Original Article

Evaluation of Steroid Therapy in COVID-19 Patients; in the Right Dose at the Right Time to the Right Patients

A Ayyıldız, ÖT Yıldırım[1], A Uçan[2], FA Ayyıldız[3]

Osmangazi University Faculty of Medicine, Department of Anesthesiology and Reanimation, Eskişehir, [1]Eskisehir City Hospital, Department of Cardiology, Eskisehir, [2]Eskişehir City Hospital, Department of Internal Medicine, Eskişehir, [3]Eskişehir City Hospital, Department of Emergency Medicine, Eskişehir, Turkey

Received: 21-Nov-2021;
Revision: 09-Aug-2022;
Accepted: 27-Feb-2023;
Published: 07-Apr-2023

Abstract

Background: Although there is still no universally accepted treatment agent, steroids have been administered chronologically at every dose and at every stage of the COVID-19 pandemic. **Aim:** We aimed to evaluate the clinical efficacy of high-dose steroid therapy and its effect on mortality in COVID-19 patients with severe pneumonia, severe Acute Respiratory Distress Syndrome (ARDS), and septic shock. **Patients and Methods:** Patients with severe pneumonia, septic shock, and ARDS due to COVID-19 who were followed up in the intensive care unit were retrospectively reviewed. **Results:** The study population was divided into two groups; the methylprednisolone pulse group (MP) (n = 55) and the dexamethasone group (Dex) (n = 39). When the values before and after treatment were compared; there was a statistically significant increase in the neutrophil/lymphocyte ratio after treatment in the MP group (p = 0.006). Although it was not statistically significant in the MP group, There was a numerical increase in D-dimer levels (p = 0.28). Thromboembolic complications developed in 2 patients in the MP group. The mortality outcomes of the groups were statistically similar (p = 0.943). **Conclusion:** We recommend steroids use in the condition that it is indicated in the critically ill group with the poor general condition. Since there is no significant difference between high-dose pulse steroid treatment and standard treatment doses, we think that the risk of complications should not be taken into account and high doses should not be used.

Keywords: *ARDS, COVID-19, pneumonia, pulse steroid, septic shock, steroid therapy*

Introduction

There is still no universally accepted treatment agent for COVID-19. Under normal conditions, immunity in a healthy individual copes with COVID-19 infection, the replication of the virus is prevented and the disease progresses mildly. When an appropriate and strong immune response is not developed, the disease progresses to the hyperinflammation phase. If the infection cannot be controlled with appropriate immune responses, the developing cytokine storm will be life-threatening. Immunosuppressive treatments started to gain importance in the pandemic after it was understood that the hyperinflammatory process and adaptive T cell response were dominant in determining the prognosis of COVID-19 infection.[1] Glucocorticoids, the best-known immunosuppressive with the longest history of use, are recommended by World Health Organization (WHO) guidelines for COVID-19 in the case of severe ARDS or septic shock development. Routine use of this therapy to reduce inflammation is not recommended.[2]

Many studies have been conducted on when steroids should be used in which indications and in which dose, and their effects on mortality, and complications encountered.[3-5] Based on these studies, high-dose steroids were widely used during the pandemic and a

Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_1950_21

Address for correspondence: Dr. A Ayyıldız, Osmangazi University Faculty of Medicine, Department of Anesthesiology and Reanimation, Eskişehir, Turkey.
E-mail: drayseayyildiz@gmail.com

How to cite this article: Ayyıldız A, Yıldırım ÖT, Uçan A, Ayyıldız FA. Evaluation of steroid therapy in COVID-19 patients; in the right dose at the right time to the right patients. Niger J Clin Pract 2023;26:280-6.

very high rate of complications was also reported during this period. Serious cardiac side effects, the elevation of d dimer and increase in thromboembolic events, increase in neutrophil-lymphocyte ratio, deep lymphopenias and increase in secondary infection rates can be counted as the main complications.[6]

Considering the studies on the subject, in the COVID-19 treatment guideline prepared on April 21, 2021, clinicians were recommended to calculate the benefit-risk in the use of steroids. It has been suggested that suppression of the inflammatory process will save clinicians time in process management and prevention of multiple organ damage, and this time should be well adjusted.[7]

The use of steroids, which are recommended to be given in the right indication, at the right timing, and at the right dose, becomes quite complicated in the intensive care unit. In our study, we aimed to evaluate the clinical efficacy of high-dose steroid therapy and its effect on mortality in COVID-19 patients with severe pneumonia, severe ARDS, and septic shock by comparing it with standard-dose steroid therapy.

