



## Effects of Pulse Dose of Corticosteroids in Hospitalized Patients with COVID-19: An Observational Study

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### ABSTRACT

**Background:** Although corticosteroids are commonly used for COVID-19 disease during the inflammatory phase, the effective doses and the best choice of corticosteroids are not yet known.

**Methods:** In the present study, the effects of non-pulse (30-250 mg/day of prednisolone equivalent) versus pulse equivalent (>250 mg/day of prednisolone equivalent) doses of corticosteroids are compared in terms of the patients' oxygen saturation, hospital mortality, and side effects. In addition, the patients were followed for 2 months for readmission and mortality.

**Results:** 270 severe or critically ill patients with COVID-19 disease were included in the study. Diabetes and hypertension were the most common comorbidities. More than 80% of the patients received corticosteroids. Pulse equivalent doses of corticosteroids were used in 36.9 % of the patients. Treatment with pulse doses of corticosteroid significantly increased the oxygen saturation in the critically ill patients. However, the pulse doses significantly increased the in-hospital mortality rate [29 (20.3%) vs. 12 (10.6%),  $p=0.036$ ] and the side effects. In addition, a trend toward higher 60-day mortality was observed in the pulse-based-treated patients [31 (21.7%) vs. 14 (12.4%),  $p=0.053$ ]. The multivariate analysis showed that having comorbidities increased the mortality risk independently [OR 3.33, CI 1.148-9.647].

**Conclusion:** The results showed that the pulse doses of corticosteroids increase the oxygen saturation, but they also can increase mortality. Further randomized controlled trials with larger sample sizes are needed to confirm our findings.

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### Introduction

The Severe Acute Respiratory Distress Syndrome-CoV2 (SARS-CoV2) is an RNA virus responsible for COVID-19. The new coronavirus was first reported in China and after a while became a world problem. It belongs to the coronavirus family with a spike protein which can bind to the Angiotensin-Converting Enzyme receptors 2 (ACE-2)

and subsequently enter the host cell, leading to direct viral toxicity and endothelial damage, an increase in thrombosis, disarrangement in immune response, hematologic lab data abnormality, and renin-angiotensin system abnormalities (1). It has a mortality rate varied from place to place from 0.17% to 1.7% (2), has infected about 180 million people, and has led to death of about 3.9 million people. Pulmonary, central nervous, renal, hepatic, gastrointestinal,

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cardiovascular, endocrine, and skin are the systems affected by COVID-19 (1). Viral incubation period, viral replication, localized pulmonary inflammation, and host response are proposed as stages of pulmonary involvement (3). The earlier data showed that cytokines including interleukin 1 $\beta$ , 2, 4, 6, 10, tumor necrosis factor alpha, and interferon  $\gamma$  increased after COVID-19 disease (4, 5). Subsequent studies showed that cytokines concentration is lower in this disease (6). The COVID-19-associated Acute Respiratory Distress Syndrome (ARDS) is a major complication and is different from the classical ARDS and associated with a higher thrombosis (7). Considering oxygen saturation, respiratory involvement, and respiratory rate, disease severity can be asymptomatic, mild, moderate, severe, and critical (7). Higher rates of deep vein thrombosis and arterial thrombosis were reported in the patients (8, 9).

Controlling viral replication by the use of antivirals, immunosuppressive agents such as tocilizumab, and inflammation control are the mechanisms for managing patients with COVID-19 (10). Corticosteroid involve genomic (requiring low dose) and non-genomic (requiring high dose) mechanisms [11]. Dexamethasone can inhibit production of cytokines including interleukin IL-1, IL-2, IL-6, IL-8, TNF, IFN-gamma, and VEGF (11). The results from RECOVERY showed that dexamethasone at a daily dose of 6 mg per day for up to 10 days along with a standard care significantly decreased the mortality rate in the patients receiving supplemental oxygen compared with those receiving the usual care alone (12). The highest effects were observed in the patients receiving invasive mechanical ventilation (12). Compared to the shorter period, the patients who received higher courses of corticosteroid treatment (> 7 days) showed a lower mortality rate (13). Methylprednisolone equivalent doses of 0.5-2 mg/kg/day for 5-10 days had been used in the previous studies (14-16). Another group of investigators used higher doses (e.g. very high or pulse doses) in the patients with a severe form of the disease (17-19). Optimum doses of corticosteroids have not been yet defined.

