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Original Article

Effect of 2 Different High-Dose Methylprednisolone Treatments on Clinical Outcomes in Severe COVID-19 Patients

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Abstract

OBJECTIVE: The present study aimed to evaluate and compare the use of 2 different high-dose methylprednisolone posology in treating severe coronavirus disease 2019 pneumonia regarding mortality and recovery time between themselves and against steroidal/non-steroidal treatment.

MATERIAL AND METHODS: Severe coronavirus disease 2019 patients followed up between March 2020 and January 2021 were included. The steroid-free treatment protocol was applied before August 2020 (non-pulse group) and a treatment algorithm containing normal and high doses of methylprednisolone was applied after August 2020 (pulse group). Patients with clinical deterioration under the normal dose of methylprednisolone were administered 250 mg or 1000 mg of methylprednisolone for 3 days. We compared the pulse and non-pulse groups, in addition to pulse subgroups with each other, for clinical outcomes.

RESULTS: A total of 138 patients were included, including 36 patients in the non-pulse group and 102 in the pulse group. In the pulse group, 70 patients received 1000 mg/day and 32 received 250 mg/day of high-dose methylprednisolone therapy. In the comparison of pulse and non-pulse patient groups, mortality rate was lower in the pulse group ($P < .001$), and the time to discharge without oxygen support was shorter. Although the patients in the 250 mg subgroup were older, there was no difference between the 250 mg and 1000 mg subgroups in terms of end of oxygen requirement, discharge with oxygen support, and mortality. In addition, the required time to reach the oxygen-free period in patients discharged without oxygen support was similar in the 2 subgroups, and the majority of patients in both subgroups reached the oxygen-free period on the 20th day after initiating methylprednisolone.

CONCLUSION: Since there was no difference in clinical improvement between the use of 250 mg or 1000 mg methylprednisolone in patients with severe coronavirus disease 2019 infection, 1000 mg methylprednisolone was not required.

KEYWORDS: Methylprednisolone, corticosteroid, treatment, anakinra, COVID-19
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INTRODUCTION

Fourteen percent of coronavirus disease 2019 (COVID-19) cases progress to severe COVID-19 pneumonia. Anti-inflammatory and anti-cytokine drugs, especially corticosteroid therapy, constitute the backbone of treating such severe COVID-19 infection.[1-3] The severe clinical course in COVID-19 is associated with an excessive and uncontrolled immune response. Severe lung injury and acute respiratory distress syndrome (ARDS) develop in relation to excessive immune response, and the disease may progress to a fatal course.[4] It has been demonstrated that immunomodulatory and immunosuppressive therapies and interleukin-blocking agents used to suppress the excessive immune response in COVID-19 disease reduce hospital stay and increase survival.[5]

Corticosteroids positively contribute to the treatment when administered with appropriate timing in ARDS and sepsis cases.[6] In addition, the benefit of using corticosteroid therapies in patients who need oxygen support in COVID-19 disease has been proven to be effective in clinical trials designed as randomized controlled.[7,8] Recent studies report that the short-term use of methylprednisolone (MTP) at a dose of 250 mg/day in severe COVID-19 pneumonia reduces mortality and the need for oxygen support and improves inflammation markers.[9,10] Although not yet clearly supported by randomized controlled studies, it has been reported in a case series that short-term treatments of 500 mg/day and 1000 mg/day MTP also reduce mortality and contribute to lung recovery.[2,11] In a multicenter retrospective cohort, Cusacovich et al[12] reported that corticosteroid pulses reduce the mortality in severe COVID-19 patients.

The present study firstly aimed to investigate the impact of the treatment regimens containing low- and high-dose steroids on reducing mortality and shortening recovery time in patients who were followed up with severe COVID-19 pneumonia and deteriorated clinically. Secondly, if steroid treatment had an impact, we aimed to evaluate whether there was a

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difference between the 250 mg/day and 1000 mg/day posology regarding clinical outcomes, recovery time, and mortality.

MATERIAL AND METHODS

Study Design and Setting

This retrospective observational study was performed in one of the country's reference hospitals for COVID-19 infection between March 2020 and January 2021. Patients over 18 years of age who were admitted to the hospital with COVID-19-related pneumonia (progressed to severe pneumonia during hospitalization), severe pneumonia, and critical illness were reviewed. Among these patients, those with clinical deterioration under standard therapy during their hospitalization period were included in the study.

An informed consent form was obtained from all patients included in the study. Ethical approval was provided by the Turkish Ministry of Health and the Ankara City Hospital Ethical Committee 2 with the number E2-21-31.