Subjects and Methods

Study design and participants

The study was carried out with the permission of Eskişehir Osmangazi University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Date: 02.03.2021, Decision No: 02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this study, the medical records of patients who were followed up in the intensive care unit of Eskişehir City Hospital between 15.11.2020 and 15.01.2021, who developed pneumonia, ARDS, and septic shock secondary to COVID-19 infection, were retrospectively reviewed. The diagnosis of COVID-19 in all patients was confirmed by computed tomography (CT) and polymerase chain reaction (PCR). Patients followed in the intensive care unit for other reasons without steroid indication, patients who died on the first day of hospitalization, and the pediatric population were excluded from the study. [Figure 1]

Treatment routine of patients

In Turkey, patients are treated with algorithms in the guidelines prepared by the Ministry of Health's COVID-19 scientific committee and constantly revised in light of current literature.[8] In accordance with the guideline algorithms, favipiravir, which was given as an antiviral treatment agent for severe COVID-19 infection, was used as standard treatment for 10 days. Patients with severe pneumonia, ARDS, and septic shock who needed

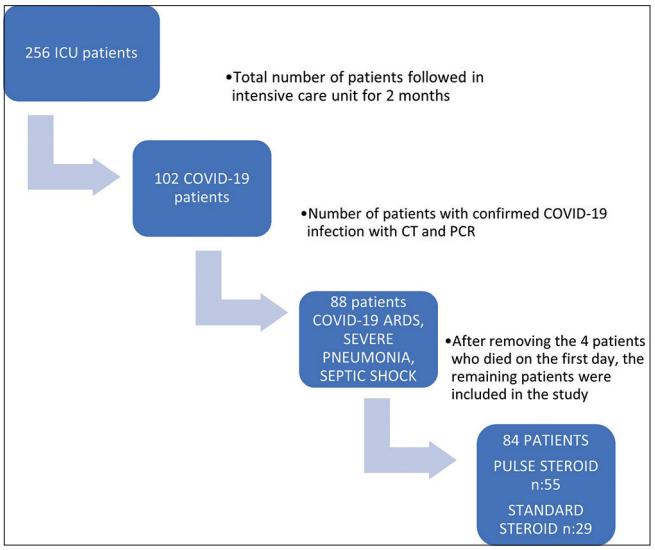

Figure 1: Inclusion/exclusion criteria

respiratory support were given 6 mg/day of dexamethasone for 10 days. Treatment with 250 mg/day (approximately 2 mg/kg/day) methylprednisolone for 3 days and then methylprednisolone equivalent to 6 mg dexamethasone was continued in patients whose oxygen demand deepened under 6 mg dexamethasone treatment. Hypoxemic respiratory failure patients were gradually oxygenated with nasal cannula-simple mask-reservoir mask-high flow nasal cannula-cpap-invasive mechanical ventilation and the patient positions were changed intermittently unless there were contraindications (pron, right side, left side, supine, mobilized, sits). Lung protective mechanical ventilator strategies were applied to patients who developed ARDS. Anti-cytokine treatments (tocilizumab and anakinra) were given to the patients in appropriate doses in case of an increase in the c reactive protein (CRP), white blood cell (WBC), and Ferritin values, which were evaluated consecutively during the course of treatment. 100 mg/day acetylsalicylic acid, 40MG: 4000 anti-Xa IU/O.4ML enoxaparin was administered to the patients to prevent the development of thrombotic complications unless there is a contraindication. Dose revisions were made according to the D-dimer levels and glomerular filtration rate of the patients.

Data collection

The data of 84 patients included in the study were taken from hospital laboratory records and intensive care observation papers.

While the patients who used 6 mg dexamethasone during their treatment constituted the standard group, the patients who were administered methylprednisolone mini-pulse therapy at a dose of 2 mg/kg/day (continued with a dose of methylprednisolone equivalent to 6 mg dexamethasone after 3 days of 250 mg IV infusion) constituted the pulse

steroid group. Demographic characteristics, comorbidities, laboratory parameters, oxygen needs, number of days of stay in the intensive care unit, and mortality status of the patients were recorded.

