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Outcomes of Steroid and Pulse Steroid Therapies in COVID-19 Inpatients Requiring Oxygen Therapy, Retrospective Case Control Study

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ABSTRACT

Background: A limited number of studies have been conducted examining the course of the disease and the effectiveness of corticosteroid treatments in patients with severe COVID-19 pneumonia requiring oxygen support. This study assessed steroid effectiveness in oxygen-dependent COVID-19 patients.

Methods: Included in the study were 670 patients who required oxygen support during their hospital stay among the 6,532 Covid-19 patients between 1 August 2020 and 1 June 2021. Demographic data, comorbidities, duration of oxygen therapy, length of hospital stay, corticosteroid treatments (dexamethasone, methylprednisolone) and pulse corticosteroid treatments (methylprednisolone ≥ 250 mg) were recorded. We analyzed data using Statistical Package for the Social Sciences Program (Version 16.0. Chicago, SPSS) and applied Shapiro-Wilk, Mann-Whitney U, Kruskal-Wallis, and Chi-square tests for statistical significance ($p<0.05$).

Results: The mean age of the patients was 64±13 (19–95) years, 55% were male, and the mean duration of hospital stay was 9±6 (1–64) days. Dexamethasone, pulse steroids, and low-dose methylprednisolone (<80 mg) were given to 41%, 13%, and 18% of patients, respectively. 31.6% required ICU admission, and the overall hospital mortality rate was 18.1%. Notably, 83% of deaths occurred within the first week.

Conclusion: Most deaths in oxygen-dependent COVID-19 patients happened within 7 days. While corticosteroids didn't impact overall mortality, dexamethasone seemed to boost discharge without ICU admission.

Keywords: COVID-19, dexamethasone, mortality, oxygen therapy, pulse corticosteroid therapy

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INTRODUCTION

It has been reported that approximately 15% of patients infected with COVID-19 require inpatient treatment, although an effective and standard therapeutic approach to hospitalized patients has yet to be established. Mortality is relatively higher in the presence of comorbidities such as obesity, DM, HT, and coronary artery disease. The treatments administered to inpatients are shaped according to the resources of the countries and the guidelines published by the local health authorities. While the use of Favipiravir was until recently a standard approach in our country, the use of dexamethasone 6 mg/day became a routine treatment in patients requiring oxygen therapy after the Recovery trial, leading clinicians to feel encouraged to administer pulse steroid therapies. Early detection and treatment of cytokine storm in patients with severe COVID-19 pneumonia who require oxygen support outside of the ICU reduces the risk of the patient going to the ICU.[1] Tocilizumab and Anakinra are effective in controlling the "cytokine storm" in severe COVID-19 pneumonia requiring oxygen, but their high cost and limited availability make them difficult to access. This, coupled with physician' inexperience in their use, can lead to treatment delays. Consequently, readily available and affordable pulse corticosteroids like dexamethasone have become commonplace in hospital settings to manage this inflammatory response. Yet, despite their widespread adoption, data on the long-term effectiveness and patient outcomes of dexamethasone and other pulse corticosteroids remain scarce. Our study fills this gap by delving deeper into the clinical course of these patients and meticulously analyzing the impact of corticosteroid therapies on their recovery trajectories. By addressing this critical knowledge gap, we aim to optimize treatment strategies and potentially streamline care pathways, ultimately improving patient outcomes and potentially reducing the risk of long-term health complications.

METHODS

Data collection and study design

Our study analyzed data from 670 patients requiring oxygen support during their hospitalization for COVID-19. These patients were drawn from a pool of 6,532 patients admitted to the Eskisehir City Hospital COVID-19 wards between August 1, 2020, and June 1, 2021. We retrospectively collected data from the hospital information management system (HIMS) and patient files, focusing on demographics (age, gender), comorbidities, PCR test results, oxygen therapy and hospital stay durations, as well as details of corticosteroid treatment received (dexamethasone, methylprednisolone, and pulse steroid therapy with methylprednisolone≥250 mg). The treatments received by the patients were recorded, including blood sugar monitoring, electrolyte monitoring, and possible side effects of the patients receiving steroids. The outcomes of the study patients were determined as "discharge from the ward", "death on the ward", "discharge from the intensive care unit", and "death in the intensive care unit".

Statistical analysis

We entrusted SPSS (IBM SPSS Ver. 16.0, IBM Corp, Chicago, USA) version 16.0 to meticulously analyze the collected data. First, we verified the normality of quantitative data using the Shapiro-Wilk test. We then employed a trio of statistical methods to uncover meaningful patterns: the Mann-Whitney U test for comparisons between two groups, the Kruskal-Wallis analysis for detecting differences among multiple groups, and the Chi-square test for exploring relationships between categorical variables. Throughout these analyses, we set a stringent significance level of $p<0.05$ to ensure the findings were statistically robust.