Patient Population

All included patients were those whose follow-up was started in the wards. Patients who needed intensive care support during their follow-up were transferred to the intensive care unit (ICU) and admitted back to the wards when the need for intensive care was ended. Disease severity was based on the WHO guideline classification. Patients with any oxygen saturation of <90% in room air, respiratory rate of >30/min, or examination finding indicating respiratory distress were categorized as having severe COVID-19 pneumonia. Those patients with ARDS, sepsis, and septic shock and those needing mechanical ventilation or vasopressor support were categorized as critically ill patients.[13]

Standard of care was constituted based on the recommendations of the Ministry of Health of the Turkish Republic COVID-19 guidelines, which includes treatment protocols that are regularly updated depending on the achievements in the literature.[14] Based on this public guideline, the time-varying treatment algorithms applied for COVID-19 patients in our center before and after August 2020 are presented in Figure 1. Before August 2020, all patients received favipiravir and anticoagulant therapy as the standard of care 1 (SOC 1). Low- or high-dose steroid treatment was not used during this period, so these patients were accepted as the non-pulse group. In case of clinical deterioration in these patients in this period, basic life support and/or tocilizumab, anakinra, intravenous immunoglobulin (IVIG), and stem cell transfusion were applied to the patients.

MAIN POINTS

- High-dose methylprednisolone (MTP) reduces mortality and shortens recovery time in severe coronavirus disease 2019 (COVID-19) infection.
- There is no difference between mortality and recovery time in the use of methylprednisolone at a dose of 250 mg/day or 1000 mg/day.
- There is no need to use a higher dose of methylprednisolone than 250 mg/day in severe COVID-19 infection.

In the updated ministry guideline, it was recommended to use 0.5-1 mg/kg of prednisolone or equivalent corticosteroid in patients who needed oxygen support due to respiratory distress and to use high-dose (≥250 mg/day) MTP in case of no response to this treatment within 24 hours. In addition, it was advised that anti-cytokine therapy should be used in patients with clinical progression under high-dose MTP therapy.[14] Based on our updated treatment algorithm, after August 2020, patients received favipiravir, anticoagulant therapy, and 0.5-1 mg/kg/day MTP (or equivalent) as the standard of care 2 (SOC 2). In case of clinical deterioration under SOC 2, firstly, patients were administered high-dose MTP therapy for 3 days. Therefore, patients with clinical deterioration during this second period were defined as the pulse group. We used 2 different MTP high doses for the pulse group, a dose of 250 mg/day and 1000 mg/day. The high dose of MTP used in patients was determined by the team of specialist physicians who followed up the patient. The MTP dose was continued as 1 mg/kg/day as of the fourth day for patients whose need for oxygen support and acute-phase reactants regressed under 3 days of high-dose MTP treatment.

If the patients' need for oxygen support did not regress and/or acute-phase reactants continued to increase after the third day of high-dose MTP, we added anakinra to the therapy. Anakinra was used at a dose of 2-10 mg/kg, divided into 4 doses.

Clinical deterioration was defined as persistent high fever, increase in oxygen support requirement within 24 hours, deepening of lymphopenia and thrombocytopenia, and increase in acute-phase response under SOC 1 and SOC 2 presented in Figure 1.

Follow-up Characteristics and Clinical Outcomes

Demographic characteristics and comorbid diseases of patients, time from symptom onset to admission, and time from symptom onset to clinical deterioration were obtained from the patient files and hospital electronic database. Fever (>38.0°C), oxygen support level [percent of fraction of inspired oxygen (FiO_2) required to keep oxygen saturation (SpO_2)>93%, and SpO_2/FiO_2 ratio were recorded. The low SpO_2/FiO_2 ratio reveals the need for higher oxygen support, which is expected to increase under treatment. The following laboratory parameters were also recorded: white blood cell, lymphocyte and platelet counts, creatine kinase, lactate dehydrogenase (LDH), C-reactive protein (CRP), procalcitonin, interleukin-6, ferritin, and D-dimer. Antiviral and anti-cytokine therapies, complications of COVID-19 disease, and the need for ICU follow-up were noted for all patients.

In order to evaluate the clinical course, fever, SpO_2/FiO_2 ratio, and laboratory parameters listed above were evaluated on the following days: (i) the day of hospital admission, (ii) the day of clinical deterioration/first day of high-dose pulse or other additional therapies, (iii) the third day of pulse therapy, (iv) the fifth day of pulse therapy, and (v) the day free of oxygen support.

Any clinical conditions, including thromboembolic events, acute renal failure under treatment, blood sugar dysregulation, or increased blood pressure, were considered the development of complications of COVID-19 disease.