The aim of the present study was to evaluate the effects of pulse doses of dexamethasone or methylprednisolone versus lower doses in the hospitalized severe and critically ill COVID-19 patients.

## Methods

This study was conducted in the period of September to December 2020 in Golestan hospital, Kermanshah province, Iran. It is a COVID-19-specific hospital with eighty beds. The study protocol was approved by the ethic committee of Kermanshah University of Medical Sciences (IR. KUMS.REC.1399.959). The sample size was calculated as followed:

$$n = \frac{(z_{1-\alpha/2})^2 p(1-p)}{d^2} = \frac{3/8416 \times 0/446(1-0/446)}{0/06^2} = 264$$

(Where p=0.566,  $\alpha$ =0.05, d=0.06).

The population of the study consisted of the severe and critically ill COVID-19 patients (O<sub>2</sub> saturation < 90%) and positive CT-scans or PCR tests who required oxygen supplements (i.e., low or high flow oxygen therapy). The patients' demographic, clinical, and laboratory data, medications, and outcomes were recorded. All the severe and critically ill COVID-19 patients were included in the present study.

The patients were followed for 2 months after being discharged from the hospital. The prednisolone equivalent doses including low, moderate, high, very high, and pulse doses were calculated for all the patients who received corticosteroids. The conversion between corticosteroid doses were calculated as follows (20):

Low dose ( $\leq$  7.5 mg prednisone equivalents a day)

Medium dose (> 7.5 mg and  $\leq$  30 mg prednisone equivalents a day)

High dose (>30 mg and  $\leq$ 100 mg prednisone equivalents a day)

Very high dose (> 100 mg prednisone equivalents a day)

Pulse Therapy (> 250 mg prednisone equivalents per day for one or a few days).

According to the available guidelines, corticosteroids are recommended for severe forms of the COVID-19 disease (7). Dexamethasone is the suggested steroids; however, dexamethasone equivalent doses of methylprednisolone, prednisolone, and hydrocortisone can also be used for these patients (7, 21). The effects of pulse equivalent doses of either methylprednisolone or dexamethasone (250-500 mg prednisolone equivalents for three consecutive days) versus non-pulse doses (<250 mg prednisolone equivalent) in the severe and critically ill COVID-19 patients were evaluated. The corticosteroid doses decreased during the hospitalization. The patients were followed for 60 days after being discharged from the hospital.

A primary outcome of the present study was the changes in oxygen saturation. In-hospital and 60-day mortality, duration of hospitalization, occurrence of thrombotic events (e.g. acute myocardial infarction, venous thromboembolism, stroke), occurrence of acute kidney injury based on the KDIGO definitions (22), and adverse effects related to corticosteroids were considered as the secondary outcomes.

The criteria offered by the National Institute of Allergy

The data analysis in this study was performed by the use of SPSS software, version-16. In order to evaluate the preliminary results in different corticosteroid dosing classes, the normal distribution of the variables in each class was assessed by the use of the Kolmogorov-Smirnov test. The qualitative variables were reported as number and percentage and analyzed by the use of the chi-square test. The Analysis of Variance (ANOVA) and the independent t-test were used to evaluate the normally-distributed quantitative variables. The Kruskal-Wallis and Mann-Whitney tests were performed for the variables that were not normally distributed in the one or both groups. The p-values less than 0.05 were considered as significant.

