

Does methylprednisolone affect time to recovery in COVID-19 pneumonia?

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ABSTRACT

Objective: Current literature has conflicting results on the role of steroids in the treatment of coronavirus disease 2019 (COVID-19) pneumonia. This study aims to evaluate the effects of steroids on clinical recovery, duration of hospitalization, and time needed for the cessation of oxygen treatment.

Patients and Methods: We retrospectively analyzed the medical records of patients hospitalized for COVID-19 between March and May 2020. Patient age, laboratory parameters, clinical stages, radiologic scores, length of hospital stay, and time needed for the cessation of oxygen supplementation were compared.

Results: Thirteen patients were treated with steroids, and 12 controls were included in the analysis. Regarding the laboratory parameters, the groups were similar except for lymphocyte percentage (9.8 ± 3.2 , 7.0 ± 2.9 ; $p=0.033$), which was higher, and D-dimer levels (0.75 ($0.60-1.43$), 1.57 ($0.91-2.29$); $p=0.047$), which were lower in the steroid group on admission. Steroid treatment provided a tendency of decrease in time to cessation of oxygen supplementation (6.23 ± 3.4 vs 7.67 ± 2.1 , $p=0.217$).

Conclusion: Although, systemic steroids, started in the subacute period, did not affect the length of hospital stay, they provided a tendency of decrease in the time until the cessation of oxygen supplementation in the subacute period.

Keywords: COVID-19, Steroids, Length of stay

1. INTRODUCTION

The new type of coronavirus, which appeared in Wuhan, the capital of China's Hubei region in December 2019, spread in a short time and caused a worldwide pandemic [1, 2]. The new type of coronavirus, named as severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), and the disease it causes, coronavirus disease-19 (COVID-19), mainly targets the lower respiratory tract [2]. Although, the infection is mild in 81% of cases, it may result in respiratory failure, septic shock, and multi-organ failure in 5%. The fatality rate of the disease has been reported as 2.1% [3].

In the course of disease in advanced stages, distal airway involvement may result in alveolar destruction. It has been demonstrated that this lung damage is associated both with the

virus and an uncontrolled immune response and an alveolar injury similar to acute respiratory distress syndrome (ARDS) [4]. On the other hand, the fact that lung compliance is preserved in some cases with hypoxemic respiratory failure suggests that there are other possible mechanisms in the development of hypoxemia other than alveolar damage [5]. In particular, it has been suggested that uncontrolled excessive inflammation tends to increase coagulation and can cause both arterial and venous thromboembolic disease. Also, the detection of pulmonary microthrombi in autopsy series supports the view of another possible cause for hypoxemia in these cases [1, 6]. The presence of hypoxemia in patients or prolonged hypoxemia is associated with prolonged hospitalization.

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Although, the use of anti-malarial agents in combination with anti-viral and macrolide antibiotics is recommended in the early treatment of the disease, the use of biologic agents may be an option in the event of an excessive inflammatory response in patients whose viral replication phase is over [7]. Corticosteroids are widely used in severe community-acquired pneumonia, especially in suppressing excessive and dysfunctional systemic inflammation [8]. Although, there are contradictory results about the use of systemic steroids in non-COVID viral infections in general, the idea that pulse-dose therapy and long-term high-dose steroid use is associated with more harm than benefit due to increased viral replication and the adverse effects of steroids [9-11]. However, it has been shown that corticosteroid therapies (usually 200-300 mg/day hydrocortisone, for 5-7 days) given at the correct dose and time in selected patient groups may have some clinical benefits and prevent pathologic deterioration [12, 13]. At the beginning of the pandemic, the use of steroids is very limited in SARS-CoV-2 infection. Wei et al. reported clinical improvement in patients who received an average of 400 mg/day hydrocortisone equivalent steroid treatment for an average of 9.5 days [14]. In July 2020, the preliminary data of the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial showed that especially patients with respiratory failure have decreased 28-day mortality in the dexamethasone treatment [15].