RESULTS

The mean age of the patients was 64±13 (19–95) years, 55% were male, and the mean duration of hospital stay was 9±6 (1–64) days. Considering comorbidities, there was a significantly high rate of patients with hypertension (41.5%), diabetes mellitus (22.8%), and asthma (11.9%). While almost all of these patients received Favipiravir therapy, five patients could not tolerate the drug, and administration was stopped. Plaquenil was added to the existing therapies of five patients, and 10 patients received convalescent plasma. Oxygen therapy was initiated in 10% of the patients who were hospitalized in the COVID-19 wards. Of the 449 patients in the study group who were discharged directly from the ward, 134 required oxygen support for 7 days, 239 for 8 to 14 days, and 76 for longer than 15 days.

The total hospital mortality rate (121/670) was 18.1% in patients admitted to the wards and initiated on oxygen therapy. Of the patients, 449 (67%) were

discharged from the inpatient wards, and nine patients died on the ward. Approximately 32% (212) of the patients who were initiated on oxygen therapy needed to be transferred to the intensive care unit.

The CS therapies administered to the study patients are summarized in Table 1.

The mortality rate was 53% in the patient group admitted to the intensive care unit, from which 100 patients were discharged. Among the non-surviving patients, 72.7% and 26.4% were over 65 and 81 years of age, respectively, while 65.2% were male. Mortality was significantly higher in males and in the patient groups with comorbidities of hypertension, diabetes mellitus, heart disease, and dementia. Moreover, 83% of the deaths occurred within the first seven days of hospitalization. The outcomes of the study patients are summarized in Table 2.

Dexamethasone and/or Pulse Steroids were used at a higher rate in the patients discharged from the ward than in those discharged from the intensive care unit, and the difference was found to be associated with the use of dexamethasone. The clinical characteristics of the patients receiving and not receiving dexamethasone are summarized in Table 3. Dexamethasone and pulse steroid therapies were found to increase the likelihood of a patient being discharged from the ward without admission to the intensive care unit ($p<0.05$).

There was no significant difference in mortality between those who received and did not receive CS (Table 4). There was no significant association between the time of CS administration and mortality according to the start of oxygen therapy.

Finally, Table 5 shows the differences in the demographic characteristics, comorbidity rates, and corticosteroid therapies of non-survivors and survivors. Statistical significance was found between the surviving and non-surviving groups in terms of age groups, gender, and comorbidities ($p<0.05$).

DISCUSSION

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.[2] For COVID-19 patients with severe ARDS or septic shock, the World Health Organization (WHO) recommends glucocorticoids. However, routine use of these drugs for general inflammation is not recommended.[3] A range of studies have delved into the question of when and how to administer steroids, evaluating the impact on mortality and complications across various indications.[4,5] Corticosteroid use in COVID-19 treatment became more common after the RECOVERY study identified a mortality reduction

Table 1. Corticosteroid therapies are administered to patients receiving oxygen therapy

Corticosteroid therapies	Rate of use
Dexamethasone	41% of patients
Pulse steroids (corticosteroids ≥250 mg)	13% of patients
Methyl prednisolone ≤80 mg	18% of patients
No corticosteroids	28% of patients

Table 2. Clinical outcomes of COVID-19 patients receiving oxygen therapy

Patient Outcomes	n	%
Discharge from the Ward	449	67%
Discharge from the Intensive Care Unit	100	14.9%
Death on the Ward	9	1.3%
Death in the Intensive Care Unit	112	16.7%
Total number of patients	670	100%

Table 3. Age, Gender, Comorbidities, Clinical Outcomes of Patients Receiving and Not Receiving Dexamethasone

	Dexamethasone Therapy			
	Not Receiving n (%)	Receiving n (%)	Total n (%)	P-value
Age groups (years)				
≤49	47 (51.6)	44 (48.4)	91 (13.6)	0.429
50–64	140 (60.1)	93 (39.9)	233 (34.8)	
65–79	151 (61.4)	95 (38.6)	246 (36.7)	
≥80	58 (58.0)	42 (42.0)	100 (14.9)	
Gender				
Female	181 (60.3)	119 (39.7)	300 (44.8)	0.560
Male	215 (58.1)	155 (41.9)	370 (55.2)	
Comorbidities				
No	146 (58.2)	105 (41.8)	251 (37.5)	0.703
Yes	250 (59.7)	169 (40.3)	419 (62.5)	
Outcomes				
Discharge from the ward	244 (54.3)	205 (45.7)	449 (67.0)	***0.001**
Discharge from the intensive care unit	75 (75.0)	25 (25.0)	100 (16.7)	
Death on the ward	6 (66.7)	3 (33.3)	9 (1.3)	
Death in the intensive care unit	71 (63.4)	41 (36.6)	112 (16.7)	
Total	396 (59.1)	274 (40.9)	670 (100.0)	

