High-dose pulse methylprednisolone vs. dexamethasone standard therapy for severe and critical COVID-19 pneumonia: Efficacy assessment in a retrospective single-centre experience from Malaysia

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ABSTRACT

Introduction: The use of dexamethasone (DXM) has been associated with decreased mortality in the patients with hypoxemia during the coronavirus disease-2019 (COVID-19) pandemic, while the outcomes with methylprednisolone (MTP) have been mixed. This real-life study aimed to evaluate the outcomes of patients with severe respiratory failure due to COVID-19 who were treated with high doses of MTP.

Materials and Methods: This retrospective cohort study enrolled hospitalised patients between May 2021 and August 2021, aged 18 years and above, with severe respiratory failure defined by a ratio of oxygen saturation to fraction of inspired oxygen (SF ratio) of less than 235. The treatment protocol involved administering high-dose MTP for 3 days, followed by DXM, and the outcomes were compared with those of patients who received DXM alone (total treatment duration of 10 days for both groups).

Results: A total of 99 patients were enrolled, with 79 (79.8%) receiving pulse MTP therapy and 20 (20.2%) being treated with DXM only. The SF ratio significantly improved from a mean of 144.49 (±45.16) at baseline to 208 (±85.19) at 72 hours ($p < 0.05$), with a mean difference of 63.51 ($p < 0.001$) in patients who received ≤750 mg of MTP. Additionally, in patients who received >750 mg of MTP, the SF ratio improved from a baseline mean of 130.39 (±34.53) to 208.44 (±86.61) at 72 hours ($p < 0.05$), with a mean difference of 78.05 ($p = 0.001$). In contrast, patients who received DXM only demonstrated an SF ratio of 132.85 (±44.1) at baseline, which changed minimally to 133.35 (±44.4) at 72 hours ($p = 0.33$), with a mean difference of 0.50 ($p = 0.972$). The incidence of nosocomial infection was higher in the MTP group compared with the DXM group (40.5% vs. 35%, $p = 0.653$), with a relative risk of 1.16 (95% CI: 0.60-2.23).

Conclusion: MTP did not demonstrate a significant reduction in intubation or intensive care unit admissions. Although a high dose of MTP improved gas exchange in patients with severe and critical COVID-19, it did not provide an overall mortality benefit compared to standard treatment.

KEYWORDS:
COVID-19; acute respiratory distress syndrome; respiratory failure; pneumonia; corticosteroids

INTRODUCTION

The year 2019 witnessed a significant milestone with the emergence of the novel coronavirus disease 2019 (COVID-19), which rapidly spread worldwide, leading to a global pandemic. COVID-19 patients can range from being asymptomatic to exhibiting varying degrees of symptoms, including mild to severe manifestations. The cytokine release syndrome triggered by COVID-19 results in a robust inflammatory response, potentially leading to severe organ dysfunction.[1] Among the severe cases, respiratory failure and the subsequent need for oxygenation support are common. Acute respiratory distress syndrome (ARDS) represents the most critical form of respiratory failure observed in the clinical spectrum of COVID-19 pneumonia, often necessitating mechanical ventilation and admission to the intensive care unit (ICU).[2]

Dexamethasone (DXM) has emerged as the preferred treatment for hypoxemic COVID-19 patients following the remarkable findings of the RECOVERY trial. This trial demonstrated improved mortality outcomes in mechanically ventilated COVID-19 patients receiving DXM (6 mg once daily for 10 days) compared to standard care.[3] Alongside DXM, the role of other systemic corticosteroids, particularly methylprednisolone (MTP), has been investigated in several small-scale clinical trials.[4-7] While these studies have provided some evidence supporting the use of MTP, the overall benefit of MTP over DXM remains uncertain and controversial. Therefore, this retrospective study aims to evaluate the clinical outcomes of patients with severe respiratory failure due to COVID-19 who received MTP compared to DXM.

MATERIALS AND METHODS

This retrospective cohort study was conducted at the University of Malaya Medical Center in Malaysia from May 2021 to August 2021. The study enrolled hospitalised patients

This article was accepted: 23 December 2023
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Table I: Sociodemographic and clinical characteristics of patients with severe and critical COVID-19 infection