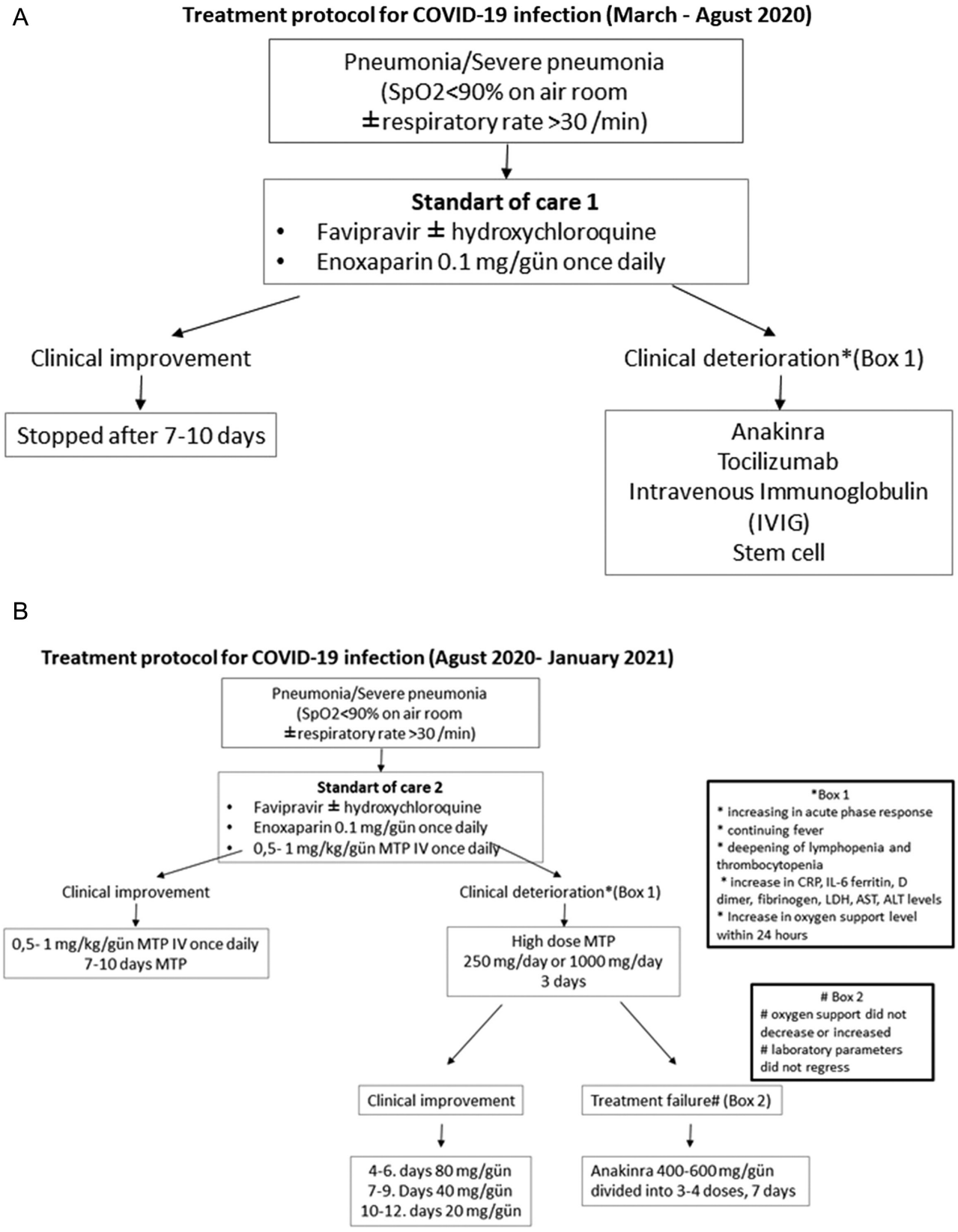

Figure 1. (A) Treatment protocol for coronavirus disease 2019 (COVID-19) infection (March-August 2020). (B) Treatment protocol for COVID-19 infection (August 2020-January 2021)

We compared the pulse and non-pulse groups in terms of primary clinical outcomes consisting of death, discharge without oxygen support, discharge with oxygen support, and time to reach period without oxygen support in patients who were discharged without oxygen. As a secondary outcome, the requirement of ICU follow-up and the development of complications were evaluated for the pulse and non-pulse groups. The need for anakinra treatment in patients unresponsive to high-dose MTP was also compared as a secondary outcome. In the same way, we compared 2 different high-dose steroid

dose subgroups within themselves for all primary and secondary outcomes.

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for Social Sciences Statistics for Windows version 25.0 (IBM Inc., Armonk, NY, USA). Descriptive statistics were presented using median and interquartile range (25th-75th percentiles) for continuous variables and frequency and percentage values for categorical variables. The Mann–Whitney *U*-test compared age, duration of symptom onset to admission and initial clinical deterioration, and clinical and laboratory findings on admission day and the initial day of MTP between pulse and non-pulse groups (absent and exist) and 250 mg versus 1000 mg. The relationship between pulse steroid use and categorical variables (gender, presence of comorbid disease, clinical severity parameters, clinical outcomes, development of complication, and requirement of hospitalization in the ICU) was investigated using the Pearson chi-square test when the test assumptions were satisfied. Otherwise, Fisher's exact test was used. Time after high-dose methylprednisolone therapy to reach an oxygen-free condition was compared between non-pulse and pulse steroid groups using Kaplan–Meier curves. Statistical significance was regarded as a *P*-value <.05 in overall comparisons.