Statistical analysis

Data were given as "median ± standart deviation" for normally distributed continuous variables and as "median (interquartile range)" for a variable which is not normally distributed and as proportions for categorical variables. The homogenity of variances was tested by the Levene test and the distribution of data for normality was tested by the Shapiro-Wilk test. Mann Whitney U test was used to compare variables that are not normally distributed and the t-test was used for normally distributed variables. The Chi-square test was used to compare categorical variables. $P < 0.05$ was considered statistically significant. Data were analyzed using SPSS 22.0 (IBM SPSS Ver. 20.0, IBM Corp, Armonk NY, USA).

Results

Patient characteristics

The mean age of the study population was 68.14 ± 12.55, and 53% (n = 45) were female. The study population was divided into two groups; the methylprednisolone pulse group (n = 55) and the dexamethasone group (n = 39). The mean age of the methylprednisolone group was 68.67 ± 12.63 and the dexamethasopne group was 67.93 ± 12.61 with no significant difference (p = 0.799). Female gender constituted 54% of the methylprednisolone group and 51% of the dexamethasone group (p = 0.805). The groups had similar APACHE II rates (17.81 ± 8.31 for the methylprednisolone group and 21.00 ± 7.56 for the dexamethasone group, $P = 0.089$). [Table 1]

The most common comorbidities of methylprednisolone and dexamethasone groups were HT (32.7% n = 18 vs 27.5% n = 8, respectively, $P = 0.628$), respiratory disorders (29% n = 16 vs 31% n = 9, respectively, $P = 0.853$) and DM (30.9% n = 17 vs 20.6% n = 6, respectively, $P = 0.318$), there was no significant difference between groups.

Laboratory findings

In the group using pulse steroids, the leukocyte count (10.81 vs 9.94, $P = 0.840$), the neutrophil count (9.85 vs 8.13, $P = 0.914$), the neutrophil/lymphocyte ratio (12.77 vs 10.60, $P = 0.696$) was higher and the lymphocyte count (0.69 vs 0.85, $P = 0.682$) was lower, but the difference was not statistically significant.

Table 1: Baseline demographic and laboratory characteristics of the patients with COVID-19

	Patients, no. (%) *n* All (84)	Methylprednisolone group (*n*=55)	Dexametazone group (*n*=29)	*P*
Age, mean±SD, y	68.14±12.55	68,67±12.63	67.93±12.61	0.799
Gender		0.805		
Male	39	25	14	
Female	45	30	15	
Coexisting disorders				
Hypertension (*n*)	26	18	8	0.628
Diabetes Mellitus (*n*)	23	17	6	0.318
Cardiovascular disorders (*n*)	16	10	6	0.781
Respiratory disorders (*n*)	25	16	9	0.853
Renal disorders (*n*)	7	3	4	0.189
Laboratory parameters				
Leukocytes x10^3/µL	10,76 (7.02-14.99	10.81 (6.93-14.53)	9.94 (7.05-15.38)	0.840
Neutrophil x10^3/µL	9.40 (6.01-12.75)	9.85 (6.07-12.47)	8.13 (5.98-14.07)	0.914
Lymphocyte x10^3/µL	0.77 (0.46-1.20)	0.69 (0.46-1.18)	0.85 (0.42-1.25)	0.682
Neutrophil/Lymphocyte ratio	12.65 (7.42-19.57)	12.77 (8.60-19.11)	10.60 (5.69-23.12)	0.696
Haemoglobin	12.40±1.99	12.51±2.12	12.18±1.71	0.471
Platelets x10^3/µL	255.88±106.27	262.85±96.05	242.65±124.13	0.411
C-reactive protein, mg/dL	128.73±87.78	124.68±87.23	136.29±89.85	0.569
Ferritin ng/mL	520.00 (212.50-1159.00)	505.00 (201.00-949.00)	541.50 (302.25-1995.25)	0.302
D-dimer µg/ml	1.59 (0.96-4.28)	1.31 (0.85-3.88)	2.15 (1.21-6.11)	0.128
Troponin I, pg/mL	19.95 (8.60-51.30)	16.90 (8.30-51.30)	22.80 (11.57-71.00)	0.400
CK-MB	1.70 (0.90-3.80)	1.50 (0.80-2.97)	2.30 (1.60-5.20)	0.052
B-type natriuretic peptide, pg/mL	105.60 (51.20-451.70)	93.80 (51.60-289.55)	259.50 (24.60-614.00)	0.344
Creatinine, mg/dL	0.91 (0.74-1.54)	0.85 (0.73-1.21)	0.98 (0.79-1.92	0.180
Glucose, mg/dL	153.00 (119.00-257.00)	186.00 (129.00-273.00)	133.00 (110.50-221.50)	0.037
APACHE	18.91±8.15	17.81±8.31	21.00±7.56	0.089

