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Is the Effect of Pulse Corticosteroid Different From the Lower Dose on Mortality in Hospitalized Patients with COVID-19 Pneumonia?

Hastaneye Yatırılan COVID-19 Pnömonisi Olgularında Pulse Kortikosteroid Tedavi Düşük Doz Kortikosteroid Tedaviye Göre Mortalite Faydası Sağlar mı?

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ABSTRACT

Introduction: *The novel coronavirus disease-2019 (COVID-19) is a disease with high mortality and morbidity. The aim of this study was to investigate the prognostic effect of pulse corticosteroid therapy in patients with COVID-19 pneumonia.*

Materials and Methods: *Patients who were hospitalized due to COVID-19 pneumonia between June 2020 and December 2020 were included in the study. All data were retrospectively obtained. Age, gender, smoking history, presence of chronic disease, and laboratory parameters of the patients were recorded. Information about radiological involvement, respiratory failure, corticosteroid treatment/pulse corticosteroid treatment status, transfer to the intensive care unit, and mortality was obtained.*

Results: *Two-hundred and sixty-one patients were included in the study. There were 231 patients in the lower dose and 30 patients in the pulse dose corticosteroid group. The median age of the patients was similar in both pulse corticosteroid and lower dose corticosteroid groups [respectively; median 59 years (IQR= 19 years) vs. 60 years (IQR= 20 years), p= 0.66]. CRP levels were significantly higher and blood lymphocyte count was significantly lower in the pulse dose corticosteroid group (p= 0.01, p= 0.02). Eight patients (3.5%) died in the lower dose corticosteroid group and five patients (16.7%) died in the pulse dose corticosteroid group; the difference was statistically significant (p= 0.01). Propensity score matching according to age, sex, respiratory failure, CRP, ferritin, and LDH levels, revealed no difference in mortality between pulse dose or lower dose corticosteroid therapy (p= 0.71).*

Conclusion: *In the context of COVID-19 treatment, the administration of pulse-dose corticosteroid therapy does not appear to confer a beneficial effect on mortality when compared to lower-dose therapy.*

Key Words: *Coronavirus disease-19; Pulse corticosteroid; SARS-CoV-2; Infectious diseases*

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ÖZ

Hastaneye Yatırılan COVID-19 Pnömonisi Olgularında Pulse Kortikosteroid Tedavi Düşük Doz Kortikosteroid Tedaviye Göre Mortalite Faydası Sağlar mı?

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Giriş: *Yeni koronavirüs hastalığı-2019 (COVID-19) yüksek morbidite ve mortaliteye yol açabilen bir hastalıktır. Çalışmamızın amacı COVID-19 pnömonisi tanısı ile yatırılan hastalarda pulse kortikosteroid tedavisinin prognoza olan etkisinin değerlendirilmesidir.*

Materyal ve Metod: *Çalışmaya Haziran 2020-Aralık 2020 tarihleri arasında COVID-19 pnömonisi tanısı ile servise yatırılan hastalar dahil edilmiştir. Veriler retrospektif elde edilmiştir. Yaş, cinsiyet, sigara öyküsü, kronik hastalık varlığı ve laboratuvar parametreleri hastane kayıtlarından elde edilmiştir. Aynı zamanda, radyolojik tutulum yaygınlığı, solunum yetmezliği, kortikosteroid/pulse kortikosteroid tedavi durumu, yoğun bakım ünitesi ihtiyacı ve mortalite verileri elde edilmiştir.*