RESULTS

One hundred thirty-eight patients with severe COVID-19 pneumonia who had clinical deterioration during hospitalization were enrolled in the study. Thirty-six patients who met the inclusion criteria before August 2020 were included in the non-pulse group, while 102 patients who met the inclusion criteria after August 2020 formed the pulse group.

Comparison of Pulse and Non-pulse Groups

Demographic and clinical characteristics of patients and laboratory findings of the pulse and non-pulse groups on the day of admission and the day of clinical deterioration are given in Table 1. Age, gender, comorbid diseases, and duration of symptom onset to initiation of clinical deterioration were similar in the 2 groups. The duration of symptom onset to admission was longer and the need for oxygen support (SpO_2/FiO_2 ratio) on the day of hospital admission was higher in the pulse group compared to the non-pulse group (*P* = .003, <.001, respectively). C-reactive protein, ferritin, and LDH values on the day of hospital admission were also higher in the pulse dose group than in the non-pulse group (*P* = .004, .004, and <.001, respectively).

In the non-pulse group, in case of clinical deterioration, 4 patients were treated with tocilizumab, 3 with anakinra, 1 with IVIG, and 2 with stem cell therapy. In the pulse group, all patients received pulse therapy in case of clinical deterioration, and 26 patients unresponsive to pulse dose MTP therapy were administered anakinra treatment.

The comparison of the patient group according to administration of pulse steroid therapy regarding primary clinical outcomes revealed that those receiving high-dose steroid therapy had lower mortality rates, higher rates of discharge without oxygen support, and a shorter time to reach oxygen-free condition (*P* < .001 for each) (Table 4, Figure 2).

Comparison for 250 mg Versus 1000 mg Subgroups

A total of 102 patients with clinical deterioration had received 2 different high doses of MTP treatment. Of them, 32 received 250 mg/day MTP and 70 had 1000 mg/day MTP. Those 2 patient subgroups administered different high doses were compared for clinical outcomes within themselves. Demographic and clinical characteristics of the patient subgroups and laboratory findings on the day of admission and the day of clinical deterioration/initial day of high doses are presented in Table 2. The patients in the 250 mg subgroup were older (*P* < .001) and had more comorbid diseases (at least 1), hypertension, and pulmonary disease compared with the 1000 mg subgroup (*P* = .02, .04, .03, respectively). Duration of symptom onset to hospital admission and duration of symptom onset to initiation of high-dose MTP (clinical deterioration) were longer in the 250 mg subgroup. Laboratory and clinical parameters were similar between the 2 subgroups, except for the leukocyte count taken on the day of clinical deter ioration/initial day of high doses, which was higher in the 250 mg/day subgroup compared to the 1000 mg/day MTP group (*P* < .001). The comparison of laboratory values on the third, fifth, and the day when the patient could breathe without oxygen support under high-dose MTP treatment is given in Table 3.

The rates of patients who required anakinra treatment due to being unresponsive to high-dose MTP were not statistically different in the 250 mg/day and 1000 mg/day subgroups (31.3% and 22.9%, respectively, *P* = .136) (Table 4).

In the non-pulse group, 9 (25%) patients underwent mechanical respiratory support, and the median duration of mechanical ventilation was 10 (2-27) days. In the pulse group, 10 (10%) patients received mechanical ventilation support, and the median duration was 5 (1-10) days. Two (6.2%) of 32 patients in the 250 mg subgroup and 8 (11.4%) of 70 patients in the 1000 mg subgroup had mechanical ventilation support, and the median duration of mechanical ventilation in these subgroups was 7 (5-9) and 5 (1-10) days, respectively. When the 2 groups were compared in terms of clinical outcomes, there was no difference in mortality and discharge rates with or without oxygen support (Table 2 and Figure 2). No difference was observed between the 250 mg/day and 1000 mg/day MTP subgroups in terms of time to reach the oxygen-free day in patients discharged without oxygen support. Most patients in both groups reached the oxygen-free period on the 20th day after starting MTP (Figure 2).

DISCUSSION

In this study, the use of low- and high-dose MTP was detected to be a significant contribution to clinical recovery and survival. The survival or oxygen-free discharge rates were significantly higher, and the time to reach the oxygen-free period was shorter in patients who received high-dose MTP than in those who did not receive it. A second critical result of our study was that this positive effect was achieved even

Table 1. Clinical and Demographic Characteristics of the Patients Based on Pulse and Non-pulse Group

