyses were presented using medians and interquartile range (IQR) for the non-

normally distributed variables. The Mann-Whitney U test was used for nonparametric tests to

compare these parameters. The chi-square test was used to compare the categorical variables between two groups. The categorical variables were presented as the frequency (% percentage). A p-value <0.05 was considered significant. SPSS statistical software version 21 was used for analyses.

RESULTS

The median age of the all patients was 69.5 whereas it was 67 for the patient group and 70 for the control group. There was not any significant difference in terms of median ages between the groups ($p=0.094$, $p>0.05$). 62,7% of the patients were male and there was no significant difference regarding to gender between the groups ($p=0.07$, $p>0.05$). Mortality rates were 71.1% for the patient group, 76,4% for the control group, and 74,6% for all patients, however these differences were not significant ($p=0.506$, $p>0.05$). There was also not any significant difference regarding to intubation rates between the groups ($p=0.292$, $p>0.005$). The median duration of intubation was 3 days for the patient group while it was 5 days for the control group however, the difference was not significant ($p=0.521$, $p>0.05$). The median duration between ICU admission of the patients and their time of intubation was 4 days for the control group whereas it was 1 day for the patient group and the difference was strongly significant ($p=0.000$, $p<0.001$). 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 (AST), and ferritin revealed a no significant difference between the groups ($p>0.05$) (Table 1).

We compared the patient and the control 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, only the patients with DM and CHF were significantly less treated with DEX ($p=0.04$, and $p=0.03$ 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 antiinflammatory drugs (NSAIDs), steroids, acetylsalicylic acid (ASA), metformin, other oral antidiabetics (OADs), insulin, proton pump inhibitors/histamine-h2 receptor blockers (PPI/H2RB), klopidoogrel, immuno-suppressive agents (IS), diuretics, inhaler treatments (IT), warfarin and antidepressants (AD) were included in the analysis. Among these, only the patients with history of insulin use were significantly less treated with DEX ($p=0.016$). There was no other significant difference regarding to history of drug use between the groups (Table 2).

Last but not least, we compared the groups with respect to the treatments patients received during their stay in the ICUs. Plasmapheresis, convalescent plasma (CP), dexamethasone, pulse steroid ([?] 250 mg of methylprednisolone), intravenous immunoglobulin (IVIG), favipiravir, tocilizumab (TOC), low molecular weight heparin (LMWH), famotidine, moxifloxacin (MOX), and broad-spectrum antibiotics (BSA), CPAP, and HFNC were included in the analysis as the applied treatments. Among these, only IVIG and CPAP therapy was found to be more frequently used in the patient group than the control group ($p=0.043$, and $p=0.001$ respectively, $p>0.05$). No other significant association was found between the other treatments and the study groups (Table 3).

DISCUSSION

First of all, we would like to evaluate whether our analysis was consistent and reliable. In 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 patient and control group (12) (13). The comparison analysis revealed no significant difference regarding neither of these parameters and we consider that this result is a reliable indicator for the comparability of DEX between these groups. Besides, since no significant difference was found with respect to these lab parameters between the groups, our result revealing no significant difference regarding mortality would also be expected and is

compatible with other analyses. As for the effects of applied treatments upon mortality rates, most of the patients received standard therapies that were recommended by the guidelines of the Ministry of Health in our country at that time. The recommended therapies for the patients with severe COVID-19 were favipiravir, steroids (dexamethasone [?] 8mg of methylprednisolone [?] 40 mg), and LMWH at the time at which the study group was treated in the ICUs. As you can see from Table 3 more than 90% of the patients received these standard therapies (percentage of the patients receiving dexamethasone + pulse steroid was between 85-90) revealing that there was no significant difference regarding the applied treatments between the groups. There was also no significant difference in terms of 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 such as DM, HT, and CAD are risk factors for advanced disease in COVID-19 (14). Concurrently, in our study group which consists of patients with severe COVID-19, median age was 69.5. While the median age was higher in the control group (70) than in the patient group (67), this difference did not reach a significant level ($p=0.094$, $p>0.05$). 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, mean age was 67 ± 12 and 74% of the treatment group consisted of male patients (15). These results are very similar to our study. We would also like to point out that PP up to 16 hours a day was also applied to all patients in our study who were able to tolerate as a part of standard therapy.