Bulgular: *İki yüz altmış bir hasta çalışmaya dahil edilmiştir. Pulse kortikosteroid uygulanan grupta 30, düşük doz kortikosteroid grubunda 231 hasta bulunmaktadır. Olguların medyan yaşları pulse kortikosteroid ve düşük doz kortikosteroid gruplarında benzer olarak bulunmuştur [sırasıyla, medyan yaş 59 (çeyrekler açıklığı= 19)'a karşı 60.5 (çeyrekler açıklığı= 20), p= 0.66]. Pulse kortikosteroid grubunda CRP düzeyleri anlamlı olarak daha yüksekken, lenfosit sayısı anlamlı olarak daha düşüktür (sırasıyla, p= 0.01 ve p= 0.02). Düşük doz kortikosteroid grubunda sekiz hasta (%3.5) ve pulse kortikosteroid grubunda beş hasta (%16.7) eksitus olmuştur, iki grup arasındaki fark anlamlıdır (p= 0.01). İki grup içinde yaş, cinsiyet, solunum yetmezliği, CRP, ferritin ve LDH düzeylerine göre eğilim skoru eşleştirmesi yapılmıştır, iki grup arasında mortalite açısından anlamlı fark saptanmamıştır (p= 0.71).*

Sonuç: *COVID-19 pnömonisi tedavisinde düşük doz ile karşılaştırıldığında pulse kortikosteroid tedavinin mortalite üzerinde pozitif bir etkisi saptanmamıştır.*

Anahtar Kelimeler: *Koronavirüs hastalığı-19; Pulse kortikosteroid; SARS-CoV-2; İnfeksiyon hastalıkları*

INTRODUCTION

The novel coronavirus disease-2019 (COVID-19) is a disease with high mortality and morbidity, which has a significant impact all over the world[1]. Although it is mostly asymptomatic, the disease progresses in some cases and can cause life-threatening consequences[2]. Therefore, it has profound medical, psychological, and financial implications globally.

Several studies conducted thus far have focused on predicting the progression of COVID-19 cases[3,4]. Out of the observed patients, 15% exhibited severe disease characterized by pneumonia findings, while 5% experienced a critical course involving organ failure and shock[5]. Studies have demonstrated that the administration of corticosteroids during the late phase of the proliferative stage, typically 5-10 days after the onset of acute respiratory distress syndrome (ARDS), inhibits cytokine activation and lowers mortality rates[6]. As experience with COVID-19 continues to evolve, the management of the disease is constantly being refined. Among the various treatment strategies, controlling the cytokine storm has gained significant importance due to its role as a crucial contributor to mortality[7]. Pulse corticosteroid treatment is employed to counteract the cytokine storm owing to its anti-inflammatory properties. The efficacy of this approach in COVID-19 treatment has been demonstrated in randomized controlled studies[8,9]. While the management of COVID-19 is being studied intensively all over the world, evaluation of the efficacy and side effects of pulse corticosteroid therapy, as well as its effects on prognosis, is a particularly important field of study.

According to the COVID-19 diagnosis and treatment guideline issued by the Turkish Ministry of Health, the utilization of pulse-dose corticosteroids in the treatment regimen is at the discretion of the attending physician. However,

it is suggested that administration (≥250 mg/day methylprednisolone, three days) be considered in patients who experience an increase in oxygen demand or acute phase markers within 24 hours despite receiving 6 mg/day dexamethasone treatment. The decision to use pulse-dose corticosteroids should take into account the associated risk factors and potential side effects as outlined in the guideline[10].

The objective of this study is to examine the potential advantages of pulse steroid therapy in the treatment of hospitalized patients diagnosed with COVID-19 pneumonia and to compare its effectiveness to lower-dose steroid therapy. The primary endpoint of the study was to evaluate in-hospital mortality rates.

MATERIALS and METHODS

Patient Selection

For this retrospective, non-interventional, single-center cohort study, we included patients diagnosed with COVID-19 pneumonia who presented to our center between June 01, 2020, and December 31, 2020. The medical data of these patients were obtained from the Hospital Information Management System. All patients underwent a nasopharyngeal swab test for the SARS-CoV-2 virus using Real-Time Reverse-Transcriptase-Polymerase-Chain-Reaction (RT-PCR). All patients had either a positive RT-PCR assay of nasal and pharyngeal swab specimens or a history of contact in the last 14 days and symptoms such as cough, fever, and shortness of breath with characteristic findings on thorax computed tomography (CT) for the confirmation of the COVID-19 pneumonia diagnosis.

