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Original article

Effective and safe profile of mini-pulse corticosteroid among COVID-19 inpatients: a case series

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Abstract: ***Background:*** The COVID-19 epidemic has spanned four waves in Vietnam, the most recent and also the most deadly of which began in April 2021. ***Methods:*** We reported on a group of University Medical Center Ho Chi Minh City patients who were diagnosed with SARS-CoV-2 infection and were suitable for mini-pulse corticosteroid therapy with 125 mg of methylprednisolone twice daily for at least three days. Demographics, clinical, laboratory, and outcome data were gathered by electronic medical report. We also compared laboratory data before and after the start of mini-pulse corticosteroid therapy, as well as between the discharged and deceased groups. ***Results:*** We gathered data on 25 patients. The average age was 61.5 ± 11.9 years, and 52% of them were male. Dyspnea was the most prevalent chief complaint. Almost all of them had at least one co-morbidity, with hypertension being the most common; all of them were put on oxygen supplementation, and 44% were started on mini-pulse corticosteroid while using a high-flow nasal cannula. Eighty-four (21%) reacted well and were discharged, whereas sixteen (4%) worsened and died. The deceased group was older than the discharged group (69.8 ± 3.1 vs. 59.9 ± 12.4, p =.005). ***Conclusion:*** Our findings suggest that methylprednisolone at a mini-pulse dosage might be an effective and safe treatment option for COVID-19 inpatients in the inflammatory stage.

Keywords: COVID-19; SARS-CoV-2; mini-pulse; methylprednisolone.

1. INTRODUCTION

COVID-19, a new pandemic, has been spreading over the world since December 2019. There have been over 182 million contractions until July 1st, 2021, with 3.9 million deaths. COVID-19 patients may experience a significant systemic inflammatory response, which may include lung damage and multiorgan failure. The anti-inflammatory effects of corticosteroids have been suggested as a way to prevent or mitigate these disastrous results.

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In patients with acute respiratory distress, corticosteroids were found to reduce all-cause mortality risk (risk ratio 0.75; CI 95%, 0.59-0.95) and mechanical ventilation length (mean difference -4.93 days; CI 95%, -7.81 to -2.06 days) [1], according to a meta-analysis of these patients compared to placebo [2]. The recommendation to utilize corticosteroids in the inpatient COVID-19 subgroup was originally mentioned in the RECOVERY study. This is a major, randomized, multi-center experiment undertaken in England, in which 6,425 COVID-19 patients were assigned to a dexamethasone therapy group for up to 10 days, or a basic treatment group. At 28 days, the mortality rate in the dexamethasone group was considerably lower than in the control group [3]. This benefit was shown in individuals who received mechanical ventilation or oxygen supplements, but not in those who did not get respiratory support. There have recently been experiments that enlisted severe COVID-19 individuals to be treated with a greater dose of corticosteroid, dubbed "mini-pulse" steroid, with promising results. This has prepared the way for a fresh method to managing this unusual and perplexing disease.

In a retrospective study [4], 262 ICU patients in a US hospital were evaluated, with 75 receiving basic care, 104 receiving methylprednisolone at least 1 mg/kg/d for 3 days or more, and 83 receiving dexamethasone at 6 mg for at least 7 days. The death rates were 41.3%, 16.4%, and 26.5%, respectively, at 50 days in the basic therapy group, methylprednisolone group, and dexamethasone group ($p < 0.01$). In the mechanical ventilation subgroup, the death rate was 42% lower in the methylprednisolone group than in the dexamethasone group (HR 0.48; CI 95%: 0.235 – 0.956, $p = 0.0385$). Pinzón et al. [5] conducted an experiment in which 216 severe COVID-19 patients were given dexamethasone at a dose of 6 mg per day for 7–10 days, while 105 others were given methylprednisolone at a level of 250–500 mg per day for 3 days, then 50 mg per day for the next 14 days. The methylprednisolone group had a lower ICU admission rate than the basic therapy group, with rates of 4.8% and 14.4%, respectively. The mortality rate was also lower in the high-dose corticosteroid group than in the control group (9.5% vs. 17.1%). COVID-19 laboratory values that reflected severity were also lowered considerably.