## Results

During the research period, 270 severe or critically ill COVID-19 patients were studied. The numbers of male and female were almost equal (53% vs. 47%). 60% of our population had at least one comorbidity. The basic characteristics of all the population are presented in Table 1.

**Table 1.** Baseline characteristics of study population.

Age (year), mean $\pm$ SD	58.81 $\pm$ 14.83
<50 n (%)	77 (28.5%)
50-65 n (%)	95 (35.2%)
> 65 n (%)	98 (36.3%)
<b>SEX</b>	
Male, n (%)	127 (47%)
Female, n (%)	143 (53%)
<b>BMI (Kg/m<sup>2</sup>), mean <math>\pm</math> SD</b>	26.97 $\pm$ 4.35
< 18.5 n (%)	3 (1.3%)
18.5-25 n (%)	73 (31.6%)
25-30 n (%)	112 (48.5%)
> 30 n (%)	43 (18.6%)
<b>Comorbidities, n (%)</b>	162 (60%)
Hypertension	106 (39.3%)
Diabetes	64 (23.7%)
COPD	7 (2.6%)
Malignancy	14 (5.2%)
CVD	53 (19.6%)
CKD	29 (10.7%)
Dialysis	13 (4.8%)
Rheumatologic disorder	13 (4.8%)
<b>Selected lab tests on admission, median <math>\pm</math> SD</b>	
FBS (mg/dl)	167.94 $\pm$ 103.05
SrCr (mg/dl)	1.48 $\pm$ 1.26
eGFR (ml/min/1.73m <sup>2</sup> )	59.23 $\pm$ 22.65
WBC (count)	8.23 $\pm$ 5.17
Hemoglobin (g/dl)	12.80 $\pm$ 1.97
Lymphocyte (cells/ $\mu$ l)	1316.13 $\pm$ 2438.31
Platelet (10 <sup>3</sup> cells/ $\mu$ l)	216.08 $\pm$ 76.61
Ferritin ( $\mu$ g/l)	277.88 $\pm$ 240.97
Fibrinogen (mg/dl)	481.18 $\pm$ 93.37
LDH (Unit/L)	755.61 $\pm$ 435.50
SpO <sub>2</sub> (%)	88.47 $\pm$ 7.09
<b>D-Dimer</b>	
+	34 (12.6%)
-	21 (7.8%)
Non checked	215 (79.6%)
<b>CRP</b>	
-	9 (3.3%)
1+	29 (2.7%)
2+	41 (15.2%)
$\geq$ 3+	121 (44.8%)
PCR, + (%)	212 (78.5%)

BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, CVD: Cardiovascular disease, CKD: Chronic kidney disease, FBS: fasting blood sugar, SrCr: serum creatinine, eGFR: estimated glomerular filtration rate, LDH: Lactate dehydrogenase, CRP: C-reactive protein, PCR: Polymerase chain reaction

The overall mortality rate was 15.6% (42/270), including 62% of critically ill patients and 5% of those who had severe illness during hospitalization. More than 80% (83%) of the patients were survived following 2 months after being discharged (Table 2). Different doses of corticosteroids were equally effective in the patients who received the low flow oxygen replacement ( $p = 0.90$ ).

**Table 2.** Outcomes of study.

Oxygen therapy, n (%)	270 (100%)
Low flow (mask with reservoir)	230 (85.2%)
NIMV	17 (6.3%)
IMV	23 (8.5%)
Duration of hospitalization (day), mean $\pm$ SD	8.91 $\pm$ 5.17
Critically ill, n (%)	50 (18.5%)
Coagulopathy, n (%)	15 (5.6%)
Myocardial infarction	6 (2.2%)
Stroke	5 (1.9%)
Pulmonary emboli	1 (0.4%)
Deep vein thrombosis	3 (1.1%)
Death, n (%)	46 (17.1%)
In hospital	42 (15.6%)
After discharge	4 (1.5%)
Hyperkalemia, n (%)	25 (9.3%)
Hypokalemia, n (%)	22 (8.1)
Hypertension, n (%)	38 (14.1%)
Hyperglycemia, n (%)	153 (56.7%)