All included patients were over 18 years of age. Most of the patients were hospitalized due to hypoxemic respiratory failure and were given low-flow oxygen support. Patients who needed intensive unit care on admission were excluded from the study to prevent bias due to clinical severity as they were expected to have a worse prognosis.

Age, gender, smoking history, presence of chronic disease, hemogram parameters, D-dimer, ferritin, albumin, C-reactive protein (CRP), and lactate dehydrogenase (LDH) levels of the patients included in the study were recorded. Information about radiological involvement, corticosteroid treatment/pulse corticosteroid treatment status, transfer to the intensive care unit, and mortality was obtained.

The patients were categorized into two groups based on the dosage of corticosteroids administered: lower dose corticosteroid group (0.5-1 mg/kg/day methylprednisolone equivalent) and pulse dose corticosteroid group (≥250 mg/day methylprednisolone equivalent, three days).

40 mg/day methylprednisolone and 6 mg/day dexamethasone were considered equivalent therefore, no distinction was made between these two groups. Since the aim of the study was to investigate the dose effect of pulse corticosteroid therapy, no comparison was made regarding the corticosteroid subtype. The corticosteroid dosage was determined by the physicians responsible for patient care, following their respective treatment protocols, and was independent of the investigators of this study.

For the evaluation of prognosis, radiological and biochemical parameters, clinical status, oxygen demand, need for intensive care, and mortality were investigated.

This study was approved by both the Ethics Committee of our hospital (29.02.2021/No: 11) and the Ministry of Health COVID-19 Scientific Research Evaluation Committee and it complies with the principles of the Declaration of Helsinki.

Statistical Analysis

All patients who were hospitalized due to COVID-19 pneumonia were included in the study. The data obtained in the study were entered into the database created in SPSS (Statistical Package for Social Sciences) 18.0 Program (SPSS Inc. Chicago, IL, USA). The suitability of the continuous variables to normal distribution was examined. The comparison of the independent subgroups of the suitable variables was made with the Student's t-test and mean and standard deviation data were given. To compare the independent subgroups of the variables, the median values and interquartile range (IQR) were calculated for the variables

that did not fit normal distribution by using the Mann-Whitney U-test. Cross-squares were created according to the cut-off value for disease severity and poor prognosis, and their distribution was made using the Chi-square test method. All comparison tests and Type 1 Error Coefficient were determined as alpha 0.05 and were then evaluated with the double-tailed test.

A propensity score match was performed to analyze the outcome of pulse corticosteroid therapy. Patients were matched according to age, sex, CRP, ferritin, LDH, and lymphocyte levels, and presence of respiratory failure (PaO_2/FiO_2 <300). Predicted probabilities were calculated. All patients matched had PaO_2/FiO_2 <300 and all had maximal oxygen support during their management period with bilateral and diffuse involvement of lungs on computed tomography. Computed tomography severity scores (CTSS) were calculated for each participant. Each lobe was visually assessed and assigned a score based on the extent of lobar involvement: score 0 represented 0% involvement, score 1 indicated less than 5% involvement, score 2 denoted 5% to 25% involvement, score 3 represented 26% to 49% involvement, score 4 indicated 50% to 75% involvement, and score 5 indicated involvement greater than 75%. The total score was obtained by summing the individual lobar scores[11].

RESULTS

Three-hundred and sixty-three patients were enrolled. One-hundred and two patients treated in the intensive care unit on admission were excluded and 261 patients who were treated in the ward were included in the study. The flow chart of the study population is seen in Figure 1.

A total of 30 patients (11.5%) were SARS-CoV-2 virus RT-PCR negative and the diagnosis was confirmed by characteristic computed tomography findings with compatible clinical findings and a history of contact with a COVID-19 patient. Ninety-five of the patients were female (36%) and 166 were male (64%). The mean age of the total study population was 59.67 ± 13.54 years.