Hence, we retrospectively analyzed the medical records of 13 patients treated with steroids because of ongoing oxygen need and 12 control patients with a similar clinical picture to evaluate the effect of steroid treatment on clinical recovery, duration of hospitalization, and the time to the disappearance of oxygen need in patients with COVID-19.

2. PATIENTS and METHODS

Patients

The study was conducted at Marmara University, School of Medicine Pulmonary and Critical Care Medicine Clinic. The permission was obtained from the Ministry of Health of the Republic of Turkey on May 10th, 2020, and ethical approval was obtained from the Marmara University, School of Medicine Clinical Research Ethics Committee (approval number: 09.2020.561).

The data of patients who were hospitalized with COVID-19 pneumonia between March 13th, 2020, and May 25th, 2020, with severe acute respiratory infection (SARI) criteria (fever, cough, and dyspnea, tachypnea, hypoxemia, hypotension, widespread radiologic findings, and confusion) and found to have positive polymerase chain reaction (PCR) test results in oropharyngeal – nasopharyngeal swab samples were retrospectively examined. Among them, patients who still require oxygen supplementation despite standard medical treatment (anti-malarial, anti-viral, and macrolide antibiotics as single or combination regimen), in which other causes of secondary hypoxemia were clinically excluded, were analyzed. None of the patients were on long-term oxygen treatment before COVID-19 pneumonia for a known chronic respiratory illness. Thirteen patients treated with steroids and 12

patients with similar clinical pictures but who were not treated with steroids were included in the final analysis (Figure 1).

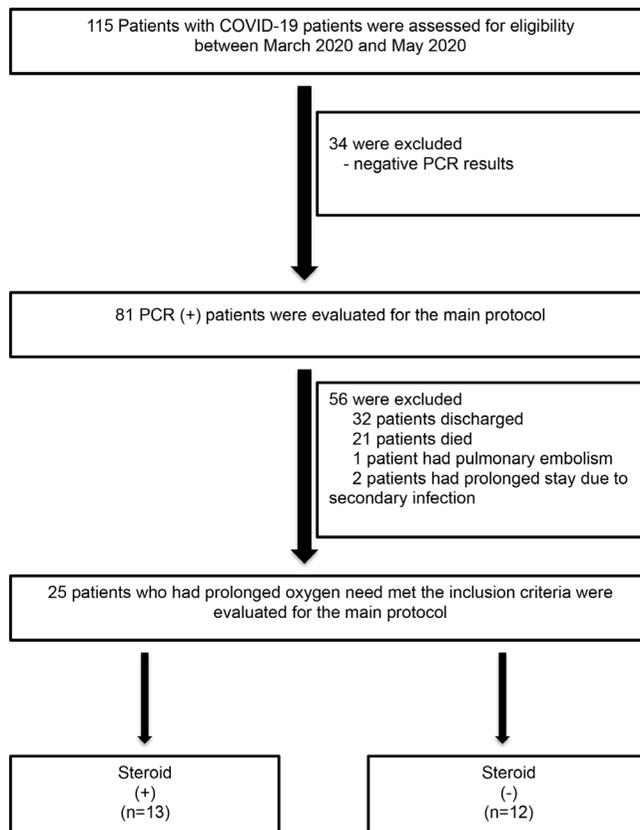


Figure 1. Flow diagram of the study

Demographics and comorbidities

All patients' gender, age, comorbid diseases (hypertension, diabetes mellitus, hyperlipidemia, chronic lung disease, coronary artery disease, congestive heart failure, thyroid dysfunction, chronic liver disease), smoking status, positive case contact history, the time between the onset of the first symptom, and the hospital admission were recorded.

Standard treatment

The treatments that patients received during their hospital stay were evaluated daily by three experts (pulmonary and critical care physicians) and treatment modifications were made according to the daily physical examinations and laboratory findings. Treatment planning for COVID-19 was implemented following the guideline prepared by the Republic of Turkey, Ministry of Health [16].