IMV: Invasive mechanical ventilation,

Sofosbuvir/daclatasvir and interferon-beta were the most commonly used antiviral medications (Table 3). Only 31.9% of the patients received remdesivir. Anticoagulants were used in 86.9% and 86% of those with severe and critical illness, respectively. Only 4 patients received tocilizumab, and they died after being discharged. The treatment with antiviral agents did not reduce the chance of mortality ( $p = 0.059$ ).

The corticosteroid therapy was initiated during the first 72 hours of admission in 83.7% (226/270) of the patients. Out of the patients who received the corticosteroid therapy upon admission, 37.7% and 45.2% received dexamethasone and methylprednisolone, respectively. Corticosteroids at pulse doses significantly increased the oxygen saturation only in the critically ill patients ( $p = 0.003$ ) and not in all patients ( $p > 0.05$ ). The basic characteristics of the patients who received the pulse and non-pulse therapies are provided in Table 3. In-hospital mortality, hypokalemia, hyperglycemia, and hypertension were significantly higher in the patients who received corticosteroid pulse doses than in the non-pulse

group (Table 4). In addition, there was a trend toward higher mortality in 60 days in the corticosteroid-pulse group. The patients in the pulse therapy had a higher disease severity (Table 3). The univariate analysis showed that having comorbidities and higher disease severity significantly increased the mortality rate, while the multivariate Cox regression analysis showed that only comorbidities increased the mortality risk independently [OR 3.33, CI 1.148-9.647].

**Table 3.** Treatment regimens

Treatment	N (%)
Interferon $\beta$ 1	230 (85.2%)
Sofosbuvir/Daclatasvir	234 (86.7%)
Remdesivir	86 (31.9%)
Colchicine	49 (18.1%)
Favipiravir	16 (5.9%)
Tocilizumab	4 (1.5%)
Anticoagulant (standard, intermediate and therapeutic doses)	
Severe illness	220 (86.9%)
Critically illness	50 (86%)

**Table 4.** Baseline characteristics of patients on pulse versus non-pulse therapy.

Outcome	(%) Pulse therapy, n	Non-pulse therapy, n (%)	P value
High-flow oxygen therapy	33 (23.1%)	6 (5.3%)	<0.001 <sup>#</sup>
Thrombotic events	8 (5.6%)	6 (5.3%)	0.921 <sup>#</sup>
Acute kidney injury	5 (3.5%)	3 (2.7%)	1.000 <sup>###</sup>
In-hospital mortality	29 (20.3%)	(10.6%) 12	0.036 <sup>#</sup>
Hyperkalemia	13 (9.1%)	12 (10.6%)	0.682 <sup>#</sup>
Hypokalemia	15 (10.5%)	4 (3.5%)	0.035 <sup>#</sup>
Hypertension	27 (18.9%)	10 (8.8%)	0.023 <sup>#</sup>
Increase in blood glucose	101 (70.7%)	51 (45.1%)	
Mild and Moderate	46 (32.2%)	24 (21.2%)	<0.001 <sup>#</sup>
Severe and life Threatening	55 (38.5%)	27 (23.9%)	

## Discussion

The results of the present study showed that the pulse doses of corticosteroids improved the O<sub>2</sub> saturation only in the critically ill patients; however, they were associated with an increased in-hospital mortality and a trend toward a higher 60-day mortality. Regarding the outcomes, there was no difference between dexamethasone and methylprednisolone at very high and high doses. In the recovery study, dexamethasone at a daily dose of 6 mg for a maximum of 10 days significantly decreased the mortality rate in all