	MTP (n=79)	DXM (n=20)	p value
Age (years)	57.5 (12.2)	62.9 (11.9)	p=0.04
Gender			
Male	47 (59.5)	12 (60.0)	p=0.48
Female	32 (40.5)	8 (40.0)	
Comorbidities			
HPT	55 (69.6)	10 (50.0)	p=0.05
DM	49 (62.0)	8 (40.0)	p=0.03
Stroke	3 (3.8)	1 (5.0)	p=0.40
Heart disease	14 (17.7)	2 (10.0)	p=0.20
Lung disease	3 (3.8)	1 (5.0)	p=0.40
Renal disease	9 (11.4)	1 (5.0)	p=0.20
Malignancy	2 (2.5)	0 (0.0)	p=0.25
COVID Category			
4	58 (73.4)	14 (70.0)	p=0.38
5	21 (26.6)	6 (30.0)	
Day of illness, median (IQR)	4 (2-7)	4 (3-6)	p=0.45
Laboratory results on admission			
Pre-Treatment			
WBC	11.12 (4.9)	9.76 (4.5)	p=0.125
ALC	1.11 (2.1)	1.11 (0.4)	p=0.494
CRP	185.73 (109.9)	108.69 (198.8)	p=0.013
Ferritin	1630.39(1181.1)	1569.24(1409.5)	p=0.431
SF ratio on admission	141 (43.17)	132 (44.17)	p = 0.44
ICU*	50 (63.3)	1 (5.0)	
MV**	18 (22.8)	4 (20.0)	
Cumulative steroid dose, median (IQR)	192 (146-313)	66 (48-81)	p<0.05
Cumulative dose MTP			
≤750mg	61 (77.2)		
>750mg	18 (22.8)		
Other medication			
Faviparavir	23 (29.1)	2 (10.0)	p=0.079
Tocilizumab	28 (35.4)	8 (40.0)	p=0.710
Baricitinib	16 (20.3)	6 (30.0)	p=0.349

Abbreviation: WBC: white blood count, ALC: absolute lymphocytes count, CRP: C-reactive protein, ICU: intensive care unit, MV: mechanical ventilation, IQR = interquartile range.
Data are presented as n (%) or mean ± standard deviation unless otherwise stated.
*Patients admitted to ICU prior treatment , **Patients were on mechanical ventilation prior treatment

aged 18 years and above who were diagnosed with category 4 and 5 COVID-19 infection. The severity of patients was categorised according to local guidelines.[8] Patients requiring oxygenation support were classified as severe (category 4), while critically ill patients were further subcategorised as 5a and 5b. Category 5a patients required non-invasive ventilation or high-flow nasal cannula therapy, while category 5b patients were intubated and received mechanical ventilation support. The severity of respiratory failure was determined by the ratio of oxygen saturation (SpO2) to the fraction of inspired oxygen (FiO2) known as the SF ratio. The correlation of the SF ratio with the partial pressure of oxygen in arterial blood (PaO2)/FiO2 (PF ratio) for assessing gas exchange in ARDS has been previously studied and recognised.[9] In this study, patients with COVID-19 having a SF ratio of <235 (correlating with a PF ratio of <200) were included. Patients with COVID-19 infection below category 4 who were treated with MTP or DXM for reasons other than COVID-19 were excluded from the study. All medical data were obtained from electronic medical records and recorded in a Microsoft Excel spreadsheet.

The patients were divided into two groups based on the treatment received. The first group consisted of patients who received pulse MTP for 3 days followed by DXM, while the second group received DXM alone. The total duration of corticosteroid therapy for both groups was 10 days. The decision regarding the dosage of MTP was based on the managing physician's clinical judgment. Patients in the first group were further categorised into those who received a lower cumulative dose (≤ 750 mg) and those who received a higher cumulative dose (> 750 mg) of MTP. Patient demographics, medical comorbidities, laboratory parameters, treatment response, complications, length of stay and overall mortality rates were analysed. This retrospective review was approved by the Institutional Ethics Board (MREC ID NO: 2021818-10486), and informed consent was waived.

Statistical Analysis

IBM Statistical Package for the Social Sciences for Macintosh (Version 26.0, Armonk, NY: IBM Corp) was used for statistical analysis. Continuous variables with normal distribution were presented with a mean (standard deviation). Non-normally distributed variables were reported as median (interquartile range [IQR]). The results were compared using the student T-test and Wilcoxon signed-rank test. P values were two-sided with a statistical significance value of <0.05. A minimum sample size of 82 is required to achieve a power of 80% using a power calculator with a two-tailed test, α power of 0.05 and p-value of 5% for statistical significance.

Table II: Gas exchange and laboratory results of patients pre and post treatment

	Pre Treatment SF ratio	Post Treatment (72 hours) SF ratio	p value	Mean difference
Gas exchange				
MTP (Dose ≤ 750mg)	144.49 (45.16)	208 (85.19)	p < 0.05	63.51 p<0.001
MTP (Dose > 750mg)	130.39 (34.53)	208.44 (86.61)	p< 0.05	78.05 p=0.001
DXM	132.85 (44.17)	133.35 (44.40)	p=0.33	0.50 p=0.972
Laboratory results				
MTP	WBC : 11.12 (4.9)	WBC : 13.75 (6.1)	0.002	
	ALC : 1.11 (2.1)	ALC : 1.30 (2.1)	0.260	
	CRP : 108.69 (198.8)	CRP : 56.5 (74.1)	0.018	
	Ferritin : 1569.24 (1409.5)	Ferritin : 1443.7 (1440.9)	0.297	
DXM	WBC : 9.76 (4.5)	WBC : 12.83 (5.4)	0.081	
	ALC : 1.11 (0.4)	ALC : 1.25 (0.6)	0.295	
	CRP : 115.73 (109.9)	CRP : 63.94 (62.9)	0.046	
	Ferritin : 1630.39 (1181.1)	Ferritin : 1055.85 (624.3)	0.071	

