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Letter

High-dose methylprednisolone pulse therapy for the treatment of patients with severe COVID-19: Results from a prospective observational study

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To the Editor:

Recent randomized controlled trials, as well as high-quality systematic reviews and meta-analyses, strongly support the use of corticosteroids in patients with coronavirus disease 2019 (COVID-19) who require oxygen support.[1] The use of pulse corticosteroid therapy has been reported in case series and studies, showing significant improvement in patients and a reduction in mortality rate.[2] In this letter, we report the mortality rate among patients with severe COVID-19 receiving pulse corticosteroids with methylprednisolone (500 mg/day) for ≥3 days and ≥24 h before intubation (median duration of therapy: 3 days) compared with standard of care.

This analysis involves 147 patients admitted to the COVID-19 Intensive Care Unit 2 at Thu Duc City Hospital (Ho Chi Minh City, Vietnam) from July 13, 2021, to August 31, 2021, whose final outcomes were revealed before September 15, 2021. These patients had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), diagnosed using a reverse transcription-polymerase chain reaction test based on a nasopharyngeal swab. The patients were classified as severe based on the national guidelines and had ferritin levels >1000 ng/mL.[3] Due to the severity of the disease and the large volume of incoming patients within the aforementioned time interval, all history taking and contact tracing activities were dismissed. There were 66 patients treated with pulse therapy (PT), and 81 patients treated with methylprednisolone (32 mg/day) according to the national guidelines (control). Upon the initiation of PT, all other corticosteroid regimens were discontinued until the duration of the therapy was completed. The median time required for the initiation of PT since the day of admission was 1 day (interquartile range: 0–3 days). The median pulse corticosteroid dosage was 6.88 mg/kg body weight (interquartile range: 7.69–8.33 mg/kg body weight). Among all other treatment options recommended within the COVID-19 Diagnosis and Treatment Guideline from the Ministry of Health, remdesivir was the only available option for two patients receiving pulse corticosteroid therapy.[3]

As these are real-life data, treated and untreated patients were not comparable according to all baseline characteristics. Thus, we applied propensity scoring to balance all characteristics between the two groups, as indicated in Table 1. Subsequently, we used Bayesian model averaging to identify predictors with high posterior probabilities accounting for mortality. Based on the results, three variables, namely PT, age, and peripheral capillary oxygen saturation (SpO_2), are key for predicting the mortality rate. In this model, the probabilities of PT, age, and SpO_2 affecting the mortality rate were 97.4%, 100%, and 98.3%, respectively. Multivariate analysis of these three key variables revealed that the use of PT was associated with an 87% decrease in the odds of in-hospital mortality (odds ratio [OR]=0.13, 95% confidence interval [CI]: 0.03–0.63, P=0.011). Each additional increase by 1 year in age was associated with a 15% increase in the odds of in-hospital mortality (OR=1.15, 95% CI: 1.06–1.24, $P<0.001$). Also, an increase by one SpO_2 percentage point was associated with a 12% decrease in the odds of in-hospital mortality (OR=0.88, 95% CI: 0.80–0.97, P=0.010). Moreover, there was no statistical difference in the number of adverse events recorded in both the treatment and control groups [Table 2]. This finding indicates that this therapy is safe. The potential impact of PT suggests the need for randomized controlled trials to further

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Table 1
Univariable analyses of factors associated with in-hospital mortality.

Variables	OR (95% CI)	*P*-value
Sex	0.86 (0.42–1.78)	0.691
Age	1.10 (1.06–1.14)	<0.001
BMI	0.92 (0.84–1.01)	0.070
PT	0.13 (0.06–0.31)	<0.001
No. of comorbidities		0.118
1	0.71 (0.30–1.67)	
2	0.26 (0.09–0.78)	
3	2.07 (0.24–17.91)	
4	0.30 (0.02–4.96)	
Body temperature	1.09 (0.92–1.30)	0.120
Respiratory rate	1.05 (1.1–11.00)	0.040
SpO_2	0.91 (0.87–0.96)	<0.001
Hypertension	0.50 (0.19–1.27)	0.152
Cardiovascular	0.46 (0.12–1.80)	0.273
Diabetes mellitus	2.02 (0.64–6.35)	0.203
Chronic respiratory	0.27 (0.06–1.26)	0.096
Obesity	0.49 (0.21–1.15)	0.106
Pregnancy	0.24 (0.04–1.51)	0.127
Stroke	17.24 (5.75–10.97)	0.693
Chronic liver disease	0.72 (−9.54 –9.21)	0.959*
Chronic renal disease	1.17 (0.12–11.53)	0.895
Immunodeficiency disease (cancer or HIV)	12.13 (−6.49 –10.93)	0.811*

* Adjusted with Firth's bias-reduced logistic regression.
BMI: Body mass index; CI: Confidence interval; HIV: Human immunodeficiency virus; OR: Odds ratio; PT: Pulse therapy; SpO_2: Peripheral capillary oxygen saturation.

Table 2
Number of adverse events and adjunctive therapies during treatment.

Characteristic	Total (n = 147)	PT (n= 66)	Control (n = 81)	*P*-value
Number of patients with adverse events during treatment				
Superinfection	0 (0.00)	0 (0.00)	0 (0.00)	NA
Opportunistic infections	59 (40.14)	17 (25.76)	32 (39.51)	0.074
Hyperglycemia	107 (72.79)	51 (77.28)	58 (71.60)	0.436
Delirium	6 (4.08)	3 (4.41)	3 (3.70)	0.828
Gastrointestinal bleeding	0 (0.00)	0 (0.00)	0 (0.00)	NA
Adjunctive therapies				
Remdesivir	2 (1.36)	2 (3.03)	0 (0.00)	0.116
Tocilizumab (IL-6 monoclonal antibody)	0 (0.00)	0 (0.00)	0 (0.00)	NA
JAK inhibitors	0 (0.00)	0 (0.00)	0 (0.00)	NA

Data are expressed as n (%).
IL-6: Interleukin-6; JAK: Janus kinase; NA: Not applicable; PT: Pulse therapy.

examine its efficacy in patients with severe COVID-19. Such trials are warranted to validate the use of high-dose pulse corticosteroids in countries with limited resources, such as Vietnam. This is of particular interest, provided that corticosteroids are affordable, whereas expensive biological agents may not be available.

Ethics approval and consent to participate

Ethical approval was obtained at Thu Duc General Hospital, Ho Chi Minh City, Vietnam (11/HDDD). All participants were in critical care and the prospective observational study nature, consent was waived and identical data was removed from the analysis.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the Github repository, https://github.com/hoanganhngo610/PulseTherapy-VN-ICUThuDuc.

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CRediT authorship contribution statement

TN Bui, HA Ngo, TA Nguyen designed the study. NM Huynh, NH Do-Tran, LD Le coordinated the study implementation and management. Data analysis was conducted by HA Ngo and NH Do-Tran. The manuscript was developed by HA Ngo, then reviewed and edited by all authors.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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