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High-Dose or Low-Dose Corticosteroids – Which Regimen is More Effective in Patients with Moderate to Severe COVID-19? A Retrospective Study

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ABSTRACT

Background: *Although several studies have assessed corticosteroid therapy as a pivotal treatment for SARS-CoV-2, the net effectiveness of corticosteroids in the treatment of COVID-19 remains controversial. This study aimed to compare the conventional use of methylprednisolone and pulse therapy to determine the best method of administration of corticosteroids in patients with SARS-CoV-2.*

Methods: *A total of 52 patients with a diagnosis of moderate to severe COVID-19 with the same conditions were retrospectively enrolled in the present study. Participants were divided into two groups based on the corticosteroid therapy regimen received during hospitalization: low-dose and high-dose methylprednisolone. Clinical outcomes, including laboratory tests, improvement of oxygen saturation, the need for invasive mechanical ventilation, length of hospital stay (LOHS) and mortality, were compared between the two groups.*

Results: *The distribution of sex, age, oxygen saturation on admission, pattern and location of lung involvement, and other medical conditions were similar between the two groups to avoid the effect of any possible confounding factor. There were no differences in laboratory tests (P=0.389), LOHS (P=0.107), improvement of oxygen saturation (P=0.721), the need for invasive mechanical ventilation and mortality (P=0.695) between groups.*

Conclusion: *Based on the results of this study, there was no significant difference in clinical outcomes of patients with COVID-19 between low- and high-dose corticosteroid regimens. Further research is warranted to determine the best method of administration of corticosteroids in these patients.*

Keywords: COVID-19, corticosteroid, methylprednisolone.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread quickly all around the world and the necessity of developing efficient therapeutic protocols to prevent or treat COVID-19 has become a critical demand due to emergence of novel strains (1).

Although several studies have assessed corticosteroid therapy as a pivotal treatment pathway as it could reduce the length of stay in intensive care unit (ICU) and that of mechanical ventilation usage, the absolute role of corticosteroids is unclear because of limited improvement in survival rate (2-4). Some reports demonstrated that methylprednisolone, a frequently used drug as the basis of treatment during the pandemic, could delay the progression of acute respiratory distress syndrome (ARDS) (5). Additionally, some studies reported that the risk of mortality decreased with the administration of methylprednisolone (6). According to other studies, corticosteroid therapy seemed to have no effect on fatality and length of hospital stay (LOHS) in patients diagnosed with COVID-19 pneumonia (4).

Moreover, several studies revealed that dministration of corticosteroid pulse therapy for COVID-19 patients had more complications, including diabetes mellitus (DM), psychosis, glaucoma, fluid retention, hypertension, weight gain, secondary infection and osteoporosis, in comparison with low-dose corticosteroids (3, 4). In contrast, pulse therapy can reduce the mortality rate, which is a vital part (7). Nevertheless, the majority of scientists and general practitioners are facing inadequate information on the net effectiveness of corticosteroids in the treatment of COVID-19 pneumonia (1).

The aim of this study is to display the difference between the conventional use of methylprednisolone and pulse therapy and demonstrate the best method of administration of corticosteroids in patients with SARS-CoV-2 infection. ❑

MATERIAL AND METHOD

Study design and patients

A retrospective study was designed and performed in cooperation with Shahid Labbafi Nejad Hospital (Tehran, Iran). All participants were informed about the study and provided their written consent. The local ethics committee approved the protocols of this study.

We retrospectively included 68 patients with symptoms and signs of coronavirus pneumonia who were referred to our emergency department between June 2021 and January 2022. Inclusion criteria for the initial screening were according to patients' clinical presentation, including SPO_2 <93%, acute respiratory distress, respiratory rate >30 *per* minute and any sign of prostration. Individuals who experienced any of the above criteria were admitted to hospital as patients with COVID-19 pneumonia with moderate severity. The absolute diagnosis was accomplished by reverse transcriptase polymerase chain reaction (RT-PCR) test and computed tomography (CT) scan. Ultimately, 52 patients who were found to be eligible based on the above-mentioned criteria were enrolled in the study.