Table 4. The effect of the corticosteroid therapies on patient outcomes

CS Support	n	Discharge from the ward	Rate of ICU admission	Discharge from the ICU	Death in the ICU	Hospital Mortality
Received Decort	274	205	25.1%	25	44	16%
Not received Decort	396	244	38.4%	75	77	19.4%
Received pulse-steroid therapy	90	62	31%	12	16	17.7%
Never received CS	322	194	39.7%	64	64	19.8%
Low-dose Prednisolone	121	84	30.5%	15	22	18.1%

ICU: Intensive Care Unit

Table 5. Demographic characteristics, comorbidity rates, and corticosteroid therapies of non-surviving and surviving patient groups

	Non-survivors n (%)	Survivors n (%)	Total n (%)	P
Age groups (years)*				
≤49	3 (3.3)	88 (96.7)	91 (13.6)	**0.001**
50–64	25 (10.7)	208 (89.3)	233 (34.8)	
65–79	57 (23.2)	189 (76.8)	246 (36.7)	
≥80	36 (36.0)	64 (64.0)	100 (14.9)	
Gender				
Female	42 (14.0)	248 (86.0)	300 (44.8)	**0.014**
Male	79 (21.4)	291 (78.6)	370 (55.2)	
Comorbidities				
No	22 (8.8)	229 (91.2)	251 (37.5)	**0.001**
Yes	99 (23.6)	320 (76.4)	419 (62.5)	
Dexamethasone				
No	77 (19.4)	319 (80.6)	396 (59.1)	0.263
Yes	44 (16.0)	230 (84.0)	274 (40.9)	
Pulse Steroids				
No	105 (18.1)	475 (81.9)	580 (86.5)	1.000
Yes	16 (17.8)	74 (82.2)	90 (13.5)	
Dexamethasone and/or Pulse Steroids				
Not Received	64 (19.9)	258 (80.1)	322 (48.1)	0.240
Received	57 (16.4)	291 (83.6)	348 (51.9)	
Methylprednisolone Alone				
No	99 (18.0)	452 (82.0)	551 (82.2)	0.998
Yes	22 (18.5)	97 (81.5)	119 (17.8)	
Total	121 (18.1)	549 (91.9)	670 (100.0)	

associated with 6mg/kg dexamethasone.[6] PST has also become widespread with the demonstration that pulse steroid administration provides a similar decrease in mortality.[7] Several studies indicate that early administration of corticosteroids, particularly dexamethasone, is associated with reduced mortality in critically ill COVID-19 patients.[8-10] Systemic corticosteroids likely reduce all-cause mortality slightly in hospitalized COVID-19 patients.[11] Early use of corticosteroids (within the first 48 hours of ICU admission) is linked to better outcomes, including lower ICU mortality and fewer complications compared to delayed administration.[8,9]

In previous studies of oxygen therapy provided outside the intensive care unit generally sought to measure the success of non-invasive mechanical ventilation methods such as Continuous Positive Airway Pressure (CPAP) or High-Flow Nasal Cannula (HFNC). Our review of literature identified only one study investigating COVID-19 patients receiving oxygen therapy outside of the intensive care unit, which was conducted in Germany and included 57 patients who did not require or did not want to be admitted to the intensive care unit among 133 inpatients initiated on oxygen support. It would seem that 76 patients not included in this study required intensive care, and that these patients needed supplemental oxygen for a mean of 8 (5–13) days and had a mean hospital stay of 12 (7–20) days. The authors reported that 13 patients died on the ward, although 12 had decided to limit the treatment.[12] When compared to our patient group, this study reports a much higher rate of intensive care need among the patients. Our study provides detailed information about the rates of deterioration and the benefit of corticosteroid support administered in addition to respiratory support in patients initiated on oxygen support on the ward, and this can be considered a strength of our study. It was found in the study that at the time when we had not yet started accepting patients with the delta variant, one out of every three inpatients who were initiated on oxygen therapy required intensive care treatment, and one out of every two patients who were admitted to the intensive care unit died. Since the publication of the Recovery trial during the third wave of the pandemic, it has become almost routine treatment to administer dexamethasone 6 mg/day to COVID-19 patients requiring oxygen therapy for 10 days or until discharge. The inclusion of patients receiving treatment during the second wave in our study allowed for a comparison of mortality between the groups that received and those that did not receive dexamethasone. The comparison of the groups receiving and not receiving dexamethasone revealed no difference in total hospital mortality, although the rate of dexamethasone use was significantly higher in the patient group who were discharged from the ward. Although the rate of intensive care requirement (25.1% < 38.4%) and the hospital mortality rate were lower (16% < 19.2%) in the dexamethasone-treated group, the difference was statistically insignificant. The Recovery trial reported significantly lower 28-day mortality in the dexamethasone group among the non-intubated patients receiving oxygen (23.3% < 26.2%).[1] There was also no difference in mortality between the groups receiving and not receiving corticosteroid therapy, although this finding should be interpreted considering that patients receiving pulse-steroid therapy may suffer relatively more severe respiratory failure. The weakness of our study is that the laboratory data of the patients during the COVID-19 treatment were not evaluated for disease severity, and so it would make no sense to compare the clinical outcomes of patients receiving pulse-steroid therapy with those receiving other CS therapies or not receiving them at all. Some 70% of the patients receiving pulse-steroid therapy, however, were discharged without the need for intensive care, which may give an idea about the success of the treatment. In our study, various confounding factors may have played a role in the lack of a significant difference in mortality between the groups that received and did not receive CS. In particular, comorbidities, disease severity, the type of oxygen support, and concomitant treatments may have influenced the outcomes. Considering these factors, isolating the effect of steroids on mortality has become challenging. Among the limited number of high-quality studies in the literature measuring the success of pulse-steroid therapies, most focus on the outcomes of patients administered pulse-steroid therapies, while others report patients being treated with concomitant anticytokine therapies such as tocilizumab. A limited number of studies have compared high-dose and low-dose CS therapies, but did not consider lung involvement and/or inflammatory laboratory parameters when determining disease severity. A number of studies have not been included in the discussion because they were carried out in intensive care units with many confounding factors.