These early trials in developed countries have set the road for a novel and potentially effective treatment to minimize mortality and ICU pressure. Despite this, clinical use of high-dose corticosteroids in COVID-19 patients is uncommon in poor nations. Understanding the clinical characteristics of COVID-19 inpatients is crucial for physicians to devise a management strategy and medical supply recruiting strategy. As a result, we undertook this study to describe demographics, co-morbidities, clinical and laboratory features, and outcomes in COVID-19 patients who received high-dose corticosteroid treatment at University Medical Center Ho Chi Minh City.

2. MATERIALS AND METHOD

This is an observational research presented in the form of a case series, conducted from August 1st 2021 to September 13th 2021 at Interventional Cardiology Department 2B, University Medical Center Ho Chi Minh City. The object of this study was to examine safety and efficacy of high-dose corticosteroid regimen in COVID-19 patients. We enrolled all SARS-CoV-2 infected patients from August 1st 2021 to September 13th 2021, matched the inclusion criteria and were treated with high-dose corticosteroid during hospital stay.

All patients over the age of 18 who agreed to participate, had a positive PCR SARS-CoV-2 test, rising oxygen supplementation in a short period, and/or high CRP, Interleukin-6, D-dimer, LDH, Ferritin concentrations, and/or extended pulmonary damage on chest X-rays met the inclusion criteria. Those with critical SARS-CoV-2 infection or severe uncontrolled illness at the time of admission, active pulmonary tuberculosis, active gastrointestinal bleeding, fulminant hepatitis B, and those who did not want to participate were all excluded. All of the eligible patients were enlisted, and data on their demographics, medical histories, clinical examinations, laboratory results, and outcomes were collected. Blood samples were taken immediately before and 24–48 hours after the last mini-pulse corticosteroid administration. The high-dose corticosteroid utilized in the study, referred to as a "mini-pulse" corticoid, was intravenous methylprednisolone at a dose of 250 mg per day for three days, then tapered to 40mg twice daily for three days, and concluded with 40mg of methylprednisolone or 6mg of dexamethasone for a total of 10 days. The main outcomes included all-cause death, length of stay, hyperglycemia-related complications or an episode of acute psychosis.

In the final analysis, we had 25 patients. Qualitative variables were presented with average ratio, meanwhile quantitative variables were presented as mean (standard deviation) or median (quartile). To compare means for quantitative variables, we used the Wilcoxon test or Mann-Whitney U for non-normally distributed data and the independent sample T-test for normally distributed data, while to evaluate connection between qualitative variables, we utilized the Fisher exact test. IPM SPSS Statistics 26 was used to run these tests, and statistical differences were recorded when $p < 0.05$. We have established an official consensus on practical mini-pulse corticosteroid use in COVID-19 inpatients to reduce selection bias.

Our study was approved by Ethics Committee for Biomedical Research at University Medical Center Ho Chi Minh City, no. 88/GCN-HĐĐĐ and each participant completed a consent form.

3. RESULTS

3.1. Patient characteristics

We recruited 25 SARS-CoV-2 infected patients who were treated with mini-pulse corticosteroids and were eligible to participate in the trial from August 1st to September 13th, 2021. Table 1 shows demographics and clinical features. The majority of the patients (19/25, or 76%) were above the age of 70. Co-morbidities were also widespread among these individuals, with 21 (84%) having at least one underlying condition, the most common being hypertension (14/21). Dyspnea was the most common complaint, affecting 22/25 patients, followed by cough and fever, which affected 20/25 patients each.

Mini-pulse steroids were started in 12 patients (48%) before they were admitted to the Interventional Cardiology 2B Department. Figure 1 depicts the moment at which a patient

was started on mini-pulse corticosteroid, with 68% of patients starting on mini-pulse corticosteroid during the first 72 hours after admission. Among the 21 successfully discharged patients, three were given a mini-pulse corticosteroid while receiving oxygen through a cannula, seven were given a mask, and eight were given a high-flow nasal cannula. The ratio of individuals who were started on mini-pulse corticosteroids during the first 72 hours of admission in the discharged group was lower than in the deceased group, although this was not statistically significant (66.67% vs. 75%, p = 0.618).