The studied population was divided into two groups based on the corticosteroid therapy regimen received during hospitalization: low-dose and-high dose methylprednisolone. The low-dose group had received 1-2 mg/kg of methylprednisolone daily for 3-5 days *via* conventional setting, while the-high dose group was given 250 or 500 mg of methylprednisolone pulse therapy daily for 3-5 days. The distribution of sex, age, oxygen saturation on admission, pattern and location of lung involvement, and other medical conditions were similar between the two groups to avoid the effect of any possible confounding factor. Additionally, the frequency of other medications prescribed based on the COVID-19 treatment protocols, including anticoagulants, remdesivir, pantoprazole and vitamin C, was similar in both groups.

Measurements

Medical interns and residents were responsible for checking the patients' general condition, oxygen saturation and the type of oxygen supplementation as a daily visit during hospitalization. All data were retrospectively extracted from hospital records of Shahid Labbafi Nejad Educational and Medical Center (Tehran, Iran).

Laboratory tests, including complete blood count (normal range: WBC=4000-11000) and differentiation, blood chemistry, coagulation test (normal range: PT 10-12, PTT 25-35), electrolytes

(normal range: Na 135-145, K 3.5-5), C-reactive protein (CRP) (normal range: lower than 3), erythrocyte sedimentation rate (ESR) (normal range: up to 50 years <15, 50-85 years <20, >85 years <30), liver enzymes (normal range: aspartate aminotransferase (AST) 10-40, alanine aminotransferase (ALT) 7-56 and alkaline phosphatase (ALP) 20-140) and renal function tests (normal range: creatinine 0.5-1.2, urea 5-20), lactate dehydrogenase (LDH) (normal range: 140-280), albumin (normal range: 3.4-5.4) and creatine phosphokinase (CPK) (normal range: 39-308 in males and 26-192 in females) were also recorded. These laboratory tests were examined for all patients every day.

Evaluating the pattern and location of lung involvement was achieved by requesting a CT scan and all patients enrolled in our study were in the early pulmonary phase of illness. All above-mentioned medical data are stored in a computerized database as well as LOHS. The age, sex, past medical history (PMH), vital signs, laboratory test results, type of oxygen supplementation, the need for noninvasive or invasive mechanical ventilation and the type of methylprednisolone administration were extracted from this database after discharge.

Statistical analysis

The results were statistically described as mean ± standard deviation (SD) for continuous variables and frequency (percentage) of categorical variables. Pearson's chi-square or Fisher exact test was used to compare categorical variables between two groups. The normality of continuous variables was checked using the Kolmogorov-Smirnov test. The independent T-test test or Mann–Whitney U test was used to compare the means of two independent groups based on the distribution of the variable. The level of significance for statistical tests was 0.05. The SPSS software version 24 (Armonk, NY: IBM Corp.) was used for statistical analysis. ❑

RESULTS

A total of 52 patients with confirmed diagnosis of COVID-19 were ultimately enrolled in the present study, including 26 patients with a mean age of 56.50±13.60 years who received low dose methylprednisolone and 26 patients with a mean age of 56.50±15.12 years who received high dose methylprednisolone. There was no significant difference in age and gender between the two groups. In each group, 17 patients were females and nine males. All patients had a history of vaccination against COVID-19. Additionally, 13 subjects had a history of DM (seven in the high-dose group and six in the low-dose group), which showed no significant difference between the two groups (P=0.749). The mean oxygen saturation was 81.5% in the low-dose group and 85.5% in the high-dose group, which was not statistically significant (p=0.242).

The most commonly seen symptoms among individuals in both groups were fatigue and myalgia (88.4%, 84.6%), dyspnea (61.5%, 53.8%) and dry cough (46.1%, 38.4%). Computed tomography (CT) scan revealed a mean of 30% pulmonary involvement with ground glass patchy pattern in each group.

Elevated levels of CRP (96.1%), ESR (86.5%) and lactate dehydrogenase (94.2%) were detected in most individuals on admission. Lymphocytosis and thrombocytosis were seen in 57.6% and 55.7% of patients, respectively. On admission, the liver function test showed high levels of AST, ALT, and ALP in 38.4%, 28.8% and 57.6% of patients, respectively. Furthermore, elevated level of urea (76.9%) was common among participants; however, increased level of creatinine (41.5%) was infrequent.