The recommended treatment scheme in this guide is hydroxychloroquine 200 mg bid maintenance after 400 mg bid loading for a total of 7-10 days [in patients with normal QT distance in electrocardiography (ECG) taken at the time of hospitalization] +/- azithromycin 250 mg/day after 500 mg/day loading for 5 days (optimal), and additional favipiravir 600

mg bid after 1600 mg bid loading in patients with high oxygen demand and respiratory distress for a total of 5 days. All patients were treated with low-molecular-weight heparin (LMWH) according to D-dimer levels at the time of hospitalization (D-dimer levels <3 mg/L were treated with 0.01 mg/kg/day once daily, D-dimer levels ≥3 mg/L were treated with 0.02mg/kg/day bid).

Laboratory parameters

In all cases, complete blood count (lymphocyte %, lymphocyte count $\times 10^3/\mu\text{L}$) D-dimer (mg/L), NT-proBNP (N terminal-proBrain Natriuretic Peptide) (ng/L), C-reactive protein (CRP) (mg/L), procalcitonin ($\mu\text{g/L}$), ferritin ($\mu\text{g/L}$), fibrinogen (mg/dL), lactate dehydrogenase (LDH) (U/L) results at admission and during hospital stay were recorded. In addition to the laboratory values on admission; the lowest values for lymphocyte percent, lymphocyte count, and fibrinogen level; the highest values for CRP, D-dimer, NT-proBNP, procalcitonin, ferritin, and LDH during hospitalization were included in the statistical analysis.

Severity of disease

Clinical staging for all patients during hospitalization was calculated based on the values on admission and worst clinical picture, according to the World Health Organization (WHO) progression scale [17] and the clinical-therapeutic staging suggested by Siddiqi et al. [18]. On the 7th-10th days, due to the continuation of the need for oxygen, re-staging was performed. Radiologic severity was assessed using computed tomography (CT) visual quantitative evaluation from 0-20 [19]. Each lung lobe was assessed for the percentage of lobar involvement and classified as none (0%), minimal (1-25%), mild (26-50%), moderate (51-75%), or severe (76-100%), with a corresponded score as 0, 1, 2, 3, or 4. The total severity score was reached by summing the five lobe scores.

Steroid treatment

The patients who still needed oxygen therapy on days 7-10 were evaluated for other possible causes of hypoxemia. H-scores were calculated for patients who were not considered as having clinical hypervolemia or pulmonary embolism or secondary bacterial infection [20] because of the risk of macrophage activation syndrome (MAS). In patients with H-scores <169, according to the opinion of the pulmonary medicine specialist in the clinic, single-dose intravenous methylprednisolone 0.5-1 mg/kg/day was started and tapered according to the need for oxygen in 7-10 days.

Statistical Analysis

Data are shown as mean \pm standard deviation (SD), median and interquartile range (IQR), 95% confidence interval (CI), and categorical variables as numbers and percentages. For comparisons between groups, the independent sample Student t-test, or when appropriate, Mann-Whitney U test was used. The

Chi-square test or when appropriate, Fisher's exact test was used for the comparison of categorical variables. All statistical tests were two-sided, and a *p*-value <0.05 was considered significant. Statistical analysis was performed using the Statistical Package for the Social Sciences, version 22.0 for Windows® system (SPSS® Inc., Chicago, Illinois, USA).

3. RESULTS

Study population and characteristics

As illustrated in Figure 1, patients hospitalized for COVID-19 pneumonia were retrospectively evaluated and a total of 25 patients (13 in the steroid group and 12 in the control group) were included in the final analysis.

The mean age of the participants was significantly higher in the steroid group (*p*=0.005); however, there was no significant difference between the groups in terms of comorbidities, smoking habits, and COVID contact (Table I).

