Original Article

What We Learned from Steroid Therapy in the COVID-19 Pandemic

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Abstract

Background: The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused a pandemic named coronavirus disease 2019 (COVID-19) that has become the greatest worldwide public health threat. Although different treatment recommendations are offered for COVID-19 infection, steroid treatment remains important. **Aim:** We aimed to demonstrate the effect of pulse steroid therapy (PST) on inflammatory markers and patient outcomes in moderate/severe COVID-19 pneumonia. **Materials and Methods:** We retrospectively analyzed the patients 18 years and older hospitalized in our hospital's COVID-19 clinics between April 1, 2020, to June 30, 2020, and July 1, 2021, to November 30, 2021. Patients in the moderate/severe COVID-19 pneumonia category, according to the World Health Organization COVID-19 guidelines, were included in the study. The demographic characteristics of the patients, treatments, inflammatory markers, and patient outcomes (need for intensive care, length of hospital stay, high-flow nasal oxygen (HFNO) requirement, mechanical ventilation (MV), and mortality rates) were recorded and analyzed. **Results:** Patients who received PST had more advanced age ($P < 0.01$), more comorbidities ($P < 0.001$), and more HFNO need ($P < 001$) compared with the patients who did not receive PST. There was no statistically significant difference between clinical outcomes: the need for intensive care, length of hospital stay, need for MV, and mortality rates ($P = 0.54$, $P = 0.3$, $P = 0.14$, and $P = 0.09$, respectively). When we evaluated the unvaccinated patients, there was a statistically significant difference in the MV need and mortality rates between those who received PST and those who did not ($P = 0.017$, $P = 0.014$, respectively). **Conclusion:** It was observed that PST provided similar mortality, ICU, and MV requirements in patients with older age and comorbidities. Lower MV requirements and mortality were observed in the unvaccinated group receiving PST compared with the unvaccinated group not receiving steroids. PST is still promising in COVID-19 infection, and more studies are needed for standard doses and applications.

Keywords: *COVID-19, pulse steroid, treatment*

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Introduction

COVID-19 pandemic has affected many people around the world. According to current WHO data, the number of people infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is more than 655 million, and the number of people who died due to COVID-19 disease is more than 6.5 million.[1]

Studies have shown higher levels of proinflammatory cytokines in serum and/or respiratory samples in patients with severe/critical disease than those with mild/moderate disease.[2,3] Considering the important role of the immune response in the pathogenesis of SARS-CoV-2, it seems that immune modulation is very important in disease

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management.[4,5] Due to the anti-inflammatory properties of corticosteroids, it was thought that they could be effective in the proinflammatory phase of COVID-19, and as a result of studies, it was the first drug group that was shown to reduce mortality in COVID-19.[4,6]

It has been suggested that due to the rapid development of organizing pneumonia secondary to SARS-CoV-2, the recommended low dose of dexamethasone may be insufficient in some patients, and pulse steroids may be considered as an option instead of dexamethasone.[7] Studies have shown that pulse steroid therapy (PST) in patients with COVID-19 reduces mortality and clinical improvement.[7,8]

This study aimed to retrospectively examine PST's effect on inflammatory markers, the need for intensive care, length of hospital stay, MV and high-flow nasal oxygen (HFNO) requirement, and mortality in moderate to severe COVID-19 pneumonia.

Materials and Methods

Our study was approved by our hospital ethics committee (2022-6) and was planned per the Declaration of Helsinki.

Patients aged 18 years and older who were hospitalized in our hospital's COVID-19 clinics between April 1, 2020, to June 30, 2020, and July 1, 2021 to November 30, 2021, with positive SARS-CoV-2 polymerase chain reaction in nasopharyngeal swabs were retrospectively analyzed. Patients in the moderate to severe pneumonia category, according to the WHO COVID-19 guidelines, were included in the study.[9]

The demographic characteristics (age, sex, and comorbid diseases), HFNO requirements, and COVID-19 vaccine information of the patients included in the study were scanned from the files or hospital electronic information system and recorded.

It was examined whether those with moderate/severe pneumonia hospitalized between April 1, 2020, and June 30, 2020, received oseltamivir, azithromycin, hydroxychloroquine, favipiravir, tocilizumab, and intravenous immunoglobulin (IVIG) plasma treatments. Between July 1, 2021, and November 30, 2021, hospitalized patients with moderate/severe pneumonia were given 250 or 500 mg methylprednisolone as PST.

C-reactive protein (CRP), leukocyte count, lymphocyte count, D-dimer, and ferritin levels were recorded in the group hospitalized between July 1, 2021, and November 30, 2021.