Abbreviation: MTP: methylprednisolone, DXM: dexamethasone. WBC: white blood count, ALC: absolute lymphocytes count, CRP: C-reactive protein. Data are presented as mean ± standard deviation.

Table III: Outcome of patients

	MTP (n=79)	DXM (n=20)	p value	Mean difference
ICU*	4 (5.1)	1 (5.0)	p = 0.34	
MV**	15 (19.0)	2 (10.0)	p = 0.30	
Patients developed nosocomial infection	32 (40.5)	7 (35.0)	p=0.653	
Overall length of stay	19.35 (± 11.4)	11.95 (±6.0)	p=0.057	-7.40 (p=0.006)
Discharge	42 (53)	10 (50)	p=0.064	
Death	37 (47)	10 (50)		

Abbreviation: ICU: intensive care unit, MV: mechanical ventilation,
Data are presented as n (%) or mean ± standard deviation.
* Patients admitted to ICU after 72 hours , ** Patients intubated after 72 hours

RESULTS

This study enrolled a total of 99 patients with severe and critical COVID-19 infection, with 79 (79.8%) receiving pulse MTP therapy and 20 (20.2%) being treated with DXM alone. Nearly two-thirds of patients in both groups had category 4 severity according to the classification system. The median duration of illness at hospital presentation was 4 days for both groups. The baseline demographics and clinical characteristics of the patients are presented in Table I. Upon admission, 50 (63.3%) patients in the MTP group received treatment in the intensive care unit (ICU), and among these patients, 22.8% required mechanical ventilation. Four (20%) mechanically ventilated patients received DXM only. The mean SF ratio for patients in the MTP group compared to the DXM group was 141 (±43.17) versus 132 (±44.17) (p = 0.44).

A cumulative MTP dose of ≤750 mg was administered to 61 (77.2%) patients, while 18 patients (22.8%) received >750 mg of MTP for a duration of 3 days. The maximum recorded cumulative MTP dose in the >750 mg group was 1500 mg, given to two patients. Significant improvement in the SF ratio was observed 72 hours after treatment in the MTP group. The SF ratio at baseline was 144.49 (±45.16) and increased to 208 (±85.19) at 72 hours (p < 0.05), a mean difference of 63.51 (p < 0.001) (Fig. 1) for patients receiving ≤ 750 mg of MTP, whereas for those receiving >750 mg, the SF ratio at baseline was 130.39 (±34.53) and increased to 208.44 (±86.61) at 72 hours (p < 0.05), with a mean difference of 78.05 (p = 0.001) (Fig. 1). In contrast, patients who received DXM only showed an SF ratio of 132.85 (±44.1) at baseline and 133.35 (±44.4) at 72 hours post-treatment (p = 0.33), with a mean difference of 0.50 (p = 0.972) (Fig. 2). The changes in gas exchange parameters from pre-treatment to 72 hours post-treatment are summarised in Table II. Notably, there was an improvement in C-reactive protein (CRP) levels at 72 hours post-treatment in both treatment groups. A comparison of laboratory parameters between the two groups at baseline and 72 hours post-treatment is provided in Table II.

Following MTP therapy, 15 patients experienced deterioration in their condition, necessitating mechanical ventilation. Additionally, four patients required admission to the intensive care unit (ICU) for close monitoring. In the DXM-only group, two patients (10%) required mechanical ventilation, and one patient was transferred to the ICU for specialised care. The incidence of nosocomial infections was higher but did not achieved statistically significance among patients treated with MTP compared to those receiving DXM alone (40.5% vs. 35%, p = 0.653). The relative risk of developing nosocomial infection from the use of MTP was 1.16 (95% CI: 0.60-2.23). The duration of hospital stay was longer in the MTP group (19.35 [± 11.4] days) compared to the DXM group (11.95 [± 6.0] days), with a p-value of 0.057. While the mortality rate was slightly lower in the MTP-treated