When we made a literature search regarding to the articles studying therapeutic value of DEX in patients with COVID-19, we could not find any randomised controlled trials conducted with large patient populations. Except one study which we mentioned above (15), a few case reports, case series, and letters to editor constitute all studies about this issue (15) (16) (17) (18) (19) (20) (21). Among these, the study conducted by Taboada et al. was the most appropriate candidate to compare our results with. In that study, clinical characteristics of 63 patients treated with long PP, DEX, and HFNC, 20 of whom with failed therapy and 43 of whom with 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. In a case series in which 11 patients were treated with helmet CPAP in the prone position with DEX infusion, 2 of these patients died and 3 of them required invasive ventilatory support (18% and 27% respectively)(17). 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 that time at which our study was conducted (22). Therefore, even some patients with $SpO_2 < 90\%$ and/or respiratory rate (RR) $> 20/\text{min}$ 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 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, 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 SpO_2 of the patients dropped to below 90% or PaO_2/FiO_2 dropped to below 200 mmHg 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 (23). Although we could not reach the data regarding the discontinuation rate of DEX during the treatment from the medical files of the patients, as ICU doctors we had to decide discontinuation of DEX infusion on several occasions especially due to bradycardia ($HR < 50 \text{ beat/min}$). If the intolerance rate would have 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.

None of the studies mentioned above compared the parameters of the patients who received DEX therapy versus patients who received standard therapy in patients with COVID-19. From this point of view, our study is unique and can contribute to the literature. Although mortality and intubation rates were lower numerically

in our study group, the difference was not statistically significant. Although there was no significant difference regarding the duration of intubation between the groups, the time between ICU admission and intubation was found to be longer in the patient group (Table 1). 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). With this result, we think that DEX proved its therapeutic value even if not as a mortality and intubation rate reducer, but as a time prolonger before intubation in our study. 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). Maybe this time prolongation effect before intubation would rebound on future trials with large sample sizes as decreased intubation and mortality rates.

Comparison of lab parameters revealed no significant difference between the groups which was considered as a healthy indicator for comparability of DEX between the groups as we mentioned before. In the study conducted by Taboada et al., lab parameters such as lymphocyte count, LDH, D-dimer, CRP, PCT, and Ferritin were compared between the group with response to DEX, HFNC, and PP therapy and the group with no response to therapy. Neither of these comparisons revealed a significant difference between the groups (15).

Our control group who were treated without DEX contained significantly more patients with DM, and CHF than the patient group (Table 2). In the similar study, no significant difference was found regarding co-existing conditions between the groups (15). HT-hyperlipidemia (15) and HT-COPD (17) were the two most common comorbidities in similar studies whereas HT and DM were the two most common co-existing condition in our study group. Predominance of the patients with DM and CHF in our control group might be caused by their fulminant course since these two co-existing conditions are known as risk factors for higher mortality (24) (25). Our hypothesis is 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 to ICU setting and thus less agitated/anxious since these patients might be frequently admitted to ICUs because of diabetic ketoacidosis. In the 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).

Among all the treatments applied to the patients with severe COVID-19, only IVIG and CPAP were significantly associated with DEX infusion (Table 3). 4 of 5 patients (80%) were treated with DEX infusion. Although IVIG group has a small number of patients the percentage is high. When we searched for the possible etiology of this situation we found out that headache, flushing, malaise, and pyretic reactions are common side effects of this therapy (26) (27). This side effects may easily cause delirium, anxiety, and agitation when occurred. Our second hypothesis for these patients is that since IVIG is a very expensive treatment option, clinicians might have applied this valuable option to younger patients with less risk factors. Therefore these patients could have remained in NIMV support for longer and received 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 patient group. However, what is surprising was that not seeing more patients receiving HFNC in the patient group. Because the standard treatment algorithm for patients with severe respiratory failure was PP + HFNC with or without sedatives, if not responsive PP + CPAP, if not responsive endotracheal intubation respectively. Possible reasons for this condition might include the lack of equipment, 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), and the choice of clinicians as a result of their experience (found ineffective?). In a similar study in which all the patients received HFNC support, there was not any significant difference regarding hospital medical treatments between the successful and failed therapy groups (15). 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 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 dosage of infusion as a concern for the withdrawal phenomenon (20). 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. Performing in a single center, the missing data regarding withdrawal rates and causes of DEX infusion, being retrospective, and having a small sample size were the limitations of our study.

CONCLUSION

In our study, although no apparent contribution of DEX on reducing mortality and intubation rates has been demonstrated, a significantly longer time before intubation was determined for this agent. Patients with DM, CHF, and on insulin therapy less required DEX infusion whereas patients treated with IVIG for severe COVID-19 more required DEX infusion. Prospective randomized controlled trials with large sample sizes are needed to decide whether DEX therapy has a positive effect on mortality and intubation rates in patients with COVID-19.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

ETHICAL APPROVAL

We obtained approval from Sakarya University Ethical Committee on 27 April 2020 with the document number "187".

PATIENTS' CONSENT

Consent for participation in this study was not obtained from patients as the data was collected from the medical record system of the hospital without disclosing the identity of participants.

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