It was planned to compare the clinical outcomes of patients who did not receive steroids on April 1, 2020, to June 30, 2020, and those who received PST on July 1, 2021, to November 30, 2021. Clinical outcomes of patients were the need for intensive care, length of hospital stay, HFNO and MV requirement, and mortality.

The collected data was analyzed using the SPSS 25.00 software (Chicago, IL, USA). Median, minimum, and maximum values were specified for descriptive data that did not fit a normal distribution, and categorical variables were expressed as numbers (*n*) and percentages (%). The Chi-square test was used to compare categorical data. Wilcoxon-signed rank test was used in dependent groups (to compare two related samples), and Mann–Whitney U-test was used in independent groups to analyze numerical data that did not comply with normal distribution. *P* value of <0.05 was considered statistically significant.

Results

A total of 185 patients out of 2123 patients who were hospitalized between April 1, 2020, and June 30, 2020, and 199 patients out of 2104 patients who were hospitalized between July 1, 2021, and November 30, 2021, with moderate/severe pneumonia in our hospital COVID-19 clinics, were included in the study. Oseltamivir, azithromycin, hydroxychloroquine, favipiravir, tocilizumab, IVIG, and convalescent plasma treatments were given to the patients who were followed up between April 1, 2020, and June 30, 2020, in line with the recommendations of that period. PST at the dose of 250-500 mg was given to patients with moderate/severe pneumonia followed between July 1, 2021, and November 30, 2021. Patients in the steroid group received an average of 3.54 days of PST [Table 1].

There were a total of 185 patients in the patient group who did not receive steroids; 95 (51.4%) were female, and 90 (48.6%) were male. There were a total of 199 patients in the patient group who received steroids; 100 (50.3%) were female, and 99 (49.7%) were male. There was no statistically significant difference between the two periods regarding sex distribution ($P = 0.82$). The mean age was 55.04 years in the group who did receive steroids and 60.09 years in the steroid group ($P < 0.001$) [Table 1].

No patients were vaccinated against COVID-19 in the group who did not receive steroids, and 117 (58.8%) in the group who received steroids were fully immunized against COVID-19 [Table 1].

When the patients in both periods were examined according to their comorbid diseases, there was no statistically significant difference in the presence of obstructive lung disease and liver disease ($P = 0.39$

and $P = 0.21$, respectively). There were more patients with type 2 diabetes mellitus (DM), hypertension (HT), chronic heart failure, chronic kidney disease (CKD), and cancer in the steroid group ($P < 0.001$, $P < 0.001$, $P = 0.001$, $P = 0.001$, and $P < 0.001$, respectively) [Table 1].

A statistically significant decrease was observed in the lymphocyte count and the levels of CRP, D-dimer, and ferritin of the patients receiving PST on the 2nd to 5th day after steroid administration compared with before steroid administration ($P < 0.001$, $P < 0.001$, $P < 0.001$, and $P = 0.005$, respectively). A statistically significant increase was observed in the white blood cell count of the patients receiving PST on the 2nd to 5th day after steroid administration compared with before steroid administration [Table 2].

In the study, both groups were examined regarding the average length of hospital stay, need for intensive care, MV and HFNO requirements during the follow-up period, and mortality rates at the end of hospital discharge. Although the need for HFNO was higher in the group receiving steroids ($P < 0.001$), there was no statistically significant difference between groups in terms of mean hospital stay, MV requirement, need for intensive care follow-up, and mortality rates ($P = 0.3$, $P = 0.14$, $P = 0.54$, and $P = 0.09$, respectively) [Table 3]. When the group who did not receive steroids was compared with the unvaccinated/incompletely vaccinated patients

Table 1: Demographic characteristics of the group receiving pulse steroids and the group not receiving pulse steroids

	Steroid (-) group *n*=185	Steroid (+) group *n*=199	*P**
Sex (F/M)	95/90	100/99	0.82
Age (median)	55.04	60.09	<0.001
COVID-19 vaccine status *n* (%)			
Unvaccinated/incompletely vaccinated	185 (100)	66 (33.2)	
Fully vaccinated	0 (0)	117 (58.8)	
Not known		16 (8)	
Comorbid disease *n* (%)			
DM	34 (18.4)	90 (45.2)	<0.001
HT	61 (33)	103 (51.8)	<0.001
KY	23 (12.4)	54 (27.1)	<0.001
KBH	0 (0)	14 (7.1)	0.001
OAH	24 (13)	33 (16.6)	0.39
KC	1 (0.5)	5 (2.5)	0.21
KA	8 (4.3)	43 (21.6)	<0.001
Treatment *n* (%)			
Pulse steroid	0 (0)	199 (100)	
Hydroxychloroquine	177 (95.7)		
Azithromycin	166 (89.7)		
Oseltamivir	156 (84.3)		
Favipiravir	53 (28.6)		
Tocilizumab	6 (3.2)		
IVIG	2 (1.1)		
Convalescent plasma	2 (1.1)		