	Pulse Group (n = 102)	Non-pulse Group (n = 36)	*P*
Age, median (IQR)	61 (50–70)	63.5 (52-71.5)	.52
Gender (male), n (%)	82 (80.4)	22 (61.1)	.02*
Comorbid disease (at least 1), n (%)	60 (58.8)	24 (66.7)	.41*
Coronary artery disease	21 (20.6)	10 (27.8)	.37*
Hypertension	42 (41.2)	14 (38.9)	.81*
Diabetes mellitus	26 (25.5)	10 (27.8)	.79*
Pulmonary disease	3 (2.9)	5 (13.9)	.03*
Clinical severity, n (%)			.86*
Pneumonia	27 (26.5)	9 (25)	
Severe pneumonia—critical disease	75 (73.5)	27 (75)	
Duration of symptom onset to admission (day), median (IQR)	7 (5-10)	3 (2.5-7.5)	.003
Duration of symptom onset to initial clinical deterioration (day), median (IQR)	9 (7–11)	9 (5.5-13.5)	.86
Clinical and laboratory findings on admission day, median (IQR)			
Fever, °C, n (%)	44 (43.1)	21 (58.3)	.12*
SpO_2/FiO_2 ratio	2.5 (1.9-3.1)	4.3 (2.6-4.5)	<.001
White blood cell, 10^9/L	7.1 (4.9-9.2)	5.5 (4.6-7.9)	.09
Lymphocyte, 10^9/L	0.7 (0.5-1)	0.9 (0.6-1.1)	.08
Platelet, 10^9/L	195 (164–265)	193 (142.5-235)	.21
C-reactive protein, g/L	0.1 (0.1-0.2)	0 (0-0.1)	.004
IL-6, pg/mL	30.6 (14.8-61.9)	35.3 (23.5-41.7)	.44
Procalcitonin, µg/L	0.1 (0-0.2)	0.1 (0-0.3)	.74
Ferritin, µg/L	530.5 (269–1132)	245 (77.5-495)	.004
D-dimer, mg/L	0.8 (0.5-1.4)	0.9 (0.4-1.9)	.94
Creatine kinase, U/L	147.5 (75–281)	87.5 (59.5-183.5)	.06
Lactate dehydrogenase, U/L	392.5 (317-525.5)	286.5 (234-417)	.000
Clinical and laboratory findings on the initial day of MTP, median (IQR)			
Fever (>38.0°C), n (%)	22 (21.6)	21 (58.3)	<.001*
SpO_2/FiO_2 ratio	2 (1.5-2.6)	2.3 (1.8-2.6)	.22
White blood cell, 10^9/L	8.7 (6.2-12.3)	6.4 (5.1-9.3)	.01
Lymphocyte, 10^9/L	0.6 (0.4-0.8)	0.7 (0.6-1.1)	.007
Platelet, 10^9/L	250.5 (198.5–314)	215 (163.5-277)	.03
C-reactive protein, g/L	0.1 (0.1-0.2)	0.1 (0-0.2)	.80
IL-6, pg/mL	28.3 (12.5-61)	55.1 (31.5-95.5)	.03
Procalcitonin, µg/L	0.1 (0-0.2)	0.1 (0.1-0.6)	.06
Ferritin, µg/L	634.5 (354.5-1361.5)	626 (161.1-1240)	.24
D-dimer, mg/L	0.7 (0.5-1.3)	1.1 (0.6-2.4)	.02
Creatine kinase, U/L	122 (67-276)	111 (64-258.5)	.87
Lactate dehydrogenase, U/L	431 (336-571)	398 (300.5-519.5)	.12

IL, interleukin; IQR, interquartile range; MTP, methylprednisolone.
*Comparison from chi-square test, if not indicated Mann–Whitney *U*-test.

with a relatively low dose of pulsed MTP of 250 mg/day. We determined no differences between 250 mg/day and 1000 mg/day doses of MTP in terms of primary or secondary outcomes and treatment failure.

Randomized controlled clinical studies demonstrated that corticosteroid treatments used at 0.5-1.0 mg/kg/day doses reduce mortality. This result has been supported by several meta-analysis studies.[7,8] In addition, comparing the use of 6