Laboratory findings and disease severity scores

Baseline (on admission) laboratory findings regarding the lymphocyte count and percentage, D-dimer, NT-proBNP, CRP, procalcitonin, ferritin, fibrinogen, and LDH were compared between the groups (Table II). There were significant differences at baseline in lymphocyte percentage (9.8 ± 3.2 , 7.0 ± 2.9 ; *p*=0.033) and D-dimer values (0.75 (0.60 - 1.43), 1.57 (0.91 - 2.29); *p*=0.047).

As shown in Table III, the lymphocyte percentage was higher in the steroid group when compared with the controls (9.8 ± 3.2 , 7.1 ± 2.8 ; *p*=0.033). There was no significant difference between the groups for the remaining laboratory parameters that were evaluated in the study protocol regarding the worst results during the hospitalization period.

Table I. Demographics and characteristics of participants (n=25)

	Steroid (+)	Steroid (-)	<i>p</i> value
Demographics			
Age, years	64.8 \pm 13.9	48.3 \pm 12.8	0.005
Male gender, %	61.5	83.3	0.225
Current smoker, %	15.4	41.7	0.144
COVID-19 (+) contact, %	46.2	41.7	0.821
Comorbidities			
Hypertension, %	30.8	41.7	0.571
Diabetes Mellitus, %	23.1	16.7	0.689
Hyperlipidemia, %	7.7	0.0	0.327
Thyroid function disorder, %	7.7	8.3	0.953
Pulmonary disease, %	15.4	25.0	0.548
Hepatic disease, %	7.7	0.0	0.327
Cardiac disease, %	0.0	16.7	0.125
Cancer, %	7.7	0.0	0.327
Chronic inflammatory disease, %	15.4	0.0	0.157

Table II. Baseline laboratory findings, radiological and clinical scores of the study population (n=25)

	Steroid (+)	Steroid (-)	p value
Laboratory			
Lymphocyte count, x10 ³ /μL	1200 ± 584.5	1116.7 ± 687.9	0.747
Lymphocyte, %	20.4 ± 10.6	12.4 ± 6.9	0.038
D-dimer, mg/L (IQR)	0.75 (0.60 – 1.43)	1.57 (0.91 – 2.29)	0.047
NT-proBNP, ng/L (IQR)	204.4 (118.01 – 512.50)	510.0 (204.0 – 2353.0)	0.159
CRP, mg/L	88.4 ± 61.63	126.8 ± 72.3	0.173
Procalcitonin, μg/ml (IQR)	0.11 (0.08 – 0.16)	0.18 (0.11 – 0.36)	0.056
Ferritin, μg/L	757.4 ± 241.5	555.4 ± 334.5	0.459
Fibrinogen, mg/dL	537.9 ± 213.0	627.2 ± 213.0	0.242
LDH, U/L	505.2 ± 400.3	544.0 ± 211.5	0.767
Radiological and Clinical Staging			
CT scores	12.5 ± 3.9	10.3 ± 4.7	0.199
WHO progression Scale	5.8 ± 1.3	5.8 ± 1.2	0.990

NT: N terminal, BNP: brain natriuretic peptide, CRP: C-reactive protein, LDH: Lactate dehydrogenase, CT: computed tomography, WHO: World Health Organization

Table III. The worst laboratory findings during hospitalization, lengths of hospital stay and time needed for cessation of oxygen requirement (n=25)