Batırel et al.[13] compared three groups of 150 patients treated with standard support therapy (Group

1), dexamethasone 6 mg/day (Group 2), and pulse-steroid therapy (methylprednisolone 250 mg/day) (Group 3). The groups were matched for disease severity (the National Early Warning Score (NEWS2)) and demographic characteristics. Despite the lack of a statistically significant difference in mortality between the groups (Groups 1/2/3: 23.8%/ 17.4%/ 7.9%), the rate of intensive care unit admission was significantly lower in the dexamethasone group, as in our study. The authors found that the need for intensive care was lower in the pulse-steroid therapy group than in the Group 1 patients, and reported a shorter ICU stay among the pulse-steroid therapy group. It should be noted that the NEWS2 score was established based on the clinical findings of the patients (respiratory rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness or new confusion, temperature), while the inflammatory marker laboratory parameters were not taken into account.[13] In another study, Cusacovich et al.[14] compared 124 patients who underwent pulse-steroid therapy at a dose of ≥100 mg for three days (92% of patients received 250 mg pulse methylprednisolone for 3 days) with 133 patients who did not receive pulse therapy, and reported significantly lower mortality in the pulse group (30.3%<42.9%).

In this study, dexamethasone was not administered to any of the patients, and so no comparison can be made of high-dose and low-dose CS therapies. In our country, especially since the fourth wave of the pandemic, the administration of pulse Prednol 250 mg has become almost routine practice in cases of clinical deterioration in the patient groups without DM or in those with known coronary artery disease. When anti-cytokine therapies are considered, these treatments are primarily administered due to their low cost.

Our study evaluated the impact of corticosteroid (CS) therapy on mortality in oxygen-treated COVID-19 patients and found no significant difference between those who received and did not receive CS. While previous studies suggest a reduction in mortality with steroid treatment, the available data do not provide a clear answer regarding the potential survival benefit of pulse-steroid therapy. Moderate-to-high doses of corticosteroids have been associated with better outcomes than low doses; however, the optimal dosage remains uncertain.

This study covers the second and third waves of the pandemic, during which physicians increasingly favored pulse-steroid therapy, particularly in patients experiencing an acute disease phase, lack of fever response, or worsening PAAC radiographic findings. In clinical practice today, pulse-steroid therapy is often considered a last resort before intensive care, making future controlled studies on this approach unlikely.

Our study has several limitations, including its retrospective design, the lack of laboratory data to assess disease severity, and the unknown stage of the disease at the time of CS administration. Additionally, potential confounding factors, such as differences in baseline characteristics and concurrent treatments, may have influenced the results. Further prospective studies with detailed disease severity assessments are needed to clarify the role of pulse-steroid therapy in COVID-19 management.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Statement

The study was approved by both the Turkish Ministry of Health and the Ethics Committee of Trakya University Faculty of Medicine (Decision Date: 27/12/2021 and No: 25/49), and all necessary administrative permissions were obtained from the Turkish Ministry of Health, the Eskisehir Provincial Health Directorate and the Office of the Chief Physician of Eskisehir City Hospital. This study was carried out following the principles of the Declaration of Helsinki and all applicable regulations.

Authors' Contribution

Concept – ZIK,SE; Design –SE; Supervision – SE; Fundings – ZIK,SE; Materials – ZIK, SE; Data collection and/or processing – ZIK; Analysis and/or interpretation – ZIK,SE; Literature review – SE; Writing – ZIK,SE; Critical review – SE

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