Table 2: Clinic characteristics of the patients with COVID-19

	Patients, no. (%) All (84)	Methylprednisolone group (*n*=55)	Dexametazone group (*n*=29)	*P*
Duration of intensive care stay, days	11.08±8.55	13.36±8.75	6.75±6.28	0.001
Need for oxygen therapy				
Nasal cannula	1.03±1.54	1.09±1.50	0.93±1.64	0.655
Reservoir mask	3.22±3.68	3.78±3.83	2.17±3.17	0.056
High flow oxygen therapy-NIV	3.57±4.80	4.60±5.25	1.62±3.02	0.001
Invasive mechanic ventilation	3.09±5.73	3.65±6.54	2.03±3.61	0.220
Need for inotropic agents, days	1.98±3.08	2.27±3.33	1.44±2.50	0.246
Mortality status		0.943		
Ex	43	28	15	
Discharge	41	27	14	

Table 3: Laboratory parameters before and after treatment in COVID-19 patients

Laboratory parameters	Methylprednisolone group (*n*=)			Dexametazone group (*n*=)		
Leukocytes x10^3/µL	10.82 (6.93-14.53)	11.43 (8.53-14.79)	0.129	9.94 (7.05-15.38)	8.6 (7.5-15.3)	0.191
Neutrophil x10^3/µL	9.85 (6.07-12.47)	9.86 (7.30-12.83)	0.052	8.13 (5.98-14.07)	7.4 (5.5-11.5)	0.211
Lymphocyte x10^3/µL	0.69 (0.46-1.18)	0.60 (0.43-0.944)	0.089	0.85 (0.42-1.25)	0.74 (0.42-1.11)	0.348
Neutrophil/Lymphocyte ratio	12.78 (8.60-19.11)	16.52 (10.34-26.46)	0.006	10.61 (5.70-23.12)	14.10 (5.34-18.19)	0.256
Haemoglobin	12.22±2.12	11.33±2.11	0.002	11.71±1.41	10.99±1.81	0.082
Platelets x10^3/µL	268.55±91.53	231.97±102.73	0.049	284.46±148.62	260.33±127.06	0.454
C-reactive protein, mg/dL	122.05±97.33	71.61±69.68	0.014	129.23±109.89	66.49±78.04	0.046
Ferritin	505.00 (201.00-949.00)	597.0 (260.0-1414.0)	0.032	541.5 (302.2-1995.2)	556 (167-2080)	0.695
D-dimer	1.31 (0.86-3.88)	2.15 (1.0-5.99)	0.281	2.15 (1.21-6.11)	2.11 (1.22-2.53)	0.347
Troponin I, pg/mL	16.90 (8.30-51.30)	52.8 (5.6-202.7)	0.019	22.8 (11.6-71.0)	14.8 (6.5-3082.1)	0.310
CK-MB	1.50 (0.80-2.97)	1.55 (0.90-4.10)	0.435	2.3 (1.6-5.7)	2.8 (1.75-5.5)	0.094
B-type natriuretic peptide, pg/mL	93.8 (51.60-289.50)	105.1 (25.7-252.9)	0.931	259.5 (24.6-614)	77.2 (62.3-5000)	0.999
Creatinine, mg/dL	0.85 (0.73-1.21)	0.82 (0.67-1.19)	0.244	0.98 (0.79-1.92	1.03 (0.72-4.81)	0.115
Glucose, mg/dL	186 (129-273)	153 (116-230.5)	0.309	133.0 (110.5-221.5)	127 (102-193)	0.551

There was no significant difference between the groups in terms of Trop I, CK MB, and BNP values. The difference between the groups in terms of glucose value is significant, and it was higher in pulse steroid use. (186 vs 133, $P < 0.03$).