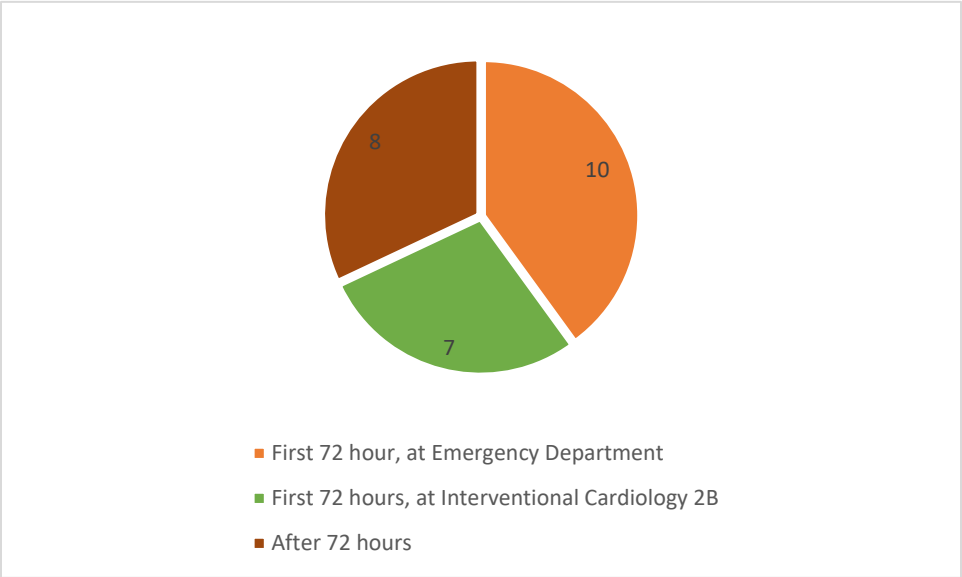

Figure 1. Time of initiating mini-pulse corticosteroid

Table 1. Demographics, clinical and treatment characteristics

Characteristics	No (N = 25)
Age	61.5 ± 11.9
Sex	
Male	13 (52)
Female	12 (48)
BMI (N = 24)	23.7 ± 2.3
Co-morbidity	
Overweight, obesity	8 (32)
Hypertension	14 (56)
Diabetes	10 (40)
Chronic pulmonary disease	2 (8)
Chronic kidney disease	1 (4)
Chronic coronary syndrome	5 (20)
Liver disease	3 (12)
Symptom	
Dyspnea	22 (88)
Cough	20 (80)
Fever	20 (80)
Sore throat	6 (24)
Chest pain	3 (12)
Taste loss	2 (8)
Hearing loss	1 (4)
Oxygen supplement	
Cannula	5 (20)
Mask	9 (36)
HFNC	11 (44)
Remdesivir	
Yes	22 (88)
No	3 (12)
Tocilizumab	
Yes	2 (8)
No	23 (92)

Table 2. Laboratory results before and after utilizing mini-pulse corticosteroid

	Before mini-pulse	After mini-pulse	*p*
WBC (N=25) (G/L)	9.7 ± 3.7	10.4 ± 3.8	0.476[w]
NEU (G/L)	8.6 ± 3.7	9.2 ± 3.7	0.459[w]
LYMP (G/L)	1.1 ± 2.3	0.6 ± 0.3	0.686[w]
HGB (N=25) (g/L)	133.4 ± 14.6	131.4 ± 15.8	0.298[t]
PLT (N=25) (G/L)	261.7 ± 117.8	285.7 ± 103.9	0.208[t]
D-dimer (N=21) (ng/mL)	1251.8 ± 1656.9	1639.8 ± 2407.8	0.259[w]
CRP (N=25) (mg/L)	87.4 ± 51.7	26.9 ± 21.7	**< 0.001[t]**
Urea (N=25) (mg/dL)	36.9 ± 15.4	43.4 ± 16.4	**0.015[w]**
Creatinine (N=25) (mg/dL)	0.9 ± 0.7	0.8 ± 0.2	**0.01[w]**
Sodium (N=25) (mEq/L)	129.8 ± 27.7	137.2 ± 4.6	0.135[w]
Potassium (N=25) (mEq/L)	3.6 ± 0.9	3.7 ± 0.5	0.427[w]

[w]Wilcoxon test; [t]independent samples T-test

Table 3. Comparison demographics and laboratory results between two groups: discharged and deceased

