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ORIGINAL ARTICLE

A High-Dose Corticosteroid Treatment Increases Coronavirus Disease of 2019 Mortality in Intensive Care Units

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ABSTRACT

Objectives: The study is aimed to investigate the association between different corticosteroid treatment regimens and clinical status, complications, mechanical ventilation requirement, and intensive care unit (ICU) mortality in individuals diagnosed with Coronavirus Disease of 2019 (COVID-19).

Materials and Methods: This is a descriptive retrospective study. Patients admitted to the ICU for COVID-19 and treated with low- or medium-dose corticosteroid therapy (methylprednisolone at a dose of 0.5-1 mg/kg for 7-10 days) were compared with patients treated with high-dose pulse corticosteroid therapy (methylprednisolone at varying doses of 250 mg, 500 mg or 1000 mg for 3-7 days) in addition to standard therapy because of increased pulmonary infiltrate and elevated inflammatory markers during clinical monitoring. All demographic and clinical data, including age, sex, clinical course, laboratory findings, discharge status, 28-day mortality, intubation status, acute physiological assessment and chronic health evaluation II score, Charlson Comorbidity Index, and sequential organ failure assessment score, were recorded.

Results: Corticosteroid treatment was administered to 689 (88.3%) of 780 COVID-19 ICU patients between April 2020 and October 2021. The overall mortality rate was 45.1% (n= 352). When the mortality rates of patients were compared according to the corticosteroid dose, the mortality rate in the low-to-medium-dose group (40%) was significantly lower than that in the high-dose group (76%). In addition, significant deterioration in laboratory and clinical parameters was observed in the high-dose corticosteroid group.

Conclusion: High mortality, adverse effects, and complications were significantly increased when high-dose corticosteroids were administered. Corticosteroid therapy should be used cautiously according to the patient's clinical condition, disease stage, comorbidities, and systemic or organ reserves.

Keywords: COVID-19, intensive care unit, corticosteroid treatment, mortality

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organization (WHO) on January 11, 2020, because of its rapid global spread following the identification of acute respiratory distress syndrome (ARDS) and pneumonia in China. Approximately 80-85% of patients are asymptomatic or present with mild upper respiratory symptoms, whereas approximately 20% present with severe clinical symptoms.[1] In addition, severe pneumonia and respiratory failure may occur in 2-5% of patients. Elevated laboratory parameters, such as D-dimer, fibrinogen, and C-reactive protein (CRP), suggest that the thrombo-inflammatory mechanism plays an active role. An intense cytokine storm with immunological and pathological mechanisms is observed in patients with a severe clinical course. The intense inflammatory process in the clinic leads to pneumonia, ARDS, respiratory failure, and hospitalization in

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about 2-9% of cases and may even require intensive care unit (ICU) and mechanical ventilation.[2]

However, aspects of the immunopathology and management of SARS-CoV-2 infection remain unresolved. Many treatment protocols are in the research phase due to uncertainty regarding the treatment of severe respiratory failure. Molnupiravir, hydroxychloroquine, favipiravir, anticoagulant therapy, and antibiotic treatment are used in the initial treatment of the disease. As the clinical course worsens, plasma, immunoglobulin, immunomodulator, tocilizumab, interleukin antibody, and steroid treatments are used as advanced treatments. Despite the intensive use of hydroxychloroquine, favipiravir, lopinavir, redeliver, ritonavir, and interferon-beta, there are many controversial studies on the effectiveness of these drugs in mortality and even the efficacy of treatment.[3] Although molnupravir reduces mortality, more clinical studies are needed to prove that.[4]