There were 231 patients in the lower-dose corticosteroid group and 30 patients in the pulse corticosteroid group. Pulse steroid treatment was given within a mean of 7.7 ± 5.32 days after diagnosis. The median age of the patients in the lower dose corticosteroid group was 59 years (IQR= 19 years), whereas, in the pulse corticosteroid group, the median age was 60.5 years (IQR= 20 years) (p= 0.66). The two groups were not different in terms of gender distribution, history of smoking, presence of comorbidities, PCR positivity, or bilateral lung

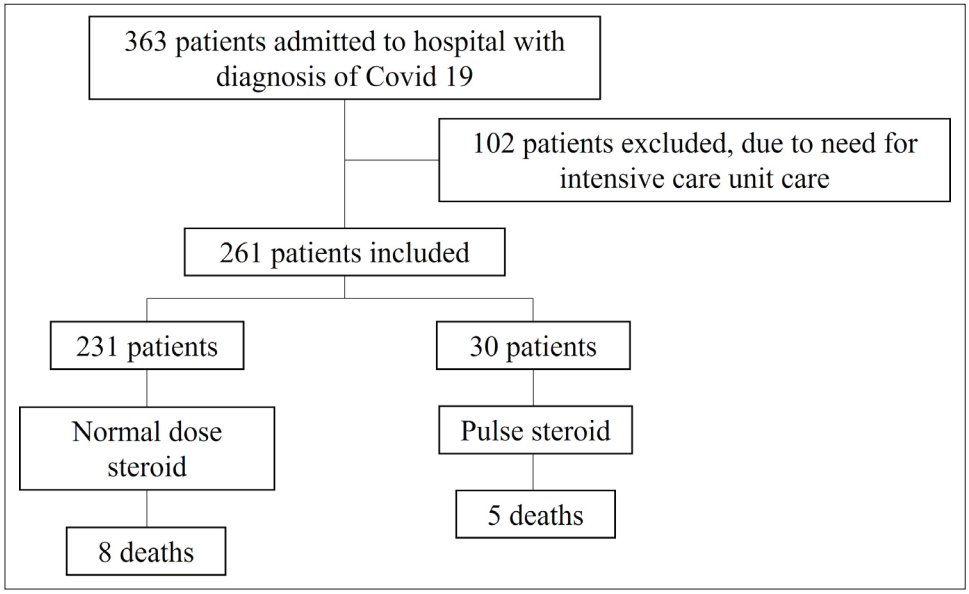

Figure 1. The flowchart of the study population.

involvement (respectively, p= 0.84; p= 0.57; p= 0.56; p= 0.76 and p= 0.38). There were more deaths in the pulse steroid group [5 deaths (16.7%) vs. 8 deaths (3.5%), p= 0.01]. C-reactive protein levels were significantly higher and blood lymphocyte count was significantly lower in the pulse corticosteroid group [respectively, 66 mg/dl (IQR= 83 mg/dL)] vs. 89.7 mg/dL (IQR= 144 mg/dL), p= 0.01 and 1100/mm^3 (IQR= 9900/mm^3) vs. 800/mm^3 (IQR= 325/mm^3), p= 0.02. Furthermore, the pulse corticosteroid group demonstrated significantly higher neutrophil counts [5200/mm^3 (IQR= 3750/mm^3) vs. 6000/mm^3 (IQR= 5275/mm^3), p=0.02], elevated blood glucose levels [118 mg/dL (IQR= 51 mg/dL) vs. 137.5 mg/dL (IQR 65 mg/dL), p= 0.02], and lower albumin levels [3.65 g/dL (IQR= 1 g/dL) vs. 3.37 g/dL (IQR= 1 g/dL), p= 0.01]. The demographic and clinical characteristics of the study population are presented in Table 1.