	Discharged (N = 21)	Deceased (N = 4)	*p*
Hospital stay	17.9 ± 7.9	14 ± 12.7	0.058[m]
Age	59.9 ± 12.4	69.8 ± 3.1	0.063[m]
Sex			0.672[f]
Male	11	2	
Female	10	2	
WBC (G/L)	9.6 ± 3.9	10.4 ± 2.5	0.394[m]
NEU (G/L)	8.5 ± 3.9	8.9 ± 2.7	0.604[m]
CRP (mg/L)	85.2 ± 52.6	98.9 ± 52.6	0.505[m]
D-dimer (ng/mL)	1536.1 ± 1778.4	812.8 ± 375.6	0.882[m]
Urea (mg/dL)	34.6 ± 12.7	48.6 ± 24.4	0.182[m]
Creatinine (mg/dL)	0.9 ± 0.8	1.1 ± 0.5	0.578[m]
Sodium (mEq/L)	130.1 ± 30.1	128 ± 7.9	0.068[m]
Potassium (mEq/L)	3.6 ± 0.9	3.5 ± 0.7	0.911[m]

[m]Mann-Whitney U test; [f]Fisher exact test

3.2. Laboratory results

Before utilizing mini-pulse corticosteroid, all patients underwent a chest X-ray, and all of them had bilateral damage, with 9 patients (36%) having ground-glass opacification, 6 patients (24%) having reticular patterns, and 10 patients (40%) showing bilateral consolidations. Table 2 shows the laboratory findings before and after mini-pulse corticosteroid treatment, with CRP, urea and creatinine concentrations substantially altered between two quantifications. CRP concentration was much lower than before administration of mini-pulse corticosteroid (26.9 ± 21.7 vs. 87.4 ± 51.7, $p < 0.001$), and creatinine concentration was similarly significantly lower than before administration (0.8 ± 0.2 vs. 0.9 ± 0.7, $p = 0.015$), while urea concentration was significantly higher than before mini-pulse usage (43.4 ± 16.4 vs. 36.9 ± 15.4, $p = 0.015$).

3.3. Outcomes

The average length of stay in the hospital was 17.9 days. Twenty-one patients (84%) were discharged, while four (16%) died (Table 3). Two of these four patients died in the Interventional Cardiology 2B Department, one from hypovolemic shock caused by psoas muscle hemorrhage and the other from septic shock. The other two patients died shortly after being transported to University Medical Center COVID-19 Intensive Care Center, both from septic shock. In our experiment, the rate of patients developing a more serious infection was 3/25 (12%). Additionally, we did not identify any cases of severe hyperglycemia-related complications or an episode of acute psychosis.

4. DISCUSSION

Our case series included 25 COVID-19 inpatients with demographics, clinical and laboratory data, and outcomes after mini-pulse corticoid treatment. The majority of the patients had at least one co-morbidity, with dyspnea being the most common reason for admission. In the first 72 hours after admission, almost all of them were treated with mini-pulse corticoid and were generally supported with high-flow oxygen supplement. CRP levels were significantly decreased after utilizing mini-pulse corticoid. Nearly all of the 25 patients healed and were discharged, although four of them became sicker and died, largely as a result of septic shock.

Our patients' clinical manifestations were identical to those in an Iran experiment [6], indicating a similar host reaction. The most prevalent symptom was dyspnea, with cough coming in second. Fever was also a common symptom in our study, however it only accounted for half of the cases in Iran. This discrepancy could be due to the presumption that our patient was infected before to admission; in contrast, only one patient (2.9%) in the Iran experiment had pneumonia. In both studies, hypertension was a prevalent co-morbidity. Inflammation response was dramatically reduced in both trials, with CRP levels much lower after utilizing mini-pulse corticoid. This is simply explained by the fact that mini-pulse steroid has a strong anti-inflammatory impact.