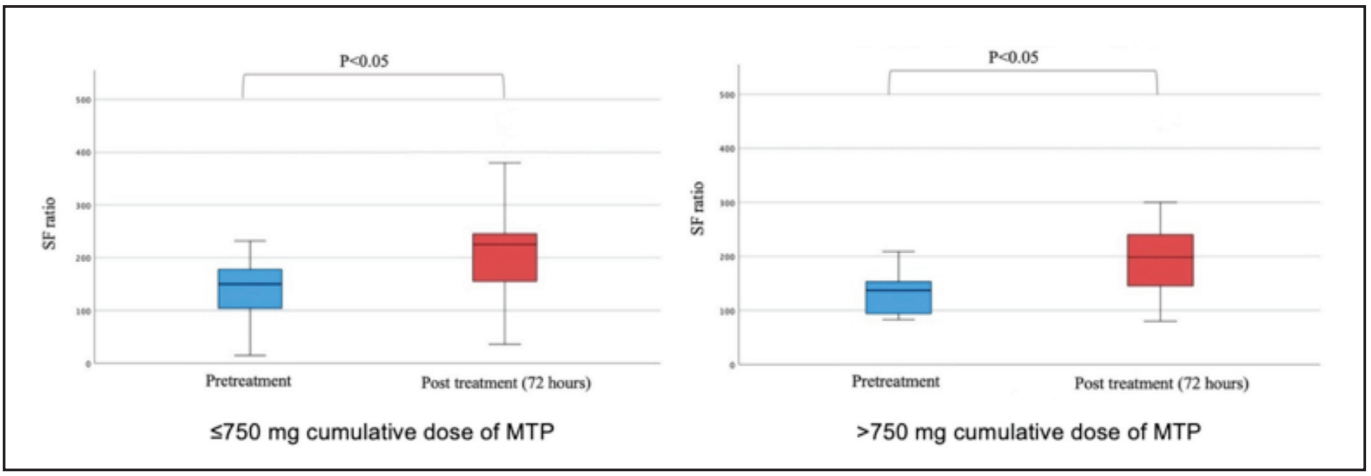

Fig. 1: SF ratio for patients treated with MTP.

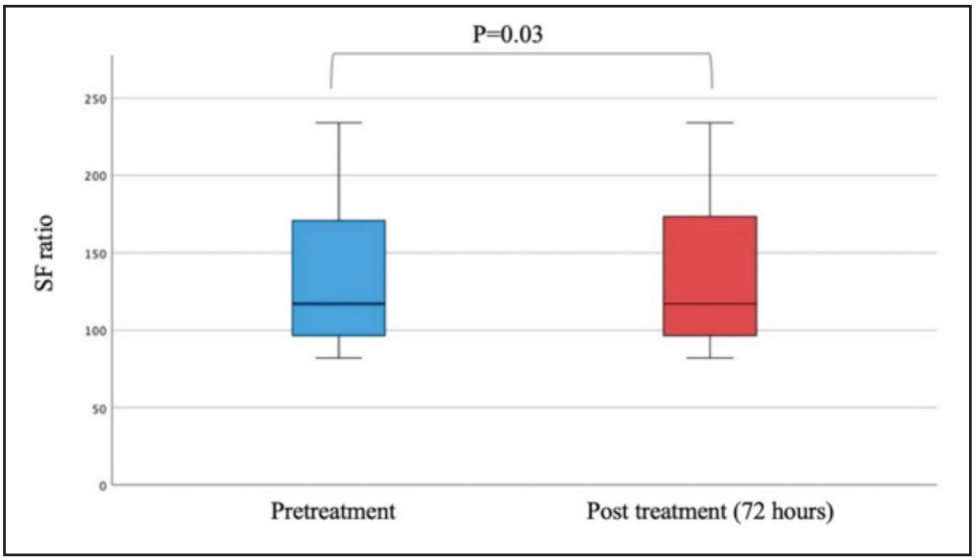

Fig. 2: SF ratio for patients who received only DXM.

group compared to the DXM group (47% vs. 50%), this difference did not reach statistical significance, with a relative risk of 0.94 (95% CI: 0.57-1.54). Detailed information on these outcomes is presented in Table III.

DISCUSSION

The spectrum of COVID-19 infection ranges from mild to severe. Approximately 20% of patients experience a severe illness that necessitates oxygen support, with 5% of these patients classified as being in the critical stage, presenting with respiratory or multi-organ dysfunction.[10] The incidence of severe to critical COVID-19 infection was high prior to widespread vaccination. Multiple treatment options, such as specific antiviral therapy and immunomodulators, have been investigated, however, none have demonstrated effectiveness against severe acute respiratory syndrome coronavirus 2.

The primary challenge posed by severe COVID-19 infection arises when patients develop ARDS and cytokine release syndrome. Numerous cytokines, including tumour necrosis factor-alpha, interleukin (IL)-1B, IL-2 IL-6, IL-8, IL-10 and interferon γ, contribute to profound systemic inflammation, leading to significant morbidity and mortality.[11] The use of glucocorticoids gained momentum due to their potent anti-inflammatory action, targeting a multitude of pro-inflammatory genes implicated in cytokine storms.[12-13] In patients with hