ORIGINAL ARTICLE

Methylprednisolone in severe COVID-19 with acute respiratory distress syndrome – less is more?

Ngu Nga Hung, MRCP(UK), Chai Chan Sin, MRCP(UK), Chan Swee Kim, MRCP(UK), Kho Sze Shyang, MRCP(UK), Yong Mei Ching, MRCP(UK), Tie Siew Teck, MRCP(UK)

Division of Respiratory Medicine, Department of Medicine, Sarawak General Hospital, Kuching, Sarawak, Malaysia

ABSTRACT

Introduction: Corticosteroids, particularly methylprednisolone, are part of the treatment for severe COVID-19 with acute respiratory distress syndrome (ARDS). In this study, we aimed to compare the mortalities of patients treated with higher versus lower doses of methylprednisolone. Secondary outcomes included oxygenation, need for mechanical ventilation, length of stay in intensive care unit (ICU), secondary infection, improvement of PaO2/FiO2 (PF) ratio, and inflammatory response as expressed by C-reactive protein (CRP).

Materials and methods: A retrospective cohort study conducted at Sarawak General Hospital from 1st June to 30th September 2021. Patients who received intravenous methylprednisolone for severe COVID-19 in the ICU were identified and divided into two groups: higher dose (cumulative dose more than 10 mg per kg) and lower dose (cumulative dose less than 10 mg per kg).

Results: Out of a total of 165 patients, 40 (24.2%) patients received higher dose methylprednisolone. There was no significant difference in socio-demographic characteristics (age, gender, body mass index), COVID-19 vaccination status, laboratory parameters (lymphocyte count, CRP, lactate dehydrogenase, D-dimer), or usage of immunomodulator therapy between the groups. Overall mortality was 23.6%. Mortality in the higher dose group was twice as high compared to lower dose group (37.5% versus 19.2%) (OR 3.79, 95% CI 1.24–11.59, $p<0.05$). In addition, the higher dose cohort developed more secondary infections (87.5%) and had longer stays in ICU (median 11 days, IQR 8–15). No significant difference was found between both cohorts in terms of CRP reduction, improvement of PF ratio, or the need for mechanical ventilation post methylprednisolone.

Conclusion: In this study, the use of higher dose methylprednisolone in COVID-19 with ARDS was not associated with better clinical outcomes. A lower dose of methylprednisolone might be sufficient in treating severe COVID-19 with ARDS.

KEYWORDS:
COVID-19, methylprednisolone, acute respiratory distress syndrome (ARDS), mortality

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first recognized in Wuhan, China in December 2019. It has rapidly spread and emerged as a great challenge to the world. The common signs of illness include fever, cough, shortness of breath, myalgia, and diarrhoea. Ideally, specific adaptive immune responses eliminate virus reproduction and preclude disease progression to severe stages. However, when protective immune responses fail, the disease enters a severe inflammatory phase with cytokine release, which causes massive damage to organs with high angiotensin-converting enzyme 2 expression.[1] Acute respiratory distress syndrome (ARDS) is the most common complication leading to the need for mechanical ventilation and admission to intensive care unit (ICU).[2] Therefore, suppressing the proinflammatory response and controlling the cytokine storm is crucial in the treatment of severe COVID-19 illness.

Since 1967, the role of corticosteroids in ARDS has been widely investigated.[3] As widespread inflammatory response is found in the lungs, corticosteroids have potential benefits in reversing the pulmonary inflammation. The use of methylprednisolone in patients with COVID-19 ARDS, particularly those with elevated inflammatory markers during admission, had been reported in few studies and case series.[4–6] Following the release of the large UK-based RECOVERY trial on June 16, 2020, the approach in treating patients with COVID-19 underwent a major change. In the RECOVERY trial, the use of dexamethasone (6mg per day for 10 days) reduced mortality by one-third in patients receiving mechanical ventilation compared to usual standard care.[7] However, it was still unclear if this benefit was from dexamethasone in particular, or a class effect of corticosteroids. The efficacy of methylprednisolone compared to dexamethasone in the treatment of severe COVID-19 pneumonia is still highly debated.[8] Furthermore, there is no evidence to clarify appropriate corticosteroid doses. Many clinically important questions remain unanswered. Hence, in this report, we aimed to compare the clinical outcome of patients receiving higher dose methylprednisolone versus lower dose methylprednisolone in hospitalized ICU patients with severe COVID-19 ARDS.

MATERIALS AND METHODS

Study design

This was a single-center, retrospective, cohort study performed in Sarawak General Hospital, Sarawak, Malaysia.

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Corresponding Author: Nga Hung Ngu
Email: nnh1228@hotmail.com" nnh1228@hotmail.com

Our hospital is located in the local epicentre of the pandemic and is a major tertiary hospital responsible for the treatment of patients with severe COVID-19. All adult patients admitted to ICU with highly suspected Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2-2) infection from 1st June to 30th September 2021 were initially selected and evaluated. Eligible patients included all adults with a positive, laboratory-confirmed test for SARS-CoV-2 developing ARDS, and treated with intravenous methylprednisolone. ARDS was defined by the presence of bilateral pulmonary infiltrates not explained by an etiology other than COVID-19, with PaO2/FiO2 (PF) ratio of less than 300.

Data collection

Electronic medical records from the critical care information system were reviewed, and data were extracted for the period between admission to discharge from ICU, or death, whichever occurred first. Epidemiological, clinical, radiologic, laboratory test results on admission and during hospitalization, treatment, complications, and outcome data were collected.

Patients were divided into two different groups, depending on the dosage of intravenous methylprednisolone administered for ARDS:

- Higher dose group: cumulative dosage of intravenous methylprednisolone more than 10 mg per kg
- Lower dose group: cumulative dosage of intravenous methylprednisolone at and less than 10 mg per kg

The dosage of higher and lower dose methylprednisolone was chosen based on our national COVID-19 management guideline[9] that recommended the use of IV methylprednisolone 2 mg per kg up to 5 days which made up a total cumulative dose of 10 mg per kg. Thus, patients who received a cumulative methylprednisolone dose of more than 10 mg per kg were grouped into the higher dose. According to our local COVID-19 management guidelines[9], IV methylprednisolone 2 mg per kg for 3 to 5 days were recommended in patient requiring higher levels of oxygen support, including category 4b, 5a, and 5b. In these local guidelines, patients requiring high flow mask are sub-classified as category 4b, while those requiring noninvasive ventilation or high flow nasal cannula (HFNC) are classified as category 5a, with category 5b denoting mechanical ventilation with or without other organ failures. In our center, the methylprednisolone dosing decisions are at the discretion of the treating physicians and intensivists.

OUTCOME

The primary outcome was the mortality between the higher dose and lower dose groups. Secondary outcomes included length of stay in ICU, rate of secondary infections, improvement of PF ratio, and inflammatory response (expressed by CRP, lactate dehydrogenase and D-dimer levels).

STATISTICAL ANALYSIS

IBM SPSS statistics 22 was used for the statistical analysis. Descriptive statistics were used to compare the baseline data. Continuous variables were described as mean (standard deviation) or median (interquartile range) depending on the distribution of data, and comparison was done by using parametric or nonparametric statistical test where appropriate. Categorical variables were reported using absolute and relative frequencies and analyzed using Chi-square.

Both unadjusted and multivariable logistic regression models were performed to investigate the effect of both dosages on primary and secondary outcomes. The multivariate model was adjusted for potential confounding factors identified at baseline data. A p-value of less than 0.05 was considered statistically significant. Sample size was calculated using Power and Sample Size calculator. From the literature prior data indicate that mortality rate with lower dose methylprednisolone is 18%.[10] If mortality in the higher dose methylprednisolone group is assumed to be 39%, a sample size of 158 is needed to reject the null hypothesis with a power of 80%, p cut-off value of 5% for statistical significance. In this study, universal sampling technique was applied, with all eligible patients during the study period recruited.

RESULTS

A total of 206 patients were admitted to ICU with positive SARS-CoV-2 infection during the four-month study period. All were evaluated based on the eligibility criteria. Patients not developing ARDS (n = 10), patients with other alternative diagnosis for ARDS (n = 25), and patients not receiving intravenous methylprednisolone (n = 6) were excluded.

In total, 165 patients including 94 (57%) males and 71 (43%) females were included in the study. Ages ranged from 18 to 83 years old with a mean ± SD of 55 ± 14.5 years. The baseline characteristics of our study population was shown in Table I. Among the 165 patients, 40 (24.2%) patients received higher dose methylprednisolone. Comparing the higher dose and lower dose groups, we found no significant differences in baseline characteristics of age, gender, comorbidities except autoimmune disease, presenting symptoms, COVID-19 vaccination status, initial PF ratio and inflammatory markers such as CRP, lactate dehydrogenase (LDH), and D-Dimer.

Primary Outcome

Overall mortality recorded in this report was 23.6% (n = 165) and was two times higher in the higher dose group than in lower dose group (37.5% versus 19.2%, respectively). The unadjusted logistic regression model showed a significantly higher risk of death in patients with ARDS receiving higher dose of methylprednisolone compared to lower dose (OR 2.52, 95% CI 1.16–5.50, $p<0.05$; Table II). After adjusting for age, gender, COVID vaccination status, mechanical ventilation, and secondary infection, the results remained statistically significant (OR 3.40, 95% CI 1.09–10.63, $p<0.05$; Table II).

Secondary outcomes

After treatment with methylprednisolone, we observed an overall improvement of PF ratio from median 116 to 202 (95% CI: 77.1–99.6, p=0.001). However, there was no significant difference in PF ratio increment between the higher dose versus lower dose groups ($p=0.552$).

Table I: Baseline demographics and clinical characteristics

	All patients (n = 165)	Low-dose (n = 125)	High-dose (n = 40)	*p* value
Age (years), mean (± SD)	55 ± 14.5	55 ± 14.0	53 ± 16.0	0.335
Men, no (%)	94 (57.0)	70 (56.0)	24 (60.0)	0.657
BMI, mean (SD)	30 ± 7.5	30 ± 7.3	30 ± 8.1	0.661
Non-smoker, no (%)	124 (75.2)	92 (73.6)	32 (80.0)	0.184
Ethnic, no (%)				
- Malay	69 (41.8)	50 (40.0)	19 (47.5)	0.852
- Chinese	33 (20.0)	25 (20.0)	8 (20.0)	0.852
- Dayak	62 (37.6)	49 (39.2)	13 (32.5)	0.852
Presenting symptoms, no (%)				
- Cough	118 (71.5)	88 (70.4)	30 (75.0)	0.575
- Fever	108 (65.5)	77 (61.6)	31 (77.5)	0.066
- Dyspnoea	78 (47.3)	66 (52.8)	12 (30.0)	0.012
- Diarrhoea	29 (17.7)	24 (19.4)	5 (12.5)	0.509
- Poor appetite	35 (21.2)	28 (22.4)	7 (17.5)	0.323
Comorbidities, no (%)				
- None	44 (26.7)	30 (24.0)	14 (35.0)	0.171
- Hypertension	103 (62.4)	83 (66.4)	20 (50.0)	0.062
- Diabetes mellitus	63 (38.2)	48 (38.4)	15 (37.5)	0.919
- Cardiovascular disease	30 (18.2)	24 (19.2)	6 (15.0)	0.549
- Renal impairment	29 (17.6)	23 (18.4)	6 (15.0)	0.623
- Autoimmune disease	7 (4.2)	2 (1.6)	5 (12.5)	0.003
Laboratories on admission, median (IQR)				
- PaO2/FiO2 ratio	147 (82 - 166)	162 (82 - 170)	112 (83 - 146)	0.521
- CRP (nmol/L)	1230 (635 - 1862)	1326 (676 - 1849)	1158.5 (609 - 1931)	0.659
- Absolute Lymphocyte count (x10^9/uL)	0.8 (0.5 – 1.2)	0.9 (0.6 – 1.2)	0.8 (0.5 – 1.2)	0.677
- LDH	514 (395 – 672)	548 (395 – 678)	497 (397 – 617)	0.656
- D-dimer	2.3 (1.2 – 6.8)	2.5 (1.2 – 7.5)	1.8 (1.3 – 6.4)	0.754
Disease severity upon admission, no (%)				
- Critical / category 5	163 (98.8)	123 (98.4)	40 (100)	0.421
- Mechanical ventilation	65 (39.4)	50 (40.0)	15 (37.5)	0.778
- Acute renal replacement therapy	20 (12.1)	15 (12.0)	5 (12.5)	0.933
Concurrent immunomodulator therapy, no (%)				
- None	129 (78.1)	96 (76.8)	33 (82.5)	0.447
- Baricitinib	28 (17.0)	24 (19.2)	4 (10.0)	0.177
- Tocilizumab	9 (5.4)	5 (4.0)	4 (10.0)	0.146
COVID-19 vaccination, no (%)				
- None	76 (46.0)	53 (42.4)	23 (57.5)	0.095
- one dose	45 (27.3)	31 (24.8)	14 (35.0)	0.207
- two doses	44 (26.7)	41 (32.8)	3 (7.5)	0.002

Values are n (%) for categorical, mean (SD) for normally distributed, or medians (IQR) for non-normally distributed data.
BMI, body mass index; CRP, C-Reactive Protein; LDH, lactate dehydrogenase.

Table II: Multivariate logistic regression analysis of factors associated with mortality

Factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	Adj. OR	95% CI	*p* value
Age > 55 (years)	2.18	1.01-4.68	0.043	2.46	0.83-7.28	0.102
Male gender	2.72	1.22-6.05	0.012	3.32	1.19-9.26	0.022
Non-COVID vaccinated	1.98	0.95-4.10	0.066	2.36	0.92-6.07	0.073
Autoimmune disease	9.12	1.69-49.07	0.002	16.6	1.59-173.83	0.019
Acute renal replacement therapy	6.55	2.44-17.60	<0.001	4.45	1.25-15.52	0.019
High-dose methylprednisolone	2.52	1.16-5.50	0.018	3.40	1.09-10.63	0.035
Mechanical ventilation	11.29	3.78-33.69	<0.001	16.11	4.15-62.42	<0.001
Secondary infection	2.30	0.97-5.43	0.052	0.506	0.15-1.63	0.255

Table III: Primary and secondary outcomes among high-dose methylprednisolone group

Outcomesa	Univariate model			Multivariate model		
	OR	95% CI	*p* value	Adj. OR	95% CI	*p* value
Primary outcome						
Mortality	2.5	1.16-5.50	0.018	3.8	1.24-11.59	0.019
Secondary outcomes						
Need for MV	1.6	0.59-4.36	0.351	1.6	0.59-4.58	0.346
Secondary infection	4.7	1.71-12.72	0.001	3.2	1.05-9.55	0.042
LOS in ICU > 7 days or death	4.3	1.85-10.2	0.001	5.3	1.98-14.93	0.001

MV, mechanical ventilation; LOS, length of stay; ICU, intensive care unit
[a]Comparison is performed with standard-dose of methylprednisolone as reference.

In terms of inflammatory response, the mean CRP level reduced significantly after methylprednisolone, from 1311 nmol/L to 507 nmol/L (95% CI: -920 to -687, p=0.001), but again, there was no significant difference in the reduction of CRP, LDH and D-dimer level between the higher dose group and lower dose group.

The overall mechanical ventilation rate in our study population was 54.5%. 65 (39.4%) patients were mechanically ventilated upon admission to ICU. Despite treatment with methylprednisolone in ICU, another 25 patients required invasive mechanical ventilation. More patients required mechanical ventilation in the higher dose group compared to lower dose group (32% vs. 22.7%, respectively) but this was not statistically significant (p=0.351; Table III).

In this study, the median (IQR) length of stay in ICU was 7 (5–12) days. Significantly longer duration of stay in ICU was observed in the higher dose cohort at 11 (8-15) days, compared to the lower dose group at 6 (4-10) days (p<0.001). Secondary infection was a common complication in ICU hospitalization. In our study population, 110 (66.7%) patients developed at least one episode of secondary infection. The commonest infections were respiratory tract infection (58.8%), followed by bacteremia (36.4%). Patients treated with higher dose methylprednisolone were at significantly higher risk of developing secondary infection compared to lower dose cohort (87.5% vs. 60.0%, p=0.001; table III). The commonest pathogens detected in our study population were *Acinetobacter baumanni*, followed by *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Multi-drug resistant *Acinetobacter baumanni* (MRO) was the most common pathogen found in both groups (35% vs. 21.2%, p=0.072). However, the high dose methylprednisolone group developed more infections from *Klebsiella pneumonia* (35%) and *Pseudomonas aeruginosa* (25%) (p<0.05).

DISCUSSION

Since the beginning of the pandemic, corticosteroids had been used extensively as part of treatment in severe COVID-19 with ARDS, in order to regulate excessive immune responses that cause systemic inflammation and tissue damage.[11,12] Administration of corticosteroids in the early pulmonary phase of illness improves oxygen saturation and inflammatory markers.[13] Treatment with methylprednisolone was found to significantly reduce recovery time, transfer to intensive care, and inflammatory markers.[8] Several studies and case series6,[13–15] had reported better outcomes and lower mortalities in COVID-19 illness, but with varying doses of methylprednisolone. There has been no evidence that a higher dose of steroids resulted in greater benefit than a lower dose.[16] Administration of methylprednisolone equivalent of 1 mg per kg per day has been recommended in moderate to severe COVID-19 with ARDS.[17]

In a retrospective study by Monreal et al, the use of higher dose methylprednisolone was associated with increased mortality in hospitalized patients with critical COVID-19 illness.[10] A similar result was seen in our study; the mortality in the higher dose cohort was twice as compared to the lower dose group. Older age has been associated with both ARDS and mortality due to declining immunocompetence.[4,18] The risk of death and need for mechanical ventilation were significantly higher in patients older than 65 years with the use of higher dose methylprednisolone.[10] Interestingly, the interaction between age and higher dose methylprednisolone was not demonstrated in our study. With our limited ICU capacity, younger patients with severe COVID-19 were more likely to be admitted to ICU during the study period. In this study, there was no significant difference found in the improvement of PF ratio, as well as the reduction of CRP, LDH, and D-dimer level between higher dose and lower dose group. In addition, the use of higher dose methylprednisolone did not reduce the need for mechanical ventilation in severe COVID-19 illness with ARDS.

On the other hand, higher doses corticosteroid was associated with more serious adverse events, especially concomitant infections.[19] Secondary infection tends to develop in severe COVID-19 patients who require ICU and advanced organ support, and it was associated with higher mortality and longer course of ICU stay.[20] In this study, we found a significantly higher occurrence of secondary infection in patients treated with higher dose methylprednisolone. A wide spectrum of secondary infection was observed and the commonest was pneumonia either ventilator or non-ventilator associated, caused by multi-drug resistant *Acinetobactor baumanni*. Therefore, prompt initiation of appropriate antimicrobials based on local surveillance and antibiogram data for secondary infections is important.[14]

LIMITATIONS

There were a few limitations in this study. First, this study was conducted in a single-centre hospital with a limited sample size. Based on calculation, we need to study 158 patients in

each arm to reject the null hypothesis with a power of 80%, p cut-off value of 5% for statistical significance. However, despite recruiting all eligible patient during the study period, the sample size was still limited. Secondly, this was a retrospective study. With the treatment decisions being at the judgment of the treating physician rather than in randomized cohorts, we were unable to exclude an indication bias completely, wherein more severe patient might receive a higher cumulative dose of methylprednisolone. On the other hand, the younger patients were prioritized for ICU admission due to limited resources in our center. This might lead to an age selection bias. Last but not least, the wide range of doses, as well as differing individual management besides the corticosteroid usage, might contribute to heterogeneity beyond our analysis.

CONCLUSION

The use of higher dose methylprednisolone in COVID-19 with ARDS was not associated with better clinical outcomes. The risks of mortality and secondary infection were higher, with longer durations of ICU stay. A lower dose of methylprednisolone might be adequate and less harmful in patients with severe COVID-19 illness with ARDS. Nevertheless, randomized, double-blind, controlled clinical trials are needed to confirm these findings.

CONFLICT OF INTEREST

There is no conflict of interest associated with the materials presented in this paper.

ETHICS

This study has been registered with the National Medical Research Register (NMRR- ID-21-02254-5QR) and obtained ethical approval from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia.

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