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Does high-dose corticosteroid treatment increase COVID-19 mortality in intensive care units?

Running title: High-dose corticosteroid increases COVID-19 mortality

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ABSTRACT
Objectives: We aimed to investigate the association between different corticosteroid treatment regimens and clinical status, complications, requirements for mechanical ventilation, and intensive care unit (ICU) mortality in individuals diagnosed with COVID-19.
Materials and Methods: This is a cross-sectional, descriptive, retrospective study. Patients admitted to the ICU for COVID-19 and treated with low-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, 500 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, APACHE II score, Charlson Comorbidity Index, and SOFA 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 dose of corticosteroids used, the mortality rate in the low-medium-dose group (40%) was statistically significantly lower than in the high-dose group (76%). In addition, a significant deterioration in laboratory and clinical parameters was observed in the high-dose corticosteroid group.
Conclusion: High mortality, corticosteroid adverse effects, and complications were found to increase significantly when high doses of corticosteroids were used. Corticosteroid therapy should be used cautiously according to the patient's clinical condition, stage of disease, comorbidities, and systemic or organ reserves.
Key words: COVID-19, intensive care unit, corticosteroid treatment, mortality

INTRODUCTION

SARS-CoV-2 was declared a global pandemic by the World Health Organization (WHO) on 11 January 2020 due to its rapid global spread following the identification of ARDS and pneumonia in China. Approximately 80-85% of cases are asymptomatic or present with mild upper respiratory symptoms, and approximately 20% present with severe clinical symptoms.[1] In addition, severe pneumonia and respiratory failure may occur in 2-5% of cases (the elevation of laboratory parameters such as D-dimer, fibrinogen, and C-reactive protein (CRP) suggests that the thrombo-inflammatory mechanism plays an active role). An intense cytokine storm with immunological and pathophysiological 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 about 2-9% of cases and may even require intensive care unit (ICU) and mechanical ventilation.[2]

There are still unresolved aspects of the immunopathology and management of SARS-CoV-2 infection. Many treatment protocols are in the research phase due to the uncertainty of treating the disease, which causes 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 treatments, immunoglobulin treatments, immunomodulator treatments, tocilizumab, interleukin antibody treatments, and steroid treatments are used as advanced treatments. Despite the intensive use of hydroxychloroquine, favipiravir, lopinavir, remdesivir, ritonavir, and interferon-beta in treatments, 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 using steroids in cases of COVID-19 with 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. Stage-1; there is no lung or specific organ involvement in the viral response phase; stage-2; there are pulmonary infiltrates in the lung in the pulmonary phase (2A is the stage where there is no hypoxemia, while 2B is when the oxygen saturation is below 96 and hypoxemia is observed), Stage-3; a hyperinflammatory stage where the lung involvement is intense (>50%). While antiviral treatment is recommended in stage-1 and stage-2A, it is thought that anti-inflammatory treatments (such as corticosteroids, interleukin antibody treatments, and CytoSorb treatments) 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 chemokines when a hyperinflammatory state develops in COVID-19 infection.[8] The corticosteroid treatment protocols used in the trials are quite different. It still needs to be determined what dose is appropriate for the therapeutic efficacy of corticosteroids in COVID-19 patients, 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-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” suggests considering the administration of pulse methylprednisolone 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 24-48 hours or demonstrate an escalation 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]

Our study evaluated the relationship between the corticosteroid treatment protocols used in the COVID-19 ICU and patients' clinical status, corticosteroid dose, complications, need for mechanical ventilation, and mortality.

MATERIAL AND METHODS

This clinical study is a cross-sectional, descriptive, retrospective study. The study population consists 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 guidelines were followed in all study phases. The study was initiated after approval from the Health Sciences University Izmir Bozyaka Training and Research Hospital Clinical Research Ethics Committee with protocol number 21.05.2020-222. The data was gathered from April 2020 to October 2021 and included corticosteroid treatment patients.