Through three stages of pathophysiology model: viral stage, pulmonary stage, and inflammatory stage, the anti-inflammatory action of corticoid and its application in the treatment of COVID-19 has been suggested since the beginning. The latter is reflected in SARS-CoV-2 contraction by an overt host immunological response that results in inflamed lung cells, activated T-cells, and the release of pro-inflammatory cytokines into the bloodstream [7]. The most researched anti-inflammatory drug in the treatment of COVID-19 is corticosteroids, with RECOVERY being the cornerstone study [3]. In this study, all COVID-19 inpatients of all stages were given 6 mg oral dexamethasone per day for up to 10 days, with favorable outcomes reported in the oxygen supplemental group. Many different corticosteroid kinds and dose levels have been investigated as a result of this study. Among these, methylprednisolone with a mini-pulse dosage of 250 mg per day for at least 3 days has shown efficacy and safety in improving clinical and laboratory responses as well as preventing progression to a more severe stage and mortality [4-6].

The theory for the greater impact of high dosage corticosteroid over low dose corticosteroid is that they function in distinct ways. The effects of corticosteroids vary depending on absorption rate, concentration at target tissue, glucocorticoid affinity for receptors, metabolism and elimination rate, and, not least, dose. The attained saturated glucocorticoid receptors would be 40 – 50% with a modest dosage comparable to 7.5 mg of prednisone or less. With this property, it is typically administered as a maintenance dosage. As the dosage is increased, so are the effects and adverse responses. The receptors would be totally saturated with a larger dosage, as in a "mini-pulse" or higher dose regimen. These dosage ranges not only maximize overall genomic effect but also boost therapeutic effects via non-genomic pathways. This distinction may result in major clinical changes. COVID-19 patients in the inflammatory stage, with severe clinical symptoms and considerably elevated inflammation markers such CRP, IL-6, LDH, Ferritin, and rapidly progressing damage on chest X-ray or computed tomography, would benefit most with high-dose corticosteroids. Our findings support the precision patient identification and timing of mini-pulse corticosteroid administration in COVID-19 patients in order to achieve the greatest efficacy with the least chance of side reactions.

Corticosteroid therapy at high doses is associated with a variety of side effects, which typically include hyperglycemia, an increased risk of infection, and an acute psychotic episode. In our trial, the number of patients who developed a more serious infection (which ultimately resulted in death) was 3/25 (12%), and all-cause mortality was 16%. According to Ko et al. , the all-cause mortality rate was 16.4 percent among COVID-19 patients receiving methylprednisolone [4]. More impressive, Edalatifard et al. found that adverse events occurred in 2/34 (5.8%) of 34 patients receiving high-dose methylprednisolone, with infection worsening in only one patient [6]. In conclusion, while a placebo-controlled trial is currently the only approach to accurately verify the association between high dosage methylprednisolone use and adverse effect ratio, our investigation found that the adverse effect rate was at least comparable to those of other trials conducted worldwide. Meanwhile, as previously noted, the rate of unfortunate events was not considerably different or even lower than that of other categories. Additionally, our study did not document any individuals who experienced severe complications from hyperglycemia or an episode of acute psychosis. Other studies conducted throughout the world likewise unable to recollect any of these effects.

When administered correctly on the right patient, mini-pulse corticosteroids might be a potential therapeutic option for COVID-19 patients. For starters, correct timing would minimize cytokine storms, delay the progression to severe presentation, and limit the requirement for mechanical ventilation and critical care. Furthermore, this beneficial impact aids in the allocation of medical resources, the reduction of medical supplies, and the reduction of staff overload. Finally, proper patient selection would reduce unfavorable risk while simultaneously maximizing the beneficial impact of mini-pulse corticosteroid. In clinical practice, given the scarcity of highly effective immunosuppressive agents, such as tocilizumab, and the catastrophic development of cytokine storm, we feel that mini-pulse steroid therapy might be a reasonable option.

Our research has several limitations. To begin with, certain clinical symptoms and test data were not documented. Instead, due to the escalation of the pandemic, we did not visit these individuals to gather more information, and we also did not evaluate the missing factors. Moreover, the small sample size would prevent the findings from being extrapolated.

Conclusion

This first investigation on utilizing mini-pulse corticosteroid in Vietnam has some parallels to other countries, where most patients responded favorably to therapy when administered appropriately. Our research focuses on a unique therapeutic method that is a potential option for reducing severe deterioration and pressure on the healthcare system.

AUTHOR CONTRIBUTIONS

TTN, VHV, HT, CDN, KDN, DN, MTTN, TTTT, TKV, TTP, UNLH were responsible for patient diagnosis, management and collected clinical and imaging information. TTN, VHV, CDN, KDN, BQT wrote the paper. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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