The median length of hospital stay was 7.7 days in the low-dose group and 6.8 days in the high-dose one, which was not significantly different between the two groups (p=0.107). Among them, two patients (7.7%) in each group required invasive mechanical ventilation. Mortality was observed in two patients in each group. Overall, no differences in laboratory tests (P=0.389), LOHS (P=0.107), improvement of oxygen saturation until discharge (P=0.721), need for invasive mechanical ventilation and mortality were observed in either group. ❑

DISCUSSION

The results of this study indicated that there was no difference between administering a high-dose or low-dose methylprednisolone regimen in terms of clinical outcomes of patients with mild to moderate COVID-19, including improvement in plasma oxygen saturation reco-

very, need for invasive mechanical ventilation, LOHS and mortality. All results were obtained while controlling for the potential influence of age, gender, PMH and drug history, as these variables were matched between the two groups.

Previous studies reported the effectiveness of corticosteroids in treating COVID-19 (8-10). Current evidence suggests that the appropriate use of corticosteroids may reduce the mortality rate, ventilator dependence and recovery time (11, 12). While previous studies have consistently reported the effectiveness of corticosteroids in treating COVID-19, the current evidence still lacks information on the efficacy of different types, dosages and timing of systemic corticosteroids (13, 14). In addition, given the potential adverse effects of corticosteroids in this patient population, it is important to carefully consider the pros and cons of different treatment regimens (15, 16).

In this regard, some studies have suggested that corticosteroids could have a dose-response effect on viral shedding and high-dose regimens delayed viral clearance and shedding period. Therefore, it is recommended that high-dose corticosteroids should be used with extreme caution in treating COVID-19 (17, 18). Specifically for patients with COVID-19-induced mild to moderate ARDS, Jamaati *et al* demonstrated that there was no clinical benefit in high-dose administration of dexamethasone (19), which was consistent with our findings. Similarly to our study, clinical outcomes of patients with mild to moderate COVID-19, including the need for invasive mechanical ventilation, mortality rate, duration of clinical improvement, LOHS and radiological changes on the CT scan, were assessed in this study.

The effectiveness of the low-dose regimen, however, remains an important finding of our study. Although some studies reported that low-dose corticosteroids had no effect on patients with COVID-19 pneumonia (20, 21), most of the studies supported the fact that prolonged administration of low-dose methylprednisolone led to lower mortality rate and need for mechanical ventilation (12). Moreover, another study assessed the effectiveness of corticosteroid therapy in the treatment of patients with COVID-19 and indicated that early, low-dose and short-term administration of corticosteroids was associated with a faster improvement in clinical symptoms. In this study, twenty-six patients received intravenous methylprednisolone at a dose of 1–2 mg/kg/day for 5–7 days. Improvement of oxygen saturation level was faster in these 26 patients; in contrast, those who did not receive methylprednisolone needed longer supplemental oxygen therapy (22).

Furthermore, adverse effects of high-dose corticosteroid regimen have been also reported in previous studies. Ueda *et al* showed that administration of methylprednisolone *via* high-dose regimen in two patients without any history of heart disease could cause atrial fibrillation shortly after pulse therapy (23). Additionally, Suchman *et al* reported seizure episodes in a 32-year-old man with lupus nephritis without any history of neurological problems after a high dose pulse of methylprednisolone (24). Therefore, it is important to note complications related to pulse therapy of methylprednisolone in this population.

The results of the current study should be interpreted in light of some limitations, with the small sample size being the main one. Our study was an observation retrospective research, while further blinded randomized clinical trials are warranted to confirm these findings. Besides, it is recommended to evaluate alternative administration pathways, including inhalation, topical and rectal usage. ❑

CONCLUSION

The results of this study revealed that there was no significant difference in clinical outcomes, including laboratory tests, LOHS, improvement of oxygen saturation until discharge, the need for noninvasive and invasive mechanical ventilation, and mortality of patients with COVID-19, between low- and high-dose methylprednisolone regimens. Further research is warranted to determine the best method of corticosteroid administration in these patients. ❑

Conflicts of interest: none declared.
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