	Steroid (+)	Steroid (-)	p value
Laboratory			
Lymphocyte count, x10 ³ /μL	807.7 ± 213.9	691.7 ± 314.7	0.289
Lymphocyte, %	9.8 ± 3.2	7.0 ± 2.9	0.033
D-dimer, mg/L (IQR)	1.78 (1.26 – 3.49)	1.56 (0.85 – 4.93)	0.538
NT-proBNP, ng/L (IQR)	155 (0 – 373)	375 (155-1204)	0.057
CRP, mg/L	144.2 ± 61.6	182.8 ± 56.5	0.118
Procalcitonin, μg/ml	0.24 (0.14 – 7.66)	0.29 (0.13 – 0.56)	0.807
Ferritin, μg/L	925.1 ± 881.1	839.9 ± 398.0	0.762
Fibrinogen, μg/dl	443.2 ± 243.1	415.4 ± 155.3	0.732
LDH, U/L	583.5 ± 374.1	681.3 ± 220.9	0.425
Clinical staging and length of hospital stay			
H-index (max)	45.4 ± 33.9	41.5 ± 19.3	0.727
WHO progression scale (max)	5.9 ± 1.8	6.1 ± 0.9	0.689
Time needed for cessation of oxygen need	6.23 ± 3.4	7.67 ± 2.1	0.217
Total length of hospital stay	18.5 ± 7.8	16.3 ± 4.7	0.406

NT: N terminal, BNP: brain natriuretic peptide, CRP: C-reactive protein, LDH: Lactate dehydrogenase, CT: computed tomography, WHO: World Health Organization

Also, there was no significant difference between the groups regarding the disease severity indices such as the WHO progression scale and H-index scores both at baseline and also considering the worst results during the hospitalization period. Most of the participants were in stage 2B in both the steroid and non-steroid groups regarding the pneumonia indices upon admission (Figure 2).

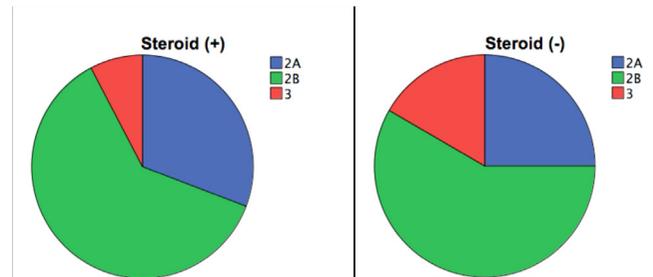


Figure 2: Pneumonia indices of patients on admission

2A: Pulmonary involvement without hypoxia

2B: Pulmonary involvement with hypoxia

3: Systemic hyperinflammation

Treatment

There were four different treatment modalities given to the participants. The hydroxychloroquine + azithromycin + favipiravir combination was preferred for 40% of the participants. Thirty-six percent were treated with hydroxychloroquine + azithromycin, 20% received hydroxychloroquine + favipiravir, and only one patient had hydroxychloroquine alone.

Steroid treatment

Methylprednisolone was started as a mean dose of 40-80 mg/day and the mean total steroid dose was 306 ± 119.8 mg, while mean steroid treatment period was 6.38 ± 3.6 days.

When cut-off points were determined for both the steroid and non-steroid groups (while patients were considered as recovered from the acute period of disease but had oxygen requirement in the 7-10th days of infection) regarding the duration till the cessation of oxygen support, it was observed that it took less time for the steroid group (6.23 ± 3.4 vs. 7.67 ± 2.1 days, p=0.217), but it was not statistically significant. Also, steroid treatment did not affect total length of hospital stay.

4. DISCUSSION

In this study, systemic steroid treatment initiated in the subacute period because of persisting oxygen requirement, despite

standard COVID-19 treatment provided a tendency of decrease in time to cessation of oxygen supplementation.

Studies conducted to date about the use of systemic steroids in viral pneumonia (e.g. influenza, SARS) have shown that systemic steroids, particularly when used in the early period, have negative consequences on viral replication [21] and increase mortality [11, 22]. However, a retrospective study in patients with SARS showed that steroids were initiated either as acute or rescue treatments reduced mortality and length of hospital stay [23].

It has been stated that in non-COVID-19 viral pneumonia that progresses to ARDS, systemic steroids have little or no effect on the length of stay in intensive care, but they may have positive effects on the need for mechanical ventilation and length of hospital stay, albeit with a low level of evidence. However, it was also emphasized that severe hyperglycemia due to steroids could be observed [24]. Considering all these data, the general belief prevents the use of systemic steroids as a standard treatment in the early period of viral pneumonia.