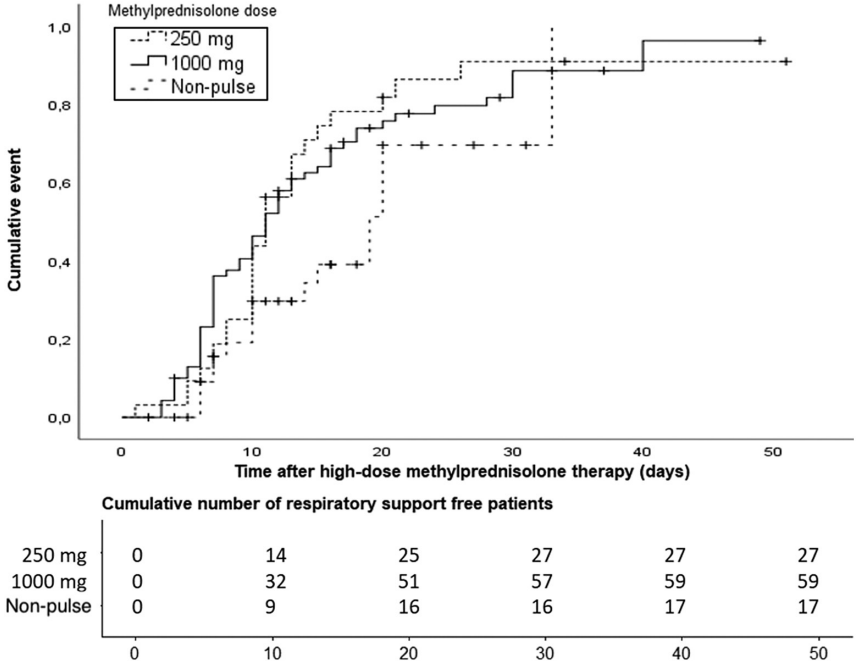

Figure 2. Time to reach free of oxygen support day.

mg dexamethasone equivalent with 250 mg MTP (3 days), it was reported that it would be a successful option in patients who did not respond to the initial low-dose corticosteroid treatment.[15] In the studies of Cusacovich et al and Edalatifard et al.[12,9] 250 mg/day (3 days) pulse therapies were administered to 124 and 34 patients, respectively, and the results were compared with the standard therapy. The authors reported that MTP pulse therapy was an effective therapeutic agent in severe COVID-19 patients and reduced mortality. Although Fernández-Cruz et al reported that the in-hospital mortality rate was similar between the patients administered low-dose or high-dose corticosteroids, a current meta-analysis in which randomized controlled studies were included concluded that high-dose MTP therapy may be a promising treatment alternative in severely ill patients.[16,17] The results of our study also support the effectiveness of high-doses steroids detected in the meta-analysis. In the present study, all the patients in the pulse group were treated with low dose (0.5-1 mg/kg/day) of MTP at the beginning of hospitalization and received high-dose MTP due to clinical deterioration. More than 90% of the patients responded well to high-dose MTP and only 8.8% died in the pulse group, whereas 52.8% died in the non-pulse group.

Pulse and non-pulse group patients were included in the study in different periods. However, their demographic characteristics, clinical features, and laboratory values on admission were not different. Moreover, the patient in the pulse group had higher CRP, LDH, and ferritin levels on the day of clinical deterioration and needed a higher level of oxygen support (lower SpO_2/FiO_2 ratio). The current literature and our centers' results indicate an association between higher levels of LDH, CRP, and ferritin and severe COVID-19 infection.[16,18] Although the patients in the pulse group had the characteristics associated with a more severe clinical course, a better clinical response was achieved by pulse therapy. Lower rates of the requirement of ICU and mortality and a shorter time to reach the oxygen-free period were detected in the pulse group. The study of López Zúñiga et al[19] reported that high-dose (1.5 mg/kg/day) corticosteroid treatment was effective in increasing survival. In addition, Ikeda et al[20] revealed that the duration of mechanical ventilator support was shorter in those who received corticosteroids than in those who did not. In the same study, it was concluded that the duration of mechanical ventilation support was shorter in patients receiving high-dose corticosteroids than in patients receiving low-dose corticosteroids. There is no consensus in the literature on the optimal type and dose of steroids that should be used in severe patients. Doses of 125-500 mg/day MTP have been used as posology in clinical studies.[9,10,12] There are no studies comparing different high doses of steroids with each other. Reports on using 1000 mg/day MTP in severe COVID-19 are limited to case series.[2,11] The fact that a high dose of 1000 mg/day of MTP was used in 70 patients in our study provides a notable experience about the results of using such a high-dose MTP in severe COVID-19 patients.

Although the patients in the 250 mg/day subgroup were older and had more comorbid diseases, their laboratory parameters were not different at admission and at the time of clinical deterioration. In addition, there were no significant differences between 32 patients treated with 250 mg/day MTP and 70 patients treated with 1000 mg/day MTP for these parameters on the third and the fifth day of pulse treatment and the day free of oxygen support. Correspondingly, the course of laboratory values was similar on the third and the fifth day of pulse treatment and the day free of oxygen support.

Anakinra treatment was used in 26 of 102 patients who received pulse therapy due to clinical failure based on the treatment algorithm. In comparison of the 250 mg/day and 1000 mg/day MTP subgroups, there was no significant difference in terms of clinical unresponsiveness and the need for

Table 2. Clinical and Demographic Characteristics of the Patients Based on the Methylprednisolone Dose

	250 mg Subgroup (n = 32)	1000 mg Subgroup (n = 70)	*P*
Age, median (IQR)	67.5 (59.5-72)	57.5 (46-66)	<.001
Gender (male)	23 (71.9)	59 (84.3)	.14*
Comorbid disease (at least 1)	24 (75)	36 (51.4)	.02*
Coronary artery disease, n (%)	7 (21.9)	14 (20)	.83*
Hypertension, n (%)	18 (56.3)	24 (34.3)	.04*
Diabetes mellitus, n (%)	10 (31.3)	16 (22.9)	.37*
Pulmonary disease, n (%)	3 (9.4)	0 (0)	.03*
Clinical severity, n (%)			.23*
Pneumonia	6 (18.8)	21 (30)	
Severe pneumonia—critical disease	26 (81.3)	49 (70)	
Duration of symptom onset to admission, median (IQR) days	7 (6-10)	7 (4-9)	.03
Duration of symptom onset to initial high-dose MTP, median (IQR) days	11 (8-12)	8.5 (6-11)	.02
Clinical and laboratory findings on admission, median (IQR) days			
Fever, °C, n (%)	12 (37.5)	32 (45.7)	.44*
SpO_2/FiO_2 ratio	2.2 (1.5–3)	2.8 (2.2-3.2)	.11
White blood cell, 10^9/L	8.6 (6.2-13.2)	5.9 (4.7-8.8)	.006
Lymphocyte, 10^9/L	0.69 (0.4-1.0)	0.75 (0.57-0.95)	.42
Platelet, 10^9/L	213.5 (162.5–261)	189.5 (164–271)	.46
C-reactive protein, g/L	0.1 (0.1-0.2)	0.1 (0.1-0.2)	.60
IL-6, pg/mL	23 (14-40)	36.9 (18-68.3)	.23
Procalcitonin, µg/L	0.1 (0-0.1)	0.1 (0-0.3)	.24
Ferritin, µg/L	400.5 (226-739.5)	600 (287–1200)	.16
D-dimer, mg/L	1 (0.5-1.8)	0.7 (0.5-1.2)	.56
Creatine kinase, U/L	110 (55–199)	163 (81–310)	.07
Lactate dehydrogenase, U/L	417 (348–494)	371 (305–528)	.24
Clinical and laboratory findings on initial pulse, median (IQR) days			
Fever, °C, n (%)	6 (18.8)	16 (22.9)	.64*
SpO_2/FiO_2 ratio	1.7 (1.4-2.4)	2.2 (1.5-2.6)	.29
White blood cell, 10^9/L	10.49 (8.18-16.83)	7.8 (5.31-11.4)	<.001
Lymphocyte, 10^9/L	0.59 (0.38-0.85)	0.63 (0.485-0.835)	.36
Platelet, 10^9/L	244 (207-331)	258 (195.5-312)	.78
C-reactive protein, g/L	0.1 (0.1-0.2)	0.1 (0.1-0.2)	.66
IL-6, pg/mL	26.5 (15.4-64.1)	29 (12.5-55.2)	.89
Procalcitonin, µg/L	0.1 (0-0.2)	0.1 (0-0.2)	.39
Ferritin, µg/L	562 (402-–1016)	709 (316.5-1413)	.54
D-dimer, mg/L	0.9 (0.5-1.6)	0.7 (0.5-1.2)	.41
Creatine kinase, U/L	100 (61-268)	127 (74-289)	.34
Lactate dehydrogenase, U/L	476 (366-571)	417 (313-572)	.16

IL, interleukin; IQR, interquartile range; MTP, methylprednisolone.
*Comparison from chi-square test, if not indicated Mann–Whitney *U*-test.

anakinra treatment. Anakinra treatment has been reported to be a safe and effective alternative treatment in severe COVID-19 patients that reduces the need for mechanical ventilation and mortality rates.[21,22]

Due to their potential anti-inflammatory effects, corticosteroids effectively suppress lung inflammation by reducing proinflammatory cytokines and excessive cytokine response in the severe phase of the disease.[23]It is known that

Table 3. Improvement of Oxygen Requirement and Laboratory Parameters After Pulse Therapy in 250 mg and 1000 mg Subgroups