Considering the duration of intensive care stay, it was observed that this duration was longer in the pulse steroid group and it was statistically significant. (13.36 ± 8.75 for the pulse steroid group vs 6.75 ± 6.28 for the dexamethasone group, $P < 0.01$). When the number of high-flow oxygen therapy support days was considered, it was observed that it was longer in the pulse group and it was statistically significant. (4.60 ± 5.25 vs 1.62 ± 3.02, $P < 0.01$). From the methylprednisolone group, 50.9% (n = 28) of the patients died and 51.7% (n = 15) of the dexamethasone group died during intensive care stay and the difference was not statistically significant (n = 0.943). [Table 2]

Before and after treatment findings

When the values before and after treatment were compared; there was a statistically significant increase in the neutrophil/lymphocyte ratio after treatment in the pulse steroid group (p = 0.006). Although it was not statistically significant in the pulse steroid group, there was a numerical increase in D-dimer levels (p = 0.28). Thromboembolic complications were recorded in 2 patients in the pulse steroid group. There was a significant decrease in hemoglobin values (p = 0.049) and platelet values (p = 0.049) in this group. Considering the inflammatory parameters, a significant decrease was observed in the CRP (p = 0.01) and ferritin (p = 0.03) levels after treatment in the pulse steroid group, while only the decrease in the CRP (p = 0.04) values was found to be significant in the dexamethasone group. While there was no significant difference between the groups in terms of cardiac markers at the beginning, a significant increase in cardiac troponin-I levels was observed in the pulse steroid group compared to the pre-treatment value after treatment (p < 0.01). CK MB and BNP values were higher in the pulse steroid group although the difference was not statistically significant [Table 3].

Discussion

Our study is a clinical study emphasizing the clinical importance of the appropriate period, appropriate patient, and appropriate dosage. This study evaluates the efficacy of standard-dose steroid therapy and relatively high-dose mini-pulse steroid therapy in the follow-up of patients with severe COVID-19 infection in the intensive care unit, changes in clinical symptoms, laboratory findings, and complications. The results of the study emphasize once again that steroids should not be given routinely but should be given to patients only during periods of severe pneumonia, ARDS, and septic shock, and that they should be started at standard doses during periods of administration. In our study, it was observed that even the mini-pulse doses, which we call relatively high, did not significantly contribute to the mortality and recovery rate, but increased the complication rate.

Steroids have been used in the treatment of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) outbreaks before, and steroid use has been found to be associated with delayed viral clearance.[9,10] A meta-analysis conducted by Russell *et al*. stated that corticosteroid use during past epidemics was associated with a delay in viral clearance from the systemic circulation and respiratory system, and they may cause many side effects such as corticosteroid-induced diabetes. Based on these studies; in the early stages of the COVID-19 epidemic, its use was not recommended because it increased complications and mortality.[11]

The importance of using corticosteroids in COVID-19 infection is largely based on data from The Randomized Evaluation of COVID-19 Therapy (RECOVERY collaborative group). In this multicenter, randomized study including 176 hospitals in England, all hospitalized patients were randomized at a rate of ½, and only one group was given 6 mg dexamethasone for 10 days. Compared to the control group, the dexamathasone group was superior in 28-day mortality. Although there were no significant results in hospitalized patients with minimal oxygen demand, significant results were found in decreasing oxygen demand in patients with high oxygen demand and requiring invasive mechanical ventilation.[3]

In the CAPE TRIAL GROUP INVESTIGATOR study, the hydrocortisone group was associated with better results than the placebo group.[3] In the REMAP-CAP study, patients with COVID-19 septic shock were evaluated and the patients receiving hydrocortisone treatment had better results in terms of the number of days without organ support for 21 days.[4] After these large-scale studies, steroids began to be widely used during the pandemic all over the world.

In the later stages of the pandemic, as the pathogenesis of the disease was understood, the use of higher doses of steroids to suppress hyperinflammation came to the fore. It has been recommended to use high doses of steroids in moderate and severe ARDS requiring intensive care admission, patients with constantly increasing oxygen demand, and requiring invasive mechanical ventilation.[12] It has been shown that methylprednisolone use in high doses reduces mortality and shortens hospital stay in severe and progressive ARDS.[13]

In a large-scale randomized controlled study conducted in 41 centers in Brazil, high-dose and low-dose dexamethasone groups were compared, and a significant difference was found in the number of days of survival and days of mechanical ventilation in the first 28 days in the high-dose group. No significant difference was observed in steroid-related side effects and mortality rates of the groups.[14]

In a meta-analysis of all steroid studies in the midst of the pandemic, Sterne *et al*. concluded that the contribution of steroids to clinical improvement is large and effective.[15]

Mareev *et al*. (WAYFARER Study) compared 1000 mg methylprednisolone pulse given for 3 days and 6 mg dexamethasone given for 3 days, and they recorded a decrease in dyspnea, an increase in sp02, and a decrease in CRP in the pulse steroid group. However, when complications were examined, they found a significant increase in D-dimer. Thromboembolic complications were observed in 4 patients and pulmonary embolism was detected in 2 patients.[6] In our patients, there was a significant decrease in CRP and Ferritin in the mini pulse group, and a numerical increase in d-dimer, although it was not statistically significant. Again, thromboembolic complications developed in 2 people in the pulse group. Steroid therapy can potentially reduce the efficacy of prophylactic therapy with low molecular weight heparin (LMWH) due to the increased risk of thrombosis. Doses and efficacy of anticoagulation prophylaxis should be checked more frequently when high doses are used in steroid use.[6]

It is obvious that the use of high-dose steroids increases the leukocyte and neutrophil counts and deepens lymphopenia and significantly increases the neutrophil/lymphocyte ratio, which significantly reflects the severity of secondary chronic inflammation. These changes appear in the form of an increased risk of developing secondary infections. In our study, the neutrophil/

lymphocyte ratio was found to be statistically high in the pulse steroid group in parallel with the literature.[16]

Another list of complications mainly caused by high-dose steroids can be listed as an increase in insulin resistance and secondary glucose metabolism disorders, an increase in the risk of cardiovascular disease, and secondary bacterial infections.[17] In our study, glucose levels in the mini-pulse steroid group were found to be statistically significantly higher than in the standard dose group. (186 vs 133, $P < 0.03$). Also, there was no significant difference between the groups in terms of cardiac markers at the beginning, a significant increase in cardiac troponin I was observed in the mini pulse group after treatment. The development of refractory hypertension, cardiomyopathy, and ischemic heart disease due to water and salt retention has been reported during high-dose steroid therapy. It has also been suggested that changes in myocardial calcium metabolism may induce arrhythmias after steroid therapy.[18] A study investigating the acute cardiac effects of high-dose steroids showed that left ventricular global longitudinal strain and ejection fraction were significantly increased in patients who underwent echocardiography in the acute period after steroid administration. Therefore, they recommended close cardiac monitoring for patients receiving high-dose steroid therapy.[17]

We treat patients according to the guidelines prepared and constantly updated by the Coronavirus Scientific Committee of the Ministry of Health.[8] And with the recommendation of the ministry's guide, we started standard dose steroid treatment for our patients with the necessary indications. We increased the steroid dose in case of increased oxygen demand during follow-up. Therefore, patients in the standard dose group either recovered in a very short time without the need for high-dose steroid treatment or died before they could switch to high-dose steroid treatment. Therefore, in our study, the number of intensive care unit stays and high-flow nasal therapy support days were statistically higher in the group given high-dose steroids. López *et al*. compared the use of methylprednisolone at doses of 0.5 mg/kg with relatively high doses of 1.5 mg/kg and found a 14% decrease in mortality.[19] However, when we looked at the mortality rate in our study, we could not see a statistically significant difference in mortality rates in the high-dose group.

Although using high doses of steroids can suppress inflammation and alleviate the infection, the fact that it increases the risk of complications so much makes us clinicians ask the question of when we should take this risk. Should we give steroids in the period when the hyperinflammatory response is most dominant or should we give them early as soon as the diagnosis is made?. In a multicenter study conducted in Iran, only patients with very low saturation, high inflammatory markers, and poor general condition were included in the study. In this study, 250 mg/day methylprednisolone was given to this patient group for 3 days and compared with the standard care group. The recovery rate was significantly higher and the mortality rate was significantly lower in the mini-pulse group.[1] In the study of Bahl *et al*., they investigated the optimal administration time of steroids and found that starting before 72 hours significantly increased mortality.[20] In light of these studies emphasizing that steroid treatment should not be given in the early period, we did not routinely administer steroids to any of our patients in the early period. Steroids were given only to patients who developed severe pneumonia, ARDS, and septic shock during their intensive care follow-up, and low doses were started routinely. In the patient population who did not respond to treatment with a low-dose steroid (6 mg dexamethasone), 2 mg/kg methylprednisolone was given to increase the steroid to relatively high doses. No significant difference was found in terms of mortality in patients with high doses.

Conclusion

The effect of steroid use on viral clearance in COVID-19 infection, especially in the early period of the disease, is not clear and we do not recommend it routinely, but we recommend its use in the condition that it is indicated in the critically ill group with the poor general condition. Since there is no significant difference between high-dose pulse steroid treatment and standard treatment doses, we think that the risk of complications should not be taken into account and high doses should not be used.

Limitation of the study

The limitations of the study can be listed as the retrospective nature of the study and the small number of patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S, *et al*. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: Results from a randomised controlled clinical trial. Eur Respir J 2020;56:2002808. doi: 10.1183/13993003.02808-2020.
2. World Health Organization. Evidence to recommendations: Methods used for assessing health equity and human rights considerations in COVID-19 and aviation .Interim guidance. Available from: https://apps.who.int/iris/bitstream/

handle/10665/338056/WHO-2019-nCoV-Aviation-evidence_equity-2020.1-eng.pdf [Last accessed on 2020 Dec 23].
3. Dequin PF, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J, *et al*. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ıll patients with COVID-19: A randomized clinical trial. JAMA 2020;324:1298-306.
4. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, *et al*. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. JAMA 2020;324:1317-29.
5. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, *et al*. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384:693-704.
6. Mareev VY, Orlova YA, Pavlikova EP, Matskeplishvili ST, Krasnova TN, Malahov PS, *et al*. Steroid pulse -therapy in patients With coronAvirus Pneumonia (COVID-19), sYstemic inFlammation And Risk of vEnous thRombosis and thromboembolism (WAYFARER Study). Kardiologiia 2020;60:15-29. [English, Russian].
7. COVID-19 Treatment Guidelines. Available from: https://www.covid19treatmentguidelines.nih.gov/. [Last accessed on 2021 May 19].
8. Bakanlığı, T. S. COVID-19 (SARS-CoV2 ENFEKSİYONU) REHBERİ. 2020. Available from: https://www.tipfak.com/wp/wp-content/uploads/2020/03/COVID-19-rehberi-23032020-1.pdf-1.pdf. [Last accessed on 2020 Jul 16].
9. Stockman LJ, Bellamy R, Garner P. SARS: Systematic review of treatment effects. PLoS Med 2006;3:1525–31.
10. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, *et al*. Corticosteroid therapy for critically ill patients with middle east respiratory syndrome. Am J Respir Crit Care Med 2018;197:757–67.
11. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395:473-5.
12. Sarzi-Puttini P, Giorgi V, Sirotti S, Marotto D, Ardizzone S, Rizzardini G, *et al*. COVID-19, cytokines and immunosuppression: What can we learn from severe acute respiratory syndrome? Clin Exp Rheumatol 2020;38:337–42.
13. Chen RC, Tang XP, Tan SY, Liang BL, Wan ZY, Fang JQ, *et al*. Treatment of severe acute respiratory syndrome with glucosteroids: The Guangzhou experience. Chest 2006;129:1441–52.
14. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, *et al*. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: The CoDEX randomized clinical trial. JAMA 2020;324:1307-16.
15. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, *et al*. Association between administration of systemic corticosteroids and mortality among critically ıll patients with COVID-19: A meta-analysis. JAMA 2020;324:1330-41.
16. Ronchetti S, Ricci E, Migliorati G, Gentili M, Riccardi C. How glucocorticoids affect the neutrophil life. Int J Mol Sci 2018;19:4090.
17. Aksakal E, Simsek Z, Aksu U, Birdal O, Ateş ES, Kalkan K, *et al*. Acute cardiac effects of high dose steroid treatment: A speckle tracking echocardiography study. J Clin Ultrasound 2019;47:351-5.
18. Jain R, Bali H, Sharma VK, Kumar B. Cardiovascular effects of corticosteroid pulse therapy: A prospective controlled study on pemphigus patients. Int J Dermatol 2005;44:285-8.
19. López Zúñiga MÁ, Moreno-Moral A, Ocaña-Granados A, Padilla-Moreno FA, Castillo-Fernández AM, Guillamón -Fernández D, *et al*. High-dose corticosteroid pulse therapy increases the survival rate in COVID-19 patients at risk of hyper-inflammatory response. PLoS One 2021;16:e0243964.
20. Bahl A, Johnson S, Chen NW. Timing of corticosteroids impacts mortality in hospitalized COVID-19 patients. Intern Emerg Med 2021;16:1593-603.