There are few studies on the use of systemic steroids in the treatment of COVID-19, and the results are confusing. In a study evaluating the risk factors of ARDS and mortality in patients with COVID-19, it was stated that the use of methylprednisolone in patients with ARDS might reduce the risk of death [25]. A meta-analysis reported a decrease in 28-day mortality for critically ill patients with COVID-19 who received steroids [26].

Unlike these studies, our patients had no ARDS and were administered steroids due to their ongoing requirement of oxygen supplementation despite the regression of COVID-19 pneumonia. A study conducted in Spain showed that pulse methylprednisolone treatment given to the patients with worsening respiratory function and increasing inflammatory markers in the second week of the disease had improved the prognosis [27]. Contrary to the study [28] showing that low-dose steroid therapy provides early clinical recovery, reduced length of stay in intensive care, and improvement in oxygenation, the WHO does not recommend routine use of steroids in the treatment of COVID-19 and only recommends its use in critically ill patients [29]. The basis of this approach was derived from reviews and meta-analyses that indicated increased mortality or ineffective results on mortality and length of hospital stay after steroid treatment [30-32]. A recent trial in Brazil also could not show the mortality benefit of methylprednisolone in hospitalized patients [33]. The patients included in our study comprised those who were passed the early period of infection. Considering the pathologic extent of the disease, a study evaluating post-mortem biopsies of patients who died of COVID-19 pneumonia found that acute fibrinous and organizing pneumonia findings were prominent, especially in the subacute period of the disease. This damage was seen to occur from an organizing pneumonia pattern characterized by intense intraalveolar fibrin deposition and fibrinous acute injury in alveolar ducts and bronchioles, and fibroblasts surrounding intraalveolar fibrin were noted in almost all patients. The authors noted that the use of corticosteroids might be beneficial in treatment with these findings [34]. In another

paper, a perspective, authors have taken into attention that, due to organizing pneumonia patterns in COVID-19, prolonged duration of corticosteroid treatment; and careful and monitored tapering should be kept in mind [35]. In our study, patients who had left the acute period marked by ongoing viral replication but had ongoing oxygen demand, there was a tendency of decreased duration until the need for oxygen disappeared in the steroid treatment group when compared with the controls. This may have been due to the limited number of patients enrolled in the study. The cause of the increased total length of stay of patients who were treated with steroids could be attributed to the time before steroid treatment. Furthermore, the development of hyperglycemia, muscle weakness, gastrointestinal bleeding, or secondary bacterial infection due to steroid use was not observed and steroid therapy was administered safely.

Limitations

The most important limitation of our study is its retrospective character and a low number of patients. However, we aimed to share the short-term results of patients treated with corticosteroids as the experience in the first period of the pandemic.

Conclusion

As a result, in patients whose viral replication phase was over but still had persisting chronic inflammation and oxygen requirement, the addition of systemic steroids to the standard treatment affects the time to discontinuation of oxygen supplementation in a positive way. It was also observed that, in terms of adverse effects, low-medium dose steroid treatment was safe for these patients who are mostly old with comorbid medical conditions. To determine the role of steroids in the treatment protocols, randomized controlled studies with a large number of patients are needed.

Compliance with Ethical Standards

Ethical approval: The permission for the study was obtained from the Ministry of Health of the Republic of Turkey on May 10th, 2020, and the ethical approval was obtained from the Marmara University, School of Medicine Clinical Research Ethics Committee (approval number: 09.2020.561).

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Conflict of Interest: The authors have no conflicts of interest to declare.

Authors' Contributions: Conception-design, data collection, writing and critical revision: DK, Conception-design, writing and critical revision: SOY, Conception-design, data analysis, writing: BB, Conception-design, critical revision: EE, Conception-design, critical revision

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