	250 mg Subgroup (n = 32)	1000 mg Subgroup (n = 70)	*P**
FiO_2/SpO_2 ratio			
Third day	1.52 (1.13-2.27)	2.04 (1.19-3.14)	.16
Fifth day	1.68 (1.18-2.69)	2.09 (1.13-3.14)	.84
White blood cell, 10^9/L			
Third day	11.1 (8.22-15.94)	10.415 (8.34-12.88)	.25
Fifth day	9.33 (7.7-12.31)	9.725 (7.3-13.36)	.07
Free of oxygen support day	8.57 (6.72-11.42)	9.41 (6.58-12.83)	.63
Lymphocyte, 10^9/L			
Third day	0.525 (0.320-0.86)	0.53 (0.43-0.78)	.75
Fifth day	0.57 (0.41-1.05)	0.7 (0.46-1.09)	.16
Free of oxygen support day	1.09 (0.86-1.74)	1.34 (0.77-1.98)	.95
Platelet, 10^9/L			
Third day	270 (237–377)	306 (230–381)	.20
Fifth day	302 (262–360)	312 (251–408)	.73
Free of oxygen support day	287 (224–374)	338 (245–394)	.31
C-reactive protein, g/L			
Third day	0.04 (0.03-0.12)	0.05 (0.03-0.1)	.88
Fifth day	0.03 (0.02-0.05)	0.02 (0.01-0.06)	.96
Free of oxygen support day	0.01 (0-0.02)	0.01 (0-0.03)	.18
Interleukin-6, pg/mL			
Third day	14.1 (59-26.2)	8.03 (4.3–23)	.19
Fifth day	12.65 (9-30.65)	13.55 (5.38–29)	.28
Free of oxygen support day	12 (5.3–19)	5.96 (3.9-15.3)	.13
Procalcitonin, µg/L			
Third day	0.05 (0.03-0.28)	0.05 (0.03-0.11)	.97
Fifth day	0.07 (0.03-0.12)	0.06 (0.03-0.13)	.15
Free of oxygen support day	0.03 (0.03-0.03)	0.04 (0.03-0.08)	.007
Ferritin, µg/L			
Third day	592 (374-1188)	703 (382-1462)	.78
Fifth day	453 (316-991)	652 (372-1517)	.41
Free of oxygen support day	373.5 (122-746)	581 (286-928)	.3
D-dimer, mg/L			
Third day	0.83 (0.67-1.58)	0.58 (0.37-0.95)	.017
Fifth day	0.99 (0.66-1.93)	0.92 (0.55-1.71)	.66
Free of oxygen support day	0.44 (0.3–1)	0.55 (0.35-1.45)	.25
Creatine kinase, U/L			
Third day	75 (45–133)	73.5 (43.5-174.5)	.44
Fifth day	51 (31-70)	53 (37-117)	.15
Free of oxygen support day	33.5 (21-60)	39 (29-73)	.10
Lactate dehydrogenase, U/L			
Third day	502.5 (384-618)	401.5 (328-527)	.010
Fifth day	432 (384-520)	388 (313-533)	.61
Free of oxygen support day	321 (275-386)	317 (258-402)	.83

*All comparisons: Mann–Whitney *U*-test.

Table 4. Primary and Secondary Outcomes for Pulse and Non-pulse Groups and 250 mg and 1000 mg Subgroups

	Pulse Group (n = 102)	Non-pulse Group (n = 36)	*P**		250 mg Subgroup (n = 32)	1000 mg Subgroup (n = 70)	
	n (%)	n (%)			n (%)	n (%)	*P**
Clinical outcomes, n (%)			<.001	Clinical outcomes, n (%)			.25
Discharged without oxygen support	85 (83.3)	17 (47.2)		Discharged oxygen support free	27 (84.4)	58 (82.9)	
Discharged with oxygen support	8 (7.8)	0 (0)		Discharged with oxygen support	4 (12.5)	4 (5.7)	
Exitus	9 (8.8)	19 (52.8)		Exitus	1 (3.1)	8 (11.4)	
				Requirement of anakinra therapy, n (%)	10 (31.3)	16 (22.9)	.14
Development of complication, n (%)	17 (16.7)	16 (44.4)	<.001	Development of complication, n (%)	7 (21.9)	10 (14.3)	.34
Requirement of intensive care unit, n (%)	44 (43.1)	29 (80.6)	<.001	Requirement of intensive care unit, n (%)	16 (50)	28 (40)	.34

*All comparisons: chi-square test.

corticosteroids regulate excessive immune response in case of sepsis[24], and are similarly effective in the severe period of COVID-19 infection.[3] The use of corticosteroids has some controversial issues regarding its short- and long-term adverse effects and disease progression capacity.[25] In our study, we could not present a result on this issue because it was a retrospective design, and the records were insufficient. However, it was reported that high-dose MTP shortens the length of ICU stays without significant side effects.[15]

This study has some limitations. In our center, there was an expert consensus that the clinical response to pulse steroid therapy was successful. Therefore, there was no patient group who was not given pulse therapy when clinical worsening occurred. We could not compare the use of high-dose MTP treatment with low-dose MTP in clinical deterioration. Due to the retrospective nature of the study, the records of adverse effects associated with corticosteroid use were insufficient. Therefore, the side effects of different high doses could not be evaluated.

In conclusion, the use of high-dose MTP in severe COVID-19 patients reduces mortality and shortens recovery time. There is no difference between the use of pulse therapy at a dose of 250 mg/day or 1000 mg/day (for 3 days) in terms of mortality, recovery time, and clinical course. A dose of 250 mg/day of MTP is as effective as 1000 mg/day dose MTP in severe COVID-19 patients, and there is no additional contribution of a higher dose than 250 mg/day in clinical recovery.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Ankara City Hospital Ethical Committee 2 (Approval No: E2-21-31, Date: 13.01.2021).

Informed Consent: Verbal/Written informed consent was obtained from the patients who agreed to take part in the study.

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