Empiric prophylaxis for pneumocystis jirovecii pneumonia (PCP) was initiated only in 1.9% of the patients receiving the pulse therapy. Nearly all the patients (97.4%) received antibiotics. Azithromycin (65.9%), ceftriaxone (70.7%), and carbapenem-vancomycin (18.1%) were the most commonly used antibiotics. Antifungal agents were used in 2.8% of the patients. The concomitant antimicrobial treatment did not reduce the mortality rate ( $p > 0.05$ ).

the patients who were on low flow oxygen and mechanical ventilation, but not in the patients who did not need oxygen supplement (12). Compared to the standard care, higher dexamethasone doses (i.e. 20 mg daily for 5 days and then 10 mg daily for another 5 days) in the patients with moderate to severe COVID-19 infections significantly decreased the ventilator-free days, duration of mechanical ventilation, and the Sequential Organ Failure Assessment (SOFA) scores; however, there was no difference between the two group

in terms of the 28-day mortality rate (24). A few studies have used the higher doses of corticosteroids. For instance, Edalatfard et al., compared methylprednisolone at daily doses of 250 mg/day for 3 days compared to the standard care, and found that pulse dose of methylprednisolone significantly decreased the mortality with no significant side effects (25). In addition, Pinzon et al., compared the pulse doses (i.e. 250-500 mg/day) for 3 days and then 50 mg/day prednisolone for 14 days with 6 mg/day dexamethasone for 7-10 days, and found that treatment with corticosteroid pulse significantly decreased the ICU admission and laboratory markers including d-dimer, LDH, and CRP (26). Similar to our results, the high doses of methylprednisolone (250-1000 mg/day) were associated with an increase in mortality rate and needs for mechanical ventilation (27). Kumar et al. showed that higher doses (>40 mg/day) versus lower doses (<40 mg/day) of methylprednisolone increased the odd ratio of mortality (28). The mortality rate of the critically ill patients was significantly higher in our study compared to the overall reported mortality rate for the ICU patients (29).

In the present study, the corticosteroid pulse treatment was associated with an increased risk of hyperglycemia, hypokalemia, and uncontrolled hypertension. However, the risk of thrombotic events, acute kidney injury, and other evaluated side effects did not increase in the pulse-receiving patients.

Most of the patients received an agent sofosbuvir/daclatasvir, the efficacy of which was not clearly evaluated. However, some studies with low sample sizes showed that sofosbuvir versus standard of care can decrease the mortality rate or duration of hospital stay (30, 31). Although remdesivir did not show a positive effect on the mortality rate, it can decrease the recovery time significantly (32). In the present study, receiving medications including sofosbuvir/daclatasvir, favipiravir, remdesivir, and interferon did not affect the mortality rate. Nearly all the patients received broad spectrum antimicrobial treatment. Most of the patients received treatment for community-acquired pneumonia regimen including azithromycin and ceftriaxone combination. These data were much higher than the data previously reported by observational studies (33, 34). However, antifungal was less prescribed in our study (35). The risk of pneumocystis jirovecii pneumonia (PCP) with the commonly used doses of corticosteroids is low, and universal prophylaxis is not recommended (36). However, the incidence PCP in the patients receiving the higher doses is unclear.

This observational study can give more information about the effects of very high and pulse doses of corticosteroids on in-hospital and 60-day mortality rates in severe to critically ill COVID-19 patients. In addition, in the limited recourse, the setting gives more information about the effective doses of corticosteroids.

Our study had some limitations: first, the observational nature of the study with a relatively small sample size has limited the definite conclusion; second, due to the

limitations, we were not able to measure some data such as D-dimer, quantitative CRP, and cytokines concentrations in all the patients. In addition, routine CT scan and test for galactomannan were not possible in our center, influencing our conclusion.

The results of the present study showed that corticosteroid pulse increased the oxygen saturations only in the critically ill patients who required high flow oxygen and mechanical ventilation. However, it can increase the in-hospital mortality rate and side effects and thus should not be recommended at this time. Further studies are needed to confirm our results.

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