DM=Type 2 diabetes mellitus, HT=Hypertension, KA=Cancer history, CKD=Chronic kidney disease, Liver Disease, HF=Heart failure, OPD=Obstructive pulmonary disease. *Chi-square was used in statistical analysis

Table 2: Inflammatory markers in the pulse steroid group

Inflammatory markers	Before pulse steroids median (min-max)	2-5 days after pulse steroids median (min-max)	*P**
CRP (mg/dL)	154 (3-423)	50 (1-284)	<0.001
WBC (cells/µL)	8600 (400-19700)	9200 (0-49,000)	<0.001
Lym (cells/µL)	800 (100-9200)	600 (0-9800)	<0.001
D-dimer (mg/dL)	0,96 (0-79)	0.7 (0-52)	<0.001
Ferritin (mg/dL)	360 (0-2070)	286 (0.6-1427)	0.005

CRP=C-Reactive protein, Lym=Lymphocyte count, WBC=Leukocyte count. *Wilcoxon-signed rank test was used for statistical analysis

in the steroid group, there was no statistically significant difference between groups in terms of mean hospital stay and need for intensive care follow-up (P = 0.08 and P = 0.28, respectively). There was a statistically significant difference between the groups in terms of HFNO and MV needs and mortality rates (P < 0.001, P = 0.01, and P = 0.014, respectively) [Table 4].

Discussion

Corticosteroids have been widely used after the RECOVERY study showed that the use of 6 mg/kg dexamethasone reduced mortality in COVID-19 infection.[4] PST has also become widespread with the demonstration that pulse steroid administration provides a similar decrease in mortality.[10]

When the prognostic factors for COVID-19 are evaluated in studies, age, sex, the presence of comorbidity, and SARS-CoV-2 virus variant type are included as risk factors.[11,12] In our study, the sex distribution was similar between the patients who received steroids and those who did not, but the steroid group had more advanced age and more comorbid diseases such as HT, DM, coronary artery disease, malignancy, and CKD. Due to the period of the study groups, the dominant variant was the alpha variant in the group who did not receive steroids, whereas it was the delta variant in the group who received steroids.[13] As a result, the steroid group had worse prognostic factors such as advanced age, more comorbidities, and virus variant type. However, the two groups had no statistically significant difference in mortality (P = 0.09). In addition, when unvaccinated patients were compared in both groups, lower mortality was found in the steroid group (P = 0.014). PST decreased mortality in unvaccinated patients with more risk factors but had similar mortality when the entire population was evaluated.

Table 3: Comparison of clinical outcome in the group receiving and not receiving steroids

	Steroid (-) group *n*=185	Steroid (+) group *n*=199	*P**
LHS/days median (min-max)	12 (1-25)	11 (3-41)	0.3
HFNO need *n* (%)	1 (0.5)	41 (20.6)	<0.001
ICU need *n* (%)	23 (12.4)	30 (15.1)	0.54
MV need *n* (%)	15 (8.1)	8 (4)	0.14
Mortality *n* (%)	16 (8.6)	8 (4)	0.09

HFNO=High-flow nasal oxygen, LHS=Length of hospital stay, MV=Mechanical ventilator, ICU=Intensive care unit. *Chi-square and Mann–Whitney U-test were used in the statistical analysis

Table 4: Comparison of clinical outcome in the group receiving steroids and not receiving steroids in unvaccinated/incompletely vaccinated patients

	Steroid (-) group *n*=185	Steroid (+) group *n*=66	*P**
LHS/days median (min-max)	12 (1-25)	10.5 (3-41)	0.08
HFNO need *n* (%)	1 (0.5)	13 (19.7)	<0.001
ICU need *n* (%)	23 (12.4)	5 (7.6)	0.28
MV need *n* (%)	15 (8.1)	0 (0)	0.017
Mortality *n* (%)	16 (8.6)	0 (0)	0.014

HFNO=High-flow nasal oxygen, LHS=Length of hospital stay, MV=Mechanical ventilator, ICU=Intensive care unit. *Chi-square and Mann–Whitney U-test were used in the statistical analysis