Regarding the use of steroids in patients with Coronavirus Disease of 2019 (COVID-19) and SARS-CoV-2 infection, steroid treatment is not recommended if the patient does not have hypoxemia.[5] However, if hypoxemia is present, steroids are used extensively to prevent thrombo-inflammation and to reduce and suppress the severity of the cytokine storm in pneumonia and ARDS. Three stages of SARS-CoV-2 disease have been defined based on clinical and laboratory findings. In stage-1, there is no lung or specific organ involvement in the viral response phase, in stage-2, there are pulmonary infiltrates in the lung in the pulmonary phase (in stage 2A, there is no hypoxemia, while in stage 2B, the oxygen saturation is below 96 and hypoxemia is observed), and in Stage-3, there is a hyperinflammatory stage where the lung involvement is intense (> 50%). Although antiviral treatment is recommended in Stage-1 and Stage-2A, it is thought that anti-inflammatory treatments (such as corticosteroids, interleukin antibody treatments, and cytokine adsorption therapy) may be more effective because of the hyperinflammation in Stage-2B and Stage-3.[6] Corticosteroids have both stimulatory and suppressive effects on the immune system, especially at high doses, depending on the duration of use and blood levels.[7] These drugs suppress inflammation and limit the effects of inflammatory cytokines and chemokine when a hyperinflammatory state develops in COVID-19.[8] The corticosteroid treatment protocols used in the trials are quite different. It still needs to be determined the appropriate dose for the therapeutic efficacy of corticosteroids in patients with COVID-19, and the use of different steroid molecules may produce different results. In patients with respiratory distress, severe lung involvement, and life-threatening organ failure, low doses of 1 mg/kg and high doses of 250 mg, 500 mg, or 1000 mg of methylprednisolone are recommended, depending on the patient's clinical assessment.[9] In the COVID-19 treatment guideline from the Turkish health authority, it was emphasized that low-to-medium-dose methylprednisolone could be started at 0.5-1 mg/kg in Stage-2B and Stage-3 patients, and then the dose can be gradually reduced over 7-10 days. In addition, the section in the guideline focusing on the treatment of severe pneumonia, ARDS, septic shock, and sepsis, recommends considering pulse methylprednisolone administration at a dosage of at least 250 mg per day for a period of 3-7 days. This treatment option may be considered for patients who experience a deterioration in their clinical status within 24 to 48 hours or demonstrate an increase in oxygen requirements despite receiving low-dose corticosteroid therapy. It has been suggested that after high-dose corticosteroid therapy, the dose may be tapered in patients with clinical worsening or high acute phase reactants.[10]

The aim of this study was to evaluate the relationship between the corticosteroid treatment protocols used in the COVID-19 ICU and the patient's clinical status, corticosteroid dose, complications, need for mechanical ventilation, and mortality.

MATERIALS AND METHODS

This clinical study is a descriptive retrospective study. The study population consisted of individuals diagnosed with COVID-19 who were admitted to our tertiary care hospital's COVID-19 ICU. The principles of the Declaration of Helsinki were followed in all the study phases. This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bozyaka Training and Research Hospital after obtaining permission from the Ministry of Health COVID-19 Scientific Research and Evaluation Commission (protocol number: 21.05.2020-222). The data were collected from April 2020 to October 2021 and included patients receiving corticosteroid treatment.

In the COVID-19 ICU, patients were treated with corticosteroids according to ethical treatment principles, considering vital signs, laboratory values, comorbidities, resorptive organ capacity, and the adverse effects of corticosteroids. In patients with ARDS, diffuse lung infiltrates, elevated clinical and imaging lung infiltrates, and elevated inflammatory markers, pulmonary steroid therapy was incorporated as an adjunct to the standard treatment protocol. According to the COVID-19 treatment guideline prepared by the health authority of our country, low-to-medium-dose methylprednisolone was started at 0.5-1 mg/kg and gradually decreased over 7-10 days. High-dose methylprednisolone was administered at 250 mg, 500 mg, or 1000 mg/day for 3-7 days to patients whose clinical condition worsened within 24-48 hours or whose oxygen requirements increased despite low-dose corticosteroid therapy. The dose was then tapered over 3-7 days.

The data collected for these patients encompassed a wide range of parameters (including age, sex, oxygen saturation levels, intubation status, clinical recovery, discharge status, length of stay, mortality, hemogram values, and selected laboratory values, such as glucose, urea, creatinine, alanine transaminase, aspartate aminotransferase, total bilirubin, creatine kinase, lactate dehydrogenase, D-dimer, and fibrinogen). Additionally, prothrombin time, activated prothrombin time, activated partial thromboplastin time, international normalized ratio, CRP, ferritin, procalcitonin (PCT), arterial blood gas values, sequential organ failure assessment (SOFA), acute physiological assessment and

chronic health evaluation (APACHE) II scores were included in the data collection process.

Statistical analysis

The normality of data distribution was determined using the Kolmogorov-Smirnov test or the Shapiro-Wilk test. Normally distributed variables are expressed as means ± standard deviations, whereas categorical variables are expressed as frequencies (n) and percentages. Variables that were not normally distributed were defined using median and interquartile range. Two group comparisons were performed by using independent Student's t-test or Mann-Whitney U test, where appropriate. Fisher's exact chi-square test or Pearson's chi-square test was used to compare categorical variables. *p* values below 0.05 were considered indicative of statistical significance.

RESULTS

After 18 months of clinical observation in the COVID-19 ICU between April 2020 and October 2021, data from 780 patients were analyzed. Of the 780 patients, 91 did not receive steroid therapy due to contraindications (gastrointestinal bleeding, hyperglycemic coma, severe acid-base electrolyte disturbances, and those receiving corticosteroid immunosuppressive therapy). Patients were 429 (55%) male and 351 (45%) female. The number of patients who received corticosteroid therapy was 689 (88.3%). The mortality rate was 45.1% (n= 352). The mortality rate was 64.9% in men (n= 229) and 35.1% in females (n= 123). The number of patients younger than 65 years was 359 (46.0%), and the number of patients 65 years and older was 421 (54.0%). Among patients younger than 65 years old, the mortality rate was 52.7% (n= 185), whereas for patients 65 years and older, the mortality rate was 47.3% (n= 167).

The mean age was 63 ± 9 years in the low-medium-dose corticosteroid group and 64 ± 12 years in the high-dose corticosteroid group. The male/female was 285 (50.6%)/278 (49.4%) in the low-medium-dose group and 53 (42.1%)/73 (59.9%) in the high-dose group. The Charlson Comorbidity Index of the groups was 10 ± 3 in the low-to-medium-dose group and 11 ± 4 in the high-dose group. There are no statistically significant differences between the two groups regarding these parameters ($p > 0.05$).

The effect of the corticosteroid treatment dose (high and low-medium-doses) given to patients with COVID-19 in the ICU on mortality and intubation of the patients is shown in Table 1.

The effects of the dose (high and low-medium-doses) on laboratory parameters, SOFA score, APACHE II score, and length of stay in COVID-19 patients receiving corticosteorid therapy in the ICU are presented in Table 2.

DISCUSSION

The aim of using corticosteroids in SARS-CoV-2 infection was to reduce pulmonary inflammation, suppress destructive inflammation, and reduce fibrosis. However, factors such as corticosteroid-related adverse effects, reversible metabolic and organ failure, complications such as hyperglycemia and gastrointestinal bleeding, and the fact that the real benefit of corticosteroids on survival is controversial limit the use of corticosteroids.[11] The WHO Rapid Evidence Appraisal for COVID-19 Therapies trial found that systemic steroids reduced 28-day mortality from all causes compared with standard care or placebo in COVID-19 disease.[12] Many studies have compared their effectiveness against COVID-19. A retrospective analysis was conducted on 200 patients diagnosed with ARDS to compare the effectiveness of different treatments for COVID-19. The study found that patients receiving methylprednisolone had a lower mortality rate than those receiving other treatments.[13] In a study conducted in Pakistan, there was no difference in ICU and ventilator use and mortality between the two groups of patients receiving dexamethasone (n= 35) or methylprednisolone (n= 65) in the intermediate ICU. Simultaneously, no statistically significant difference was observed in adverse effects.[14] The literature on corticosteroid treatment has revealed no difference in efficacy after administering equivalent doses of corticosteroid. Our study used methylprednisolone, which is readily available in our hospital. Low-dose (0.5 mg/kg) or medium-dose (1 mg/kg) methylprednisolone was administered

Table 1. Effect of dose on mortality and intubation among patients with COVID-19 receiving corticosteroid treatment in the ICU

	Corticosteroid therapy dose		Total (n%)	*p* value	χ^2
	Low-medium dose (n%)	High dose (n%)			
Mortality					
Yes	225 (40)	96 (76)	321 (46.6)	< 0.0001	54.2
No	338 (60)	30 (24)	368 (53.4)		
Total	563 (81.7)	126 (18.3)	689		
Intubation					
Yes	304 (54)	98 (78)	402 (64.4)	< 0.0001	24.0
No	259 (46)	28 (22)	287 (35.6)		
Total	563 (81.7)	126 (18.3)	689		

Pearson's chi-squared analysis was used and $p < 0.05$ was considered significant, ICU: Intensive care unit, COVID-19: Coronavirus disease 2019

Table 2. Effect of dose on laboratory parameters, SOFA score, APACHE II score and length of stay among patients with COVID-19 receiving corticosteroid treatment in the ICU

	Corticosteroid therapy dose		
Parameters	**High dose**	**Low-medium dose**	***p* value**
Hemoglobin	9.7 ± 2.2	11.7 ± 1.7	$p < 0.0001$
Leukocyte*	9550 ± 5900	8600 ± 5300	$p = 0.075$
Thrombocyte*	211000 ± 153000	209000 ± 140000	$p = 0.887$
Glucose*	109.2 ± 79.2	82.2 ± 33.6	$p < 0.0001$
Urea*	41.4 ± 33.9	37.3 ± 22.1	$p = 0.092$
Creatinine*	3.2 ± 0.9	1.6 ± 0.7	$p < 0.0001$
ALT*	44.6 ± 36.4	42.2 ± 25.5	$p = 0.369$
AST*	70.4 ± 20.5	67.7 ± 21.0	$p = 0.177$
Bilirubin-total*	4.0 ± 3.9	1.6 ± 1.2	$p < 0.0001$
CK*	641.0 ± 766.1	185.5 ± 32.1	$p < 0.0001$
LDH*	111.9 ± 48.8	108.2 ± 51.1	$p = 0.459$
D-dimer*	1425.5 ± 658.2	616.2 ± 582.2	$p < 0.0001$
Fibrinogen	990.2 ± 298.3	602.3 ± 198.7	$p < 0.0001$
PT*	13.6 ± 15.4	9.9 ± 10.1	$p < 0.0002$
aPTT	38.6 ± 15.2	29.7 ± 4.3	$p < 0.0001$
INR*	2.4 ± 2.7	1.6 ± 3.2	$p = 0.048$
CRP**	410.2 ± 111.3	291.1 ± 12.3	$p < 0.0001$
Ferritin*	446.5 ± 389.7	212.4 ± 297.7	$p < 0.0001$
PCT*	41.3 ± 9.2	32.9 ± 4.5	$p < 0.0001$
SOFA score	13.2 ± 2.6	8.5 ± 1.6	$p < 0.0001$
APACHE II score	21.2 ± 3.3	16.1 ± 2.3	$p < 0.0001$
Length of stay*	11.4 ± 6.0	7.7 ± 5.9	$p < 0.0001$

Independent t-test was used and $p < 0.05$ was considered significant. *Mann-Whitney U test was used, ** Pearson's chi-square test was used, SOFA: Sequential organ failure assessment, APACHE: Acute physiological assessment and chronic health evaluation, COVID-19: Coronavirus disease 2019, ALT: Alanine transaminase, AST: Aspartate aminotransferase, CK: Creatine kinase, LDH: Lactate dehydrogenase, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, CRP: C-reactive protein, PCT: Procalcitonin

to patients in the mild and moderate clinics. During clinical observation, the weekly dose was reduced in patients who received corticosteroids for 7 or 10 days and showed clinical improvement. High-dose methylprednisolone (250, 500, and 1000 mg/day was given for 3-7 days, after which the weekly dose was gradually reduced in patients with clinical worsening within 24 or 48 hours.

The randomized evaluation of COVID-19 therapies trial, a significant multicenter randomized controlled trial, was conducted in the United Kingdom to assess the efficacy of corticosteroids in patients diagnosed with COVID-19. This trial was designed to compare mortality rates between the corticosteroid-treated groups and the standard care groups and to evaluate the effectiveness of other potential treatments, such as hydroxychloroquine, favipiravir, and lopinavir/ritonavir, in patients hospitalized for COVID-19. In the corticosteroid group, patients received oral or intravenous dexamethasone at a dose of 6 mg daily until discharge after 10 days of clinical observation. The primary outcomes examined in this study were 28-day mortality, clinical improvement, and the need for mechanical ventilation. Results from the study revealed a mortality rate of 22.9% in the group receiving dexamethasone (n= 2104) compared with 25.7% in the standard care group (n= 4321).[15] A single-center retrospective study by Fernández-Cruz et al.[16] no significant difference in survival and mortality was observed between patients with COVID-19 pneumonia treated with steroids and those treated with high-dose pulse steroids or 1 mg/kg/day steroids. In patients receiving corticosteroids (n= 126), the mortality rate was 76%, whereas the ICU mortality

rate was 45.1% for all patients (n= 780) and 40% for those receiving low-to-medium-dose corticosteroids (n= 563). Higher mortality rates were observed in patients receiving high-dose corticosteroids. However, limited information is available on the use of high-dose corticosteroids. In a study by So et al.[17] involving seven patients, a 3-day pulse steroid treatment (500-1000 mg/day methylprednisolone) was administered and gradually discontinued, successfully weaning off mechanical ventilation within 1 week. In contrast to other studies, our study showed that patients receiving high-dose corticosteroids had more extended stays in the ICU and higher rates of mechanical ventilation and intubation. Specifically, the intubation rates were 54% and 78% in the low- and medium-dose groups, respectively.

In a prospective randomized controlled trial of pulse steroid therapy in Iran, standard care and treatment (n= 34) were compared with 250 mg intravenous methylprednisolone for three days in addition to this treatment (n= 34) in terms of cure and death rates. The study findings showed a notable favorable difference associated with the use of methylprednisolone. However, these results need to be interpreted, taking into account several limitations in the study design and the relatively small sample size.[18] In the study by Monreal et al.,[19] an observational study retrospectively compared high-dose (≥ 250 mg/day) (n= 177) and standard-dose (≤ 1.5 mg/kg/day) (n= 396) methylprednisolone treatments in patients with severe COVID-19. The study revealed a statistically significant increase in mortality in patients receiving high-dose corticosteroids compared with those receiving standard-dose therapy (18.6% vs. 39%). This difference could be attributed to the greater disease severity observed in the high-dose corticosteroid group. However, it is worth noting that similar mortality rates were observed in younger individuals, suggesting that factors other than age may contribute to the outcomes. It has been emphasized that it is necessary to be very careful when administering pulse steroid therapy, especially in patients over 70. Our study was consistent with the patient characteristics and findings of Monreal et al.[19] One of the similarities in our study was that the patients who received high-dose corticosteroids had clinically worsening symptoms. The mortality rates were 76% and 40% in the high- and low-dose corticosteroid groups, respectively. In addition to higher mortality rates in patients receiving high-dose corticosteroids, high APACHE, SOFA, fibrinogen, D-dimer, hemoglobin, urea, creatinine, hyperglycemia due to adverse effects, and serious complications, such as gastrointestinal bleeding and renal failure, were more common. In a study conducted in our country, patients with ARDS and COVID-19 were treated with methylprednisolone at different doses (low or high) and durations. This study aimed to compare various factors, such as lactate levels, PCT levels, neutrophil-to-lymphocyte ratio, intubation time, weaning time, need for hemoperfusion, length of stay, and prognosis among the treatment groups. It has been reported that different doses and durations of methylprednisolone. The study's limited number of patients and some data collection limitations have been emphasized.[20]

CONCLUSION

In conclusion, when using corticosteroids for COVID-19, the treatment strategy should be determined after considering the adverse effects of steroids and systemic complications. Corticosteroid treatment should be carefully applied according to the patient's clinical situation, disease stage, comorbidities, and systemic or organ reserves.

The mortality rate was lower with low- and medium-dose steroid use in corticosteroid treatments for COVID-19. In addition to high mortality rates, high-dose steroids are associated with increased adverse effects and complications. The evidence on steroid treatment for COVID-19 is insufficient, and more evidence-based systematic clinical trials are needed to establish an appropriate corticosteroid protocol.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bozyaka Training and Research Hospital after obtaining permission from the Ministry of Health COVID-19 Scientific Research and Evaluation Commission (protocol number: 21.05.2020-222).

Authorship Contributions

Surgical and Medical Practices: İ.D., H.Ö., Ş.Ç., Concept: İ.D., İ.Y., H.Ö., Ş.Ç., Design: İ.D., İ.Y., H.Y., Data Collection or Processing: İ.D., İ.Y., H.Ö., Ş.Ç., Analysis or Interpretation: İ.D., İ.Y., H.Y., Literature Search: İ.Y., H.Y., Writing: İ.D., İ.Y., H.Y.

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