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Comparison of the Efficacy of High-Dose Methylprednisolone and 6 mg Dexamethasone in Treatment in Patients with Severe COVID-19 Pneumonia

Şiddetli COVID-19 Pnömonisi Olan Hastalarda Yüksek Doz Metilprednizolon ve 6 mg Deksametazonun Tedavi Etkinliğinin Karşılaştırılması

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ABSTRACT

Introduction: *The course of SARS-CoV-2 disease has a clinical spectrum ranging from mild upper respiratory tract infection to fulminant pneumonia. The use of corticosteroids is recommended in the treatment of severe COVID-19 pneumonia. The present study aimed to compare the efficacy of high-dose methylprednisolone and dexamethasone treatment in patients hospitalized with severe COVID-19 pneumonia.*

Materials and Methods: *The participants were divided into Group M, receiving ≥250 mg intravenous methylprednisolone therapy, and Group D receiving 6 mg intravenous dexamethasone therapy. The efficacy of treatments, length of hospital stays, ventilator requirements, anti-cytokine treatment requirements, and mortality rates were evaluated in both groups.*

Results: *Two hundred eighty-eight (69.1%) patients received dexamethasone and 129 (30.9%) received methylprednisolone. While overall mortality in the study was 11%, this rate was 10.4% in Group D and 12.4% in Group M (p> 0.05). The rate of patients requiring intensive care was 15.8% in total, with a rate of 14.6% in Group D and 18.6% in Group M (p> 0.05). However, the total length of hospital stay was nine (7-39) days in Group M and 13 (7-29) days in Group D (p= 0.009). Anticytokines were required in 14.4% of the patients during treatment [40 in Group D, 20 in Group M (p> 0.05)].*

Conclusion: *In this study, it was determined that early methylprednisolone treatment shortened the hospital stay. In addition, there was no statistically significant difference between Group M and Group D in terms of mechanical ventilation requirement, which showed an additional positive effect. However, mortality rates in patients receiving dexamethasone were found to be lower than in those receiving methylprednisolone, yet this difference did not reach statistical significance.*

Key Words: *COVID-19; Steroid treatment; Mortality rate; Length of hospital stay; Ventilator requirement*

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ÖZ

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Giriş: *SARS-CoV-2 hastalığının seyri, hafif üst solunum yolu infeksiyonundan fulminan pnömoniye kadar uzanan bir klinik spektruma sahiptir. Şiddetli COVID-19 pnömoni tedavisinde kortikosteroid kullanımı önerilir. Bu çalışmada hastanede yatan şiddetli COVID-19 pnömoni olgularında yüksek doz metilprednizolon ve deksametazon tedavi etkinliğinin karşılaştırılması amaçlandı.*

Materyal ve Metod: *Katılımcılar, ≥250 mg intravenöz metilprednizolon tedavisi alan grup M hastaları ve 6 mg intravenöz deksametazon tedavisi alan grup D hastaları olarak ikiye ayrıldı. Her iki gruptaki hastalarda tedavilerin etkinliği, hastaların hastanede kalış süreleri, ventilatör gereksinimleri, anti-sitokin tedavi gereksinimleri ve mortalite oranları değerlendirildi.*

Bulgular: *Olguların 288'i (%69.1) deksametazon ve 129'u (%30.9) metilprednizolon tedavisi alıyordu. Çalışmada genel mortalite %11 iken bu oran grup D'de %10.4, grup M'de %12.4 idi (p> 0.05). D grubu hastalarda %14.6 ve M grubu hastalarda %18.6 olmak üzere toplamda yoğun bakıma ihtiyaç duyan hastaların oranı %15.8 idi (p> 0.05). Ancak hastanede kalış süresi M grubu hastalarda dokuz (7-39) gün, D grubu hastalarda ise 13 (7-29) gündü (p= 0.009). Tedavi süresince hastaların %14.4'ünde antisitokinlere ihtiyaç duyuldu. Bunların 40'ı D grubu, 20'si M grubunda yer alan olgulardı (p> 0.05).*