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 adverse effects of corticosteroids. In patients with ARDS, diffuse lung infiltrates, elevated clinical and imaging lung infiltrates, and heightened 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-medium-dose methylprednisolone was started at 0.5-1 mg/kg and gradually decreased over 7-10 days. High-dose methylprednisolone was given 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, gender, oxygen saturation levels, intubation status, clinical recovery, discharge status, length of stay, mortality, hemogram values, selected laboratory values such as glucose, urea, creatinine, alanine transaminase (ALT), aspartate aminotransferase

(AST), total bilirubin, creatine kinase (CK), lactate dehydrogenase (LDH), D-dimer, and fibrinogen. Additionally, prothrombin time (PT), activated prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), C-reactive protein (CRP), ferritin, procalcitonin (PCT), arterial blood gas values, as well as sequential organ failure assessment (SOFA) and acute physiological assessment and chronic health evaluation (APACHE) II scores were included in the data collection process.
Results were presented using different statistical measures depending on the nature of the variables. Normally distributed variables are expressed as means ± standard deviations, categorical variables as frequency (n) and %. Variables not normally distributed were defined using the median and interquartile range. The normality of data distribution was determined using the Kolmogorov-Smirnov test or the Shapiro-Wilk test. Means were compared between groups using the t-test, and medians were compared using the Mann-Whitney U test. Fisher's exact chi-squared or Pearson's chi-squared test was used to compare categorical variables. *p* values below 0.05 were considered significant.

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, hyperglycaemic 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 (cortisone) 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 women (n=123). The number of patients under 65 years of age 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), while 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. Gender distribution as 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, respectively. Charlson Comorbidity Index (CCI) of the groups was 10±3 in the low-medium-dose group and 11±4 in the high-dose group. There is no statistically significant difference between the two groups for these parameters ($p>0.05$).

The effect of the cortisone treatment dose (high and low-medium-doses) given to COVID-19 patients in the intensive care unit on mortality and intubation of the patients and statistical data on these are shown in Table 1.
The effect 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 cortisone therapy in the intensive care unit and statistical data on these are given 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 REACT (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] There are many studies comparing their effectiveness in COVID-19. A retrospective analysis was conducted on 200 patients diagnosed with acute respiratory distress syndrome (ARDS) to compare the effectiveness of different treatments for COVID-19. The study found that patients receiving methylprednisolone had a lower mortality rate than other treatments.[13] In a study conducted in Pakistan, there was no difference in ICU and ventilator use and mortality between 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 states no difference in efficacy after administering equivalent doses of cortisone. Our study used methylprednisolone, which is readily available in our hospital. Low-dose of 0.5 or medium-dose of 1 mg/kg methylprednisolone was given to patients with 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 mg, 500 mg, 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 RECOVERY (Randomised Evaluation of COVID-19 Therapies) trial, a significant multi-center randomized controlled trial, was conducted in the United Kingdom to assess the efficacy of corticosteroids in patients diagnosed

with COVID-19. The trial was designed to compare mortality rates between groups receiving corticosteroids and those receiving standard care 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 either oral or intravenous dexamethasone at a dose of 6 mg daily until discharge after ten days of clinical observation. The primary outcomes examined in the study included 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 to 25.7% in the standard care group (n=4321).[15] A single-center retrospective study by Fernandez et al.[16] found no significant difference in survival and mortality 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%, while 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 research is available on the use of high-dose corticosteroids. In a study by So et al.[17] involving seven cases, a 3-day pulse steroid treatment (500-1000 mg/day methylprednisolone) was administered and gradually discontinued, successfully weaning off mechanical ventilation within one week. In contrast to other studies, our research showed that patients receiving high doses of corticosteroids had more extended stays in the ICU and higher rates of mechanical ventilation and intubation. Specifically, the intubation rate was 54% in the low-medium-dose group and 78% in the high-dose group.

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 using methylprednisolone. However, these results need to be interpreted, taking into account several limitations in the design of the study 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 severe COVID-19 patients. The study showed a statistically significant increase in mortality in patients receiving high-dose corticosteroids compared to 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 were clinically worse. The mortality rate was 76% in the high-dose corticosteroid group and 40% in the low-medium dose group. In addition to the higher mortality rates in patients receiving high-dose corticosteroids, high APACHE, SOFA, fibrinogen, D-dimer, hemoglobin, urea, creatinine, hyperglycemia due to adverse effects, serious complications such as gastrointestinal bleeding, renal failure were more common. In a study conducted in our country, ARDS patients with COVID-19 were treated with methylprednisolone using different doses (low or high) and durations. The study aimed to compare various factors such as lactate levels, procalcitonin levels, neutrophil-lymphocyte ratio, intubation time, weaning time, need for haemoperfusion, length of stay, and prognosis among the treatment groups. It has been reported that there is no effect of different doses and duration of methylprednisolone. The study's limited number of patients and some data collection limitations have been emphasized.[20]

In conclusion, when using corticosteroids for COVID-19 infection, the treatment strategy should be determined by 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.

CONCLUSION

It can be seen that the mortality rate was lower with low and medium-dose steroid use in corticosteroid treatments for COVID-19 disease. In addition to high mortality, high-dose steroids are associated with increased adverse effects and complications. The evidence on steroid treatment in 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 initiated after the approval of the Health Sciences University Izmir Bozyaka Training and Research Hospital Clinical Research Ethics Committee (protocol number: 21.05.2020-222).

Authorship Contributions

Concept: I.D., Design: I.D., I.Y., Data Collection or Processing: I.D., H.O., S.C., Analysis or Interpretation: I.D., I.Y., Literature Search: I.D., I.Y., H.Y., Writing: I.D., I.Y., H.Y.

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LEGENDS

TABLE I - The Effect of Dose on Mortality and Intubation in COVID-19 Patients Receiving Cortisone Treatment in Intensive Care Unit

	Cortisone Therapy Dose				
	Low-Medium-Dose *n (%)*	**High-Dose** *n (%)*	**Total** *n (%)*	***p* value**	**χ^2**
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-Square analysis was used and p<0.05 was considered significant.

TABLE II - The Effect of Dose on Laboratory Parameters, SOFA score, APACHE II score and Time of Stay in COVID-19 Patients Receiving Cortisone Treatment in Intensive Care Unit

	Cortisone Therapy Dose		
Parameters	**High-Dose**	**Low-Medium-Dose**	***p* value**
Hemoglobin	9.7±2.2	11.7±1.7	***<0.0001***
Leukocyte*	9550±5900	8600±5300	0.075
Thrombocyte*	211000±153000	209000±140000	0.887
Glucose*	109.2±79.2	82.2±33.6	***<0.0001***
Urea*	41.4±33.9	37.3±22.1	0.092
Creatinine*	3.2±0.9	1.6±0.7	***<0.0001***
Alanine transaminase*	44.6±36.4	42.2±25.5	0.369
Aspartate aminotransferase*	70.4±20.5	67.7±21.0	0.177
Bilirubin-Total*	4.0±3.9	1.6±1.2	***<0.0001***
Creatine kinase*	641.0±766.1	185.5±32.1	***<0.0001***
Lactate dehydrogenase*	111.9±48.8	108.2±51.1	0.459
D-Dimer*	1425.5±658.2	616.2±582.2	***<0.0001***
Fibrinogen	990.2±298.3	602.3±198.7	***<0.0001***
PT*	13.6±15.4	9.9±10.1	***0.0002***
APTT	38.6±15.2	29.7±4.3	***<0.0001***
INR*	2.4±2.7	1.6±3.2	***0.048***
C-reactive protein**	410.2±111.3	291.1±12.3	***<0.0001***
Ferritin*	446.5±389.7	212.4±297.7	***<0.0001***
Procalcitonin*	41.3±9.2	32.9±4.5	***<0.0001***
SOFA Score	13.2±2.6	8.5±1.6	***<0.0001***
APACHE II Score	21.2±3.3	16.1±2.3	***<0.0001***
Length of stay*	11.4±6.0	7.7±5.9	***<0.0001***

Independent t-test was used and p<0.05 was considered significant.

**Mann-Whitney U test was used.*

*** Pearson Chi-Square test was used.*