Although COVID-19 manifests in the form of pulmonary involvement, in the progressive course of the disease, a systemic inflammatory response is observed with excessive production of cytokines and chemokines in the hyperinflammatory phase after the hypoxic phase.[14] In this process, D-dimer, ferritin, and CRP levels increase, and regressions are observed after steroid treatment. This study observed a statistically significant decrease in CRP, D-dimer, and ferritin levels, and lymphocyte counts when the pre- and poststeroid values were compared in patients receiving steroid therapy. Although the relationship between inflammatory markers and mortality was not demonstrated in our study, studies have reported that a higher level of inflammatory markers is a poor prognostic factor.[15] In a retrospective study conducted in our country, without a control group, a 10-day treatment protocol of 1 g intravenous methylprednisolone for 3 days followed by 1 mg/kg methylprednisolone for 7 days was administered to 30 patients who were followed in the ICU and whose disease was considered to be in the hyperinflammation stage. When surviving and deceased patients were compared, it was observed that ferritin, CRP, and procalcitonin levels measured at the 72nd hour and 7th day after PST decreased significantly in the surviving patient group.[16]

It was reported in a study from Spain that there was a 14% decrease in mortality when 30 mg dexamethasone or 125 mg methylprednisolone was given for 2-5 days to 64 patients with 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 lactate dehydrogenase ≥300 U/L).[17] In another study evaluating the efficacy of steroids, the need for ICU and MV was similar in the group who received PST and the group who did not. The mortality rate was found to be lower, and the length of stay in the ICU was found to be shorter in the group receiving PST.[18] In another study, no effect of PST on mortality was observed.[19] In our study, although the group receiving PST was older, had more comorbidities, and

needed more HFNO, ICU, and MV needs, mortality rates were similar compared with the group who did not receive steroids. When the unvaccinated/incompletely vaccinated patients in the steroid group were compared with the unvaccinated group, which did not receive steroids, although there were two different period variants (alpha and delta), a statistically significant decrease in HFNO and MV need and mortality rates were observed in the steroid group, which had more advanced age and more comorbidities.[20]

In the group to which PST was not given, 84.3% of the patients were given oseltamivir, 89.7% azithromycin, 95.7% hydroxychloroquine, 28.6% favipiravir, 6% tocilizumab, 2% IVIG, and 2% convalescent plasma therapy according to the COVID-19 guideline recommendations of the Ministry of Health of our country at that time. Apart from tocilizumab, other treatments are no longer included in the guidelines today, and tocilizumab remains among the strong treatment recommendations of the WHO.[21]

Azithromycin is a macrolide antibacterial drug, and its use is not recommended in the treatment of COVID-19 pneumonia because it has insufficient efficacy and increases the risk of antibiotic resistance.[22] Although hydroxychloroquine was used as an antimalarial and immunomodulatory drug in the early period of the pandemic, it was no longer used due to its ineffectiveness against COVID-19 infection and cardiac adverse effects.[23] Favipiravir, however, is no longer recommended because it does not contribute positively to the prognosis of the disease, and its use has undesirable effects on liver and kidney function tests.[24] Studies related to IVIG therapy are still available, and it is not currently recommended to treat COVID-19.[25] Convalescent plasma therapy is no longer a valid treatment method.[26]

Limitations

Since the results of the study are a single-center retrospective study, they should be evaluated together with multicenter and comprehensive examinations. The lack of a standard protocol for steroid treatment given to COVID-19 patients and the fact that it is based on the clinical experience of physicians leads to a subjective practice. This situation can be considered as one of the limiting factors. Due to the study design, two different variable periods were compared. However, the results show that PST provides clinical improvement even in the worse prognostic group.

Conclusion

Even though the pulse steroid group was older, had higher comorbidity, and was exposed to the delta variant with a worse prognosis, the need for ICU and MV and mortality rates in the steroid group were like those in the nonsteroid group. PST is still promising in COVID-19 infections; more studies are needed for standard doses and applications.

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Conflicts of interest

There are no conflicts of interest.

References

1. WHO COVID-19 Dashboard. Geneva: World Health Organization 2020. Available online: https://covid19.who.int/. [Last accessed on 2023 Feb 15].
2. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. J Infect 2020;80:607-13.
3. Wong RSY. Inflammation in COVID-19: From pathogenesis to treatment. Int J Clin Exp Pathol 2021;14:831-44.
4. Chappell L, Peter H, Wei SL, Jonathan RE, Marion M, Jennifer LB, *et al*. Dexamethasone in hospitalized patients with Covid-19—preliminary report. The New England journal of medicine 2020.
5. Mehta J, Rolta R, Mehta BB, Kaushik N, Choi EH, Kaushik NK. Role of dexamethasone and methylprednisolone corticosteroids in coronavirus disease 2019 hospitalized patients: A Review. Front Microbiol 2022;13:813358.
6. 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 ill patients with COVID-19: A meta-analysis. JAMA 2020;324:1330-41.
7. Kory P, Kanne JP. SARS-CoV-2 organising pneumonia: 'Has there been a widespread failure to identify and treat this prevalent condition in COVID-19?' BMJ Open Respir Res 2020;7:e000724.
8. 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.
9. World Health Organization. Clinical management of COVID-19: Living guideline, 13 January 2023. World Health Organization; 2023. (WHO/2019-nCoV/clinical/2023.1).
10. Mohanty RR, Biswa Mohan Padhy, Meher BR. Effectiveness of pulse dose methyl prednisolone in management of COVID 19: A systematic review and meta-analysis of observational studies. J Pharm Pharm Sci 2022;25:110-23.
11. Li J, Huang DQ, Zou B, Yang H, Hui WZ, Rui F, *et al*. Epidemiology of COVID-19: A systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. J Med Virol 2021;93:1449-58.
12. Ong SWX, Chiew CJ, Ang LW, Mak TM, Cui L, Toh MPHS, *et al*. Clinical and virological features of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern: A retrospective cohort study comparing B.1.1.7 (Alpha), B.1.351 (Beta), and B.1.617.2 (Delta). Clin Infect Dis 2022;75:e1128-36.
13. Choi JY, Smith DM. SARS-CoV-2 variants of concern. Yonsei Med J 2021;62:961-8.
14. 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.

15. Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: A meta-analysis. Ther Adv Respir Dis 2020;14:1753466620937175.
16. Bindal A. Effect of pulse steroid therapy on mortality in severe Covid-19 pneumonia. Medical Journal of Suleyman Demirel University 2021:479-86.
17. Bai C, Chotirmall SH, Rello J, Alba GA, Ginns LC, Krishnan JA, *et al*. Updated guidance on the management of COVID-19: From an American thoracic society/European respiratory society coordinated international task force (29 July 2020). Eur Respir Rev 2020;29:200287.
18. Batırel A, Demirhan R, Eser N, Körlü E, Tezcan ME. Pulse steroid treatment for hospitalized adults with COVID-19. Turk J Med Sci 2021;51:2248-55.
19. Yaqoob H, Greenberg D, Hwang F, Lee C, Vernik D, Manglani R, *et al*. Comparison of pulse-dose and high-dose corticosteroids with no corticosteroid treatment for COVID-19 pneumonia in the intensive care unit. J Med Virol 2022;94:349-56.
20. CDC. SARS-CoV-2 Variant Classifications and Definitions 2023. Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html 2023. [Last accessed on 2023 Feb 15].
21. WHO rapid evidence appraisal for COVID-19 therapies (REACT) working group, Shankar-Hari M, Vale CL, Godolphin PJ, Fisher D, Higgins JPT, *et al*. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: A meta-analysis. JAMA 2021;326:499-518.
22. Kamel AM, Monem MSA, Sharaf NA, Magdy N, Farid SF. Efficacy and safety of azithromycin in Covid-19 patients: A systematic review and meta-analysis of randomized clinical trials. Rev Med Virol 2022;32:e2258.
23. Bansal P, Goyal A, Cusick A 4th, Lahan S, Dhaliwal HS, Bhyan P, *et al*. Hydroxychloroquine: A comprehensive review and its controversial role in coronavirus disease 2019. Ann Med 2021;53:117-34.
24. Bosaeed M, Alharbi A, Mahmoud E, Alrehily S, Bahlaq M, Gaifer Z, *et al*. Efficacy of favipiravir in adults with mild COVID-19: A randomized, double-blind, multicentre, placebo-controlled clinical trial. Clin Microbiol Infect 2022;28:602-8.
25. Focosi D, Franchini M, Tuccori M, Cruciani M. Efficacy of high-dose polyclonal intravenous immunoglobulin in COVID-19: A systematic review. Vaccines (Basel) 2022;10:94.
26. Sekine L, Arns B, Fabro BR, Cipolatt MM, Machado RRG, Durigon EL, *et al*. Convalescent plasma for COVID-19 in hospitalised patients: An open-label, randomised clinical trial. Eur Respir J 2022;59:2101471.