Sonuç: *Bu çalışmada erken metilprednizolon tedavisinin hastanede kalış süresini kısalttığı saptanmıştır. Ayrıca mekanik ventilasyon ihtiyacı açısından M grubu ve D grubu arasında istatistiksel olarak anlamlı bir farklılığın olmaması bu konuda da olumlu bir etkisi olduğunu göstermiştir. Bununla birlikte deksametazon alan hastalardaki ölüm oranları metilprednizolon alanlara göre daha düşük bulunmuş ancak bu, istatistiksel anlamlılığa ulaşmamıştır.*

Anahtar Kelimeler: *COVID-19; Steroid tedavisi; Mortalite hızı; Hastanede kalış süresi; Ventilatör ihtiyacı*

INTRODUCTION

Coronavirus disease-2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was first reported in December 2019 in Wuhan, China, and the World Health Organization (WHO) designated COVID-19 a global pandemic on March 11, 2020. SARS-CoV-2, which led to a global public health emergency, is known to be the third beta coronavirus epidemic of the twenty-first century after severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)[1,2].

The course of SARS-CoV-2 disease has a clinical spectrum ranging from mild upper respiratory tract infection to fulminant pneumonia, which progresses to life-threatening respiratory failure, acute respiratory distress syndrome (ARDS), and multi-organ failure in some cases[3]. Identifying effective measures for the management of COVID-19 based on disease pathogenesis is crucial, given its relatively high infectivity, rapid progression of lung involvement, and the absence of definitive effective treatment. Although various empirical therapeutic options have been presented in the literature, no effective therapeutic options are available to treat severe COVID-19 cases[4,5].

The host immune response plays a key role in the pathophysiology of severe COVID-19, and COVID-19 pneumonia is associated with both hyperinflammation and immunoparalysis[6]. The clinical presentation of the severe form of the disease is remarkably similar to ARDS seen in SARS and MERS[7]. Although several agents targeting the inflammatory response have been investigated, there is no strong evidence for the benefit of new treatments. It is known that corticosteroids exert beneficial effects both in the suppression of hyperinflammation and in the treatment of ARDS. It also offers an easily accessible and cost-effective therapeutic option[8,9]. The efficacy of methylprednisolone has been demonstrated in many studies on MERS-CoV and SARS-CoV. Therefore, it is thought that

corticosteroids may be effective in severe COVID-19 patients, as observed in experience from the SARS and MERS outbreaks. Appropriate anti-inflammatory therapy to suppress the cytokine storm is essential to prevent progression to irreversible ARDS and multi-organ failure[10-12]. The benefit of dexamethasone treatment in COVID-19 patients was first reported in the RECOVERY trial[13]. Accordingly, dexamethasone treatment at a dose of six mg decreased 28-day mortality in patients with COVID-19 pneumonia requiring supplemental oxygen. WHO advised against the use of corticosteroid therapy at the onset of the pandemic, however, has updated its recommendation for the treatment of severe and critically ill COVID-19 patients to give systemic corticosteroids as of September 2020[9,14]. However, the use, optimal dose and duration of another corticosteroid to achieve a better clinical outcome in COVID-19 have not yet been elucidated[15]. In animal models, it has been shown that methylprednisolone penetrates the lung tissue at higher rates than dexamethasone and therefore may be more effective in lung injury[16]. In light of all this information, the present study aimed to compare the efficacy of high-dose methylprednisolone and dexamethasone in patients hospitalized with severe COVID-19 pneumonia in terms of length of hospital stay, ventilator requirement, the requirement for anti-cytokine therapies, and mortality.

MATERIALS and METHODS

The procedures performed during the single-center, retrospective study were carried out in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Committee of Fırat University (date: 16 September 2021).

Study Population

The records of the patients who were hospitalized between August 2020 and May 2021 in our hospital with a real-time PCR-confirmed SARS-CoV-2 infection were investigated. Inclusion criteria included being older than 18 years of age, having fever and respiratory tract infection findings, widespread involvement in thorax tomography, and accompanying ≥1 of the criteria for severe pneumonia. Resting oxygen saturation of 90% or less (oxygenation index $PaO_2/FiO_2 \leq$ 300 mmHg in a patient receiving oxygen), respiratory rate of ≥30/min, presence of dyspnea, or the need for oxygen therapy with a reservoir mask providing FiO2 ≥60% are among the classification criteria for severe pneumonia[17].

Patients who did not meet the criteria for severe pneumonia and were younger than 18 years of age, had diabetes with very high blood sugar levels, were pregnant or immunosuppressed, had any contraindications for corticosteroids, or were intubated or taking corticosteroids for <7 days were excluded from the study.

Study Design

Data on demographics, medical history, the use of other targeted COVID-19 therapies, including tocilizumab, anakinra, and favipiravir, and clinical and laboratory (C-reactive protein, white blood cell, lymphocyte, serum procalcitonin level, lactate dehydrogenase levels) findings were obtained retrospectively. All patients were assessed by lung computed tomography at the time of admission. In addition, ventilation requirement, length of hospital stay, and mortality were recorded during the study.

Group M included patients who received ≥250 mg of high-dose intravenous methylprednisolone therapy. The general approach to the management of methylprednisolone therapy is to administer a high dose for the first three days, followed by 1 mg/kg for three days, and then 0.5 mg/kg for the remaining days, to be completed within 10 days. Group D included patients who received six mg of intravenous dexamethasone therapy. For dexamethasone, the treatment approach was to maintain the standard therapeutic dose for 10 days.

Statistical Analysis

Data analysis was performed with SPSS 22 software (SPSS Inc., Chicago, Illinois). The normal distribution of the variables was tested using visual methods (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/ Shapiro-Wilk's test). For continuous variables with normal distribution, mean ± standard deviation

(SD) was provided, whereas those without normal distribution were expressed using median [interquartile range (IQR)]. Categorical variables were expressed as counts and percentages. The comparison of values was performed by the Mann-Whitney U test or Student's t-test as appropriate for quantitative variables and by Pearson's Chi-square test or Fisher's exact test for categorical variables. For multiple comparisons, analyses were performed with one-way ANOVA or Kruskal-Wallis test. A p value of less than 0.05 was considered statistically significant.

RESULTS

Of the 417 patients included in the study, 173 (41.5%) were female and 244 (58.5%) were male. The median age was 61 (20-95) years, 61 (20-95) years in female patients, and 60 (21-94) years in male patients (p> 0.05). 226 (54.1%) patients were ≥60 years old. The median age of patients receiving methylprednisolone (Group M) was 61 years, with a range of 31-92, and the median age of patients receiving dexamethasone (Group D) was 61 years, with a range of 20-95 (p> 0.05). Seventy (54.3%) patients in Group M and 174 (60.4%) patients in Group D were male (p> 0.05). Table 1 shows the number of patients who received methylprednisolone and dexamethasone, as well as the number of patients who died, according to their age, gender distribution, and age groups.

51.7% (n= 216) of our patients had a high fever at admission, while 287 (68.8%) of the patients had at least one comorbidity. The median laboratory values of all patients included in the study were as follows: white blood cell 5.9 (1.1-47.5) K/uL; lymphocyte 0.95 (0.41-22.0) K/uL, ferritin 348 (9.6-5695) ng/mL, troponin 0.01 (0.0-18.8) ng/mL, lactate dehydrogenase (LDH) 359 (18-1255) IU/L, creatine phosphokinase 94 (13-2828) IU/L, creatinine 0.91 (0.41-9.82) mg/dL, D-dimer 0.66 (0.1-70) ng/mL, C-reactive protein (CRP) 69.2 (3.1-211) mg/dL, procalcitonin 0.14 (0.12-81) ng/mL, alanine aminotransferase 28 (3-360) IU/L, aspartate aminotransferase 37 (13-374) IU/L and international normalized ratio 0.98 (0.77-1.47). The baseline values of Group M and Group D patients are given in Table 2.

All patients received low molecular weight heparin of 4000 IU as standard treatment. All study cases were patients who were given corticosteroid therapy early in the course of treatment, as soon as oxygen demand occurred. Accordingly, 288 (69.1%) of the cases were receiving dexamethasone and 129 (30.9%) methylprednisolone treatment. Data on antibacterial, antiviral, and anticytokine treatments of Group M and Group D are given in Table 3.

While overall mortality in the study was 11% (n= 46), this rate was 10.4% (n= 30) in Group D and 12.4% (n= 16) in Group M (p> 0.05). While the mean age of the Group D patients with a mortal course was 76 (51-94), it was 75 (61-92) in Group M. There was no statistical difference between the two groups (p> 0.05). The rate of patients requiring intensive care was 15.8% (n= 66) in total, with a rate of 14.6% (n= 42) in Group D and 18.6% (n= 24) in Group M (p> 0.05). However, the total length of hospital stay was nine (7-39) days in Group M and 13 (7-29) days in Group D (p= 0.009).

Table 1. Distribution of patients by age groups

Age	Female (n)	Male (n)	Group M (n)	Group D (n)	Mortality (n)	Total n (%)
<30	5	7	-	12	-	12 (2.9)
30-39	4	13	1	16	-	17 (4.1)
40-49	17	32	20	29	-	49 (11.8)
50-59	50	63	39	74	3	113 (27.1)
60-69	31	66	33	64	11	97 (23.3)
70-79	39	28	15	52	17	67 (16.1)
>80	27	35	21	41	15	62 (14.9)
Total n (%)	173 (41.5)	244 (58.5)	129 (100)	288 (100)	46 (11)	417 (100)

Table 2. Characteristics of group M and group D patients

Characteristics (min-max)	Group M (n= 129)	Group D (n= 288)	p
Fever, n (%)	70 (54.2)	146 (50.6)	0.098
Comorbidities, n (%)			
Diabetes mellitus	42 (32.6)	74 (26.1)	0.107
Hypertension	19 (14.7)	36 (12.5)	0.317
Lung diseases	8 (6.3)	19 (6.6)	0.550
Chronic kidney disease	10 (7.8)	27 (9.4)	0.369
Coronary artery disease	20 (19.2)	42 (14.6)	0.457
Immunocompromised	9 (7)	20 (6.9)	0.569
Laboratory findings, n (%)			
White blood cell, K/uL	5.0 (1.8-30.1)	6.3 (1.1-47.5)	0.072
Lymphocyte count, K/uL	0.96 (0.41-22.0)	0.95 (0.25-11.6)	0.093
Ferritin ng/mL	334 (9.6-5695)	346 (12.9-5624)	0.979
Troponin, ng/mL	0.01 (0.0-0.92)	0.01 (0.0-18.8)	0.087
Lactate dehydrogenase, IU/L	386 (18-1144)	354 (54-1255)	0.108
Creatine phosphokinase, IU/L	112 (13-1415)	96.5 (14-2828)	0.925
Creatinine, mg/dL	0.9 (0.47-9.82)	0.93 (0.41-8.49)	0.159
D-dimer, ng/mL	0.69 (0.22-13.6)	0.6 (0.1-70)	0.06
C-reactive protein, mg/dL	64.9 (3.3-211)	66 (3.1-211)	0.355
Procalcitonin, ng/mL	0.13 (0.12-75)	0.14 (0.12-81)	0.475
Alanine aminotransferase, IU/L	24 (7-360)	29 (3-332)	0.413
Aspartate aminotransferase, IU/L	36 (14-278)	37 (13-374)	0.363
International normalized ratio	0.99 (0.77-1.34)	0.97 (0.78-1.47)	0.354

Table 3. Treatment data of Group M and Group D

Characteristics	Group M (n= 129)	Group D (n= 288)	p
Concomitant therapies, n (%)			
Antibiotics	42 (32.6)	74 (26.1)	0.107
Convalescent plasma	10 (7.8)	36 (12.5)	0.141
Anti-cytokine	20 (15.5)	40 (13.9)	0.384
Hydroxychloroquine	-	2 (0.7)	-
Favipiravir	122 (94.6)	270 (93.7)	0.479

Anticytokines (tocilizumab or anakinra) were required in 14.4% (n= 60) of the patients during the course of treatment. While 40 (13.9%) of them were in Group D, 20 (15.5%) were in Group M (p> 0.05). However, there was no statistically significant difference between Group D and Group M in terms of the need for intensive care, and hospitalization days among patients receiving anti-cytokine therapy (p> 0.05), whereas mortality was observed only in Group D (Table 4).

Table 4. Characteristics of patient subgroups receiving anticytokine therapy

Characteristic	Group M (n= 20)	Group D (n= 40)	p
Intensive care requirement	9 (22.5%)	5 (25%)	0.535
Length of hospital stay (days)	13 (7-20)	11 (7-39)	0.749
Mortality	0	2 (5%)	-

DISCUSSION

Since the emergence of COVID-19, the world population has faced unprecedented stress. Although it has been nearly two years since COVID-19 first emerged and widespread vaccine interventions have been implemented, by June 21, 2022, 539.893.858 people had been infected, with 6.324.112 of the cases resulting in death, or causing serious conditions in some of the survivors. The lack of currently available treatment is an obstacle to ending this pandemic[18]. In some cases, healthcare professionals may need to make treatment decisions without substantial evidence until an effective approach is obtained. However, extensive data have been reported as a result of continuing studies evaluating the COVID-19 disease, which help understand the disease's characteristics and inform its management. To date, no antiviral drugs have shown full efficacy against SARS-CoV-2, and studies mainly focus on complications such as ARDS and cytokine release syndrome associated with COVID-19. These severe conditions, which can progress to death, are reported to be associated with systemic inflammation due to irregular autoinflammatory response characterized by an increase in tumor necrosis factor-alpha (TNF alpha) and interleukin (IL) 1B, IL-2, IL-6, IL-8, IL-10[19]. As a result, corticosteroids, which have potent anti-inflammatory properties, have started to be recommended for treatment[20].

In this study, we aimed to compare the therapeutic effect of methylprednisolone[21] which is known to have higher lung penetration, with dexamethasone, another corticosteroid recommended for COVID-19 patients.

A direct correlation was established between increased disease severity and demographic characteristics such as advanced age and male gender in COVID-19 patient cohorts[22,23]. Spagnuolo et al.[24] have investigated moderate-to-severe COVID-19 patients and have found that the median age was 63.5 years, with male gender dominancy. The role of the presence of comorbidities, which is known to be a risk factor for the course of moderate-to-severe COVID-19, has been consistent in many studies. In particular, diabetes and arterial hypertension are common comorbidities seen in COVID-19 patients and have been suggested to pose a risk factor for serious and fatal cases of COVID-19[25,26]. Furthermore, several studies have indicated that high fever during admission is reported more frequently in severely ill patients than in non-severe patients[22,23]. Among the laboratory parameters, increased CRP, ferritin, LDH, D-dimer values, and lymphopenia were specifically found to be associated with the disease progression[27].Demographic characteristics and clinical and laboratory findings of our severe COVID-19 pneumonia patients included in our study are consistent with the current literature.

Despite the lack of effective agents to treat severe COVID-19, non-antiviral immunosuppressive treatments are known to reduce intensive care requirements and the mortality rate[27]. Since the emergence of COVID-19, many treatment options such as tocilizumab, plasma therapy, antibiotics, antivirals, and corticosteroids have been studied. In our study, all severe COVID-19 patients who needed oxygen but were not intubated were receiving corticosteroid therapy. In COVID-19 patients, dexamethasone and methylprednisolone have been the most studied corticosteroids[28]. Recently, the results of the RECOVERY trial changed the treatment guidelines and it was determined that the use of six mg dexamethasone reduced the need for mechanical ventilation and had a positive effect on mortality, especially in patients who required oxygen support[13]. In the SARS epidemic that occurred in Guangzhou, China in 2003, the infection was associated with a clinical picture similar to the current COVID-19 disease. Zhao et al.[29] compared different treatment models including the administration of different antibiotics, antivirals, and different doses of corticosteroids in patients with SARS-CoV pneumonia, and they found that the mortality rate and the need for mechanical ventilation decreased in patients who received high doses of methylprednisolone for only 5-14 days. Edalatifard et al.[30] randomized patients with COVID-19 pneumonia to receive standard care and methylprednisolone 250 mg daily for three days and determined that the clinical improvement was higher, and the mortality rate was lower in the methylprednisolone group ($p< 0.001$). In a study

comparing clinical deterioration, progression to ARDS, and transfer to the intensive care unit in moderate-severe COVID-19 patients treated with dexamethasone and high-dose methylprednisolone before mechanical ventilation, it was noted that these rates were lower in patient groups who received methylprednisolone[31]. Our outcomes are consistent with the above-mentioned results, although there was no statistically significant difference in terms of the need for intensive care and mortality between Group M and Group D. In many studies, it has been reported that patients treated with methylprednisolone have a shorter recovery time and earlier discharge from the hospital[31,32]. Similarly, in our study, the length of hospital stay was significantly shorter in patients receiving methylprednisolone compared to the group of patients receiving dexamethasone.

Early anti-inflammatory treatment, as is well known, can lower the risk of death when compared to standard treatment alone. Especially in the early stages of severe COVID-19 pneumonia, concurrent use of an anticytokine agent and a glucocorticoid is recommended[33]. This intervention may facilitate aggressive inflammatory control in individuals with severe pulmonary involvement and significant signs of inflammation from the first days of hospitalization. In our study, we found that 14.4 percent (n= 60) of our patients required anti-cytokines during their treatment. There was no statistical difference in terms of the need for intensive care and duration of hospitalization in Group M and Group D patients of the subgroup receiving anti-cytokine treatment accompanied by corticosteroid treatment. In terms of mortality, it is worth noting that deaths occurred only in Group D patients, and the rate is quite low when compared to the overall patient population.

In studies of COVID-19, differences in dosage and administration of corticosteroids have led to insufficient conclusions about the efficacy of these agents[12]. Ranjbar K. et al.[32] started the methylprednisolone dose at two mg/kg per day and reduced to half a dose every five days, while Edalatifart M. et al.[30] continued at 250 mg/day for three days and then discontinued. Although the dose and duration of methylprednisolone administration in these studies are different from our study, the results are consistent.

CONCLUSION

In conclusion, our study could help healthcare providers manage COVID-19 disease, which currently has no effective treatment. However, the study has some limitations: It is a retrospective study, the sample size is limited, and there is insufficient post-discharge data. Furthermore, it is unclear if the results we achieved are dependent on the active component or the application of the pulse steroid dose.

The role of methylprednisolone in the treatment of COVID-19 has been evaluated in many studies which suggested that it reduces undesirable effects[34,35]. In this study, it was determined that early methylprednisolone treatment shortened the hospital stay. In addition, there was no statistically significant difference between Groups M and D in terms of the need for mechanical ventilation, which showed a positive effect on this matter as well. In addition, patients receiving dexamethasone had a lower mortality rate (16 vs 30) than those receiving methylprednisolone, although this difference did not reach statistical significance. Even though our study yielded important data, we believe that larger prospective studies are required to determine which corticosteroid agent provides the most benefit, and the appropriate timing, dose, and duration in this high-risk population.

ETHICS COMMITTEE APPROVAL

This study was approved by Fırat University Non-Invasive Research Ethics Committee (Decision no: 2021/09-17, Date: 16.09.2021).

CONFLICT of INTEREST

None of the authors had conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: ŞÖB, MAA, KD

Analysis/Interpretation: ŞÖB, AA

Data Collection or Processing: ŞÖB, SU, MAA

Writing: ŞÖB, MAA, SU

Review and Correction: ŞÖB, KD, AA

Final Approval: ŞÖB, KD, AA

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