Table 1. Number of days between the COVID-19 RT-PCR test and the estimated time that the antibody levels reach the ELISA test treshold by linear regression model

	Lower dose steroid group (n= 231)	Pulse dose steroid group (n= 30)	P values
Age	59 (19)	61 (21)	0.66
Gender, male, n (%)	146 (63.2)	20 (66.7)	0.84
Smoking status, n (%)			
Active	52 (22.5)	6 (20)	0.57
Ex-smoker	124 (53.7)	19 (63.3)	
Never smoker	55 (23.8)	5 (16.7)	
Comorbidities, n (%)	132 (59.2)	16 (53.3)	0.56
Diabetes mellitus	50 (21.6)	7 (23.3)	0.82
Hypertension	73 (31.6)	8 (26.7)	0.68
Cardiovascular disease	30 (13)	2 (6.7)	0.55
COPD*	25 (10.8)	0	**0.09**
Malignancy	10 (4.3)	3 (10)	0.18
Rheumatoid arthritis	2 (0.9)	0	1.00
Asthma	3 (1.3)	2 (6.7)	0.1
Other	13 (5.6)	6 (20)	**0.02**
COVID† PCR ‡ positivity, n (%)	205 (88.7)	26 (86.7)	0.76
Lung involvement, bilateral, n (%)	217 (93.9)	30 (100)	0.38
Deaths, n	8 (3.5)	5 (16.7)	**0.01**
Laboratory findings			
Leukocytes/mm^3	7400 (4300)	7500 (5725)	0.15
Neutrophils/mm^3	5200 (3750)	6000 (5275)	**0.02**
Lymphocytes/mm^3	1100 (9900)	800 (325)	**0.02**
Hemoglobin gr/dL	13.3 (2)	13.4 (2)	0.51
Thrombocytes/mm^3	244.000 (129.000)	235.500 (168.750)	0.80
CRP§ mg/dL	66 (83)	89.7 (144)	**0.01**
Ferritin U/l	363.1 (531)	344.2 (517)	0.77
D-dimer ng/l	1104 (1356)	1029 (1512)	0.65
Albumin mg/dL	3.65 (1)	3.37 (1)	**0.01**
LDH‖, U/l	299 (1022)	356 (284)	0.46
Blood glucose, mg/dL	118 (51)	137.5 (65)	**0.02**

The results are presented as medians (interquartile range) unless otherwise specified. *: Chronic obstructive pulmonary disease, †: Coronavirus disease-2019, ‡: Polymerase chain reaction, §: C-reactive protein, ‖: Lactate dehydrogenase.

The pulse corticosteroid group (n= 30) was compared with propensity-matched control of 30 patients with high dose corticosteroid group for 28-day mortality. Matching was achieved by calculating predicted probabilities according to age, gender, CRP, lymphocyte, ferritin, and LDH levels. Computed tomography severity scores (CTSS) for COVID-19 pneumonia were calculated from baseline CT scans obtained on the day of hospital admission. Both groups had similar CTSS values [median 16 (IQR= 8) vs. median 15 (IQR= 9), respectively]. All patients were given maximal low-flow oxygen support during their management and PaO_2/FiO_2 values were below 300. Three patients died in the lower corticosteroid dose group (10%), while there were five deaths in the pulse corticosteroid group (16.7%). A statistically significant difference was not present between the two groups (p= 0.71). The matched groups did not exhibit any significant differences in terms of age, gender, and other clinical parameters, except for lower levels of hemoglobin in the lower dose corticosteroid group, which approached significance [12.5 g/dL (IQR 2 g/dL) vs. 13.4 g/dL (IQR 2 g/dL); p= 0.06]. Also, there were no patients with COPD in the pulse steroid groups. Data are presented in Table 2.

Table 2. Propensity score matching of the study population according to age, gender, CRP, LDH, ferritin, and lymphocyte levels

	Lower dose steroid group (n= 30)	Pulse dose steroid group (n= 30)	P values
Age	60 (23)	60.5 (20)	0.69
Gender, male, n (%)	19 (63.3)	20 (66.7)	1.0
Smoking status Active Ex-smoker Never smoker	 9 (30) 16 (53.3) 5 (16.7)	 6 (20.0) 19 (63.3) 5 (16.7)	0.65
Comorbidities, n (%)	23 (76.7)	16 (53.3)	0.10
Diabetes mellitus	9 (30)	7 (23.3)	0.77
Hypertension	13 (43.3)	8 (26.7)	0.28
Cardiovascular disease	5 (16.7)	2 (6.7)	0.42
COPD	5 (16.7)	0	0.05
Malignancy	1 (3.3)	3 (10)	0.61
CTSS*, n (%)	15 (9)	16 (8)	
Deaths, n (%)	3 (10)	5 (16.7)	0.71
Laboratory findings			
Leukocytes/mm^3	8050 (5025)	7500 (5725)	0.55
Neutrophils/mm^3	6000 (4325)	6000 (5275)	0.57
Lymphocytes/mm^3	700 (650)	800 (325)	0.38
Hemoglobin gr/dL	12.5 (2)	13.4 (2)	0.06
Thrombocytes/mm^3	234.500 (184.750)	235.500 (168.750)	0.9
CRP†, mg/dL	98.3 (94)	89.7 (144)	0.78
Ferritin, U/l	420.8 (661)	344.2 (517)	0.46
D-dimer, ng/l	1603.5 (1842)	1029 (1512)	0.58
Albumin, mg/dL	3.6 (1)	3.37 (1)	0.27
LDH‡, U/l	325 (225)	356 (284)	0.98
Blood glucose, mg/dL	138.5 (80)	137.5 (65)	0.91

The results are presented as medians (interquartile range) unless otherwise specified. *: Computed tomography severity score, †: C-reactive protein, ‡: Lactate dehydrogenase.

DISCUSSION

In this study, no evidence of superiority was found for pulse corticosteroid therapy compared to lower-dose corticosteroid therapy in patients with COVID-19 pneumonia. Patients in the pulse steroid group had higher neutrophil and lower lymphocyte counts, higher CRP levels, and lower albumin levels. Although there were more deaths in the pulse steroid group, propensity score matching revealed no difference in mortality between the two groups.

The first positive results for corticosteroid therapy in the treatment of COVID-19 were obtained in the Recovery study[12]. The patients were divided into two groups: those receiving 6 mg/day dexamethasone or standard treatment. In the preliminary results of this study, it was shown that the use of dexamethasone for up to 10 days in the respiratory failure group reduced 28-day mortality compared to standard therapy. However, no evidence was found to suggest that dexamethasone provided any benefit to patients who were not receiving respiratory support at the time of randomization. The results indicated the possibility of harm in this subgroup. The benefit was clear in patients who were treated for more than seven days after symptom onset during the hyperinflammatory phase of the disease. However, definitive and high-quality evidence is still lacking regarding the optimal dosage and timing of corticosteroid treatment.

Especially in severe cases, the use of pulse-dose corticosteroid treatment has been brought into question and documented in the literature through case reports. In the published cases from Peru, two patients with COVID-19 were treated at home due to the unavailability of hospital beds[13]. Despite receiving conventional COVID-19 medication, two patients exhibited symptoms and signs of severe disease. After three methylprednisolone pulses, both patients recovered and did not require ICU admission. The researchers concluded that early administration of corticosteroid treatment, which suppressed inflammation, prevented the onset of cytokine storm in patients. In our study, we aimed to assess the effectiveness of pulse corticosteroids in COVID-19 patients with elevated inflammatory markers and worsening respiratory failure, based on the hypothesis of the beneficial impact of pulse corticosteroid therapy.

In a study by Cruz et al., initial treatment with pulse dose steroid therapy was not associated with in-hospital mortality[14]. In another study from Spain, 318 patients who had cytokine storm findings (IL-6 ≥40 pg/mL and/or two of the following: CRP ≥100 mg/L, D-dimer ≥1000 ng/ml, ferritin ≥500 ng/mL and LDH ≥300 U/L) were evaluated[15]. High-dose corticosteroid pulse therapy (1.5 mg/kg/24h methylprednisolone or dexamethasone equivalent) was administered to 64 (20.1%) of the patients. A significant decrease in mortality was observed in the group receiving high-dose corticosteroid pulse therapy compared to the low-dose group[15].

Although most studies have primarily focused on investigating the effectiveness of corticosteroid use in the early stages of lung involvement, there have been reports of its efficacy in the late pulmonary phase based on case series[16]. Patients who did not respond to standard treatments and low-dose corticosteroid treatment were administered 1000 mg/day methylprednisolone for three days on the 14^{th}, 16^{th}, 19^{th}, and 29^{th} days, and treatment response was observed in all patients and after the treatment, the patients were extubated. These cases have demonstrated that methylprednisolone can be effective when used in the late phase of patients with respiratory failure, providing successful treatment outcomes [16]. In contrast to the study mentioned, our study focused on administering corticosteroid treatment during the earlier phases of lung involvement. Recently, a study that evaluated the efficiency of add-on pulse corticosteroid therapy, was published in our country[17]. Four hundred fifty patients with respiratory failure were included in this study. The patients were divided into three groups: those receiving standard therapy, high-dose corticosteroid therapy (6 mg/day dexamethasone equivalent), and add-on pulse corticosteroid therapy (250 mg/day methylprednisolone). The need for ICU admission and mechanical ventilation was significantly low

in the high-dose steroid group compared to the other two groups[17]. Mortality rates were similar in all groups. However, the length of stay in the intensive care unit was the shortest in the add-on pulse corticosteroid group compared to the standard therapy group. Pulse steroid therapy was considered a viable treatment option for individuals who did not respond to high-dose corticosteroids. This approach resulted in shorter durations of ICU and hospital stays, although it did not have a significant effect on mortality rates[17].

There are studies that demonstrate the beneficial effects of pulse steroid therapy, including a reduction in mortality rates when compared to standard care[8,18,19]. However, a recent meta-analysis showed no significant mortality benefit or reduction in the need for ICU care when comparing pulse doses of corticosteroids to lower doses[20]. Furthermore, a recently published double-blind randomized controlled study comparing pulse doses with lower doses of corticosteroid therapy found no benefit of corticosteroid pulses in the management of COVID-19 patients[21]. The primary endpoint of this study was hospital discharge without the need for oxygen. Our results also confirmed the lack of survival benefit with pulse corticosteroid therapy over lower dose corticosteroid therapy.

Firstly, it was not conducted as a randomized controlled trial, which may introduce confounding variables and potential selection bias. Despite our efforts to address these concerns through subgroup propensity score matching, accounting for factors such as baseline radiological involvement, oxygen requirement, and inflammatory markers, residual biases may persist. Second, it reflects the experience of a single center with a limited number of patients, therefore the results cannot be generalized. Finally, COVID-19 variant mutations were not examined as a subgroup in our study. This may have affected the pulse corticosteroid treatment response.

CONCLUSION

In conclusion, based on the available evidence, pulse corticosteroid therapy does not appear to provide any significant mortality benefit compared to lower-dose therapy in the treatment of COVID-19. It is important to note that most studies on this topic have a retrospective design, indicating the need for prospective studies to establish the optimal dosage and timing of corticosteroid therapy in patients with COVID-19.

ETHICS COMMITTEE APPROVAL

This study was approved by the Health Sciences University İzmir Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Ethics Committee (Decision no: 11, Date: 29.02.2021).

CONFLICT of INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: GP, CK, ÖÖ

Analysis/Interpretation: All of authors

Data Collection or Processing: SE, DSU, ÖSU, MG, FG, ÖB, MB

Writing: GP, ÖÖ

Review and Correction: SE, DSU, ÖSU, MG, FG, ÖB, MB, ÖÖ

Final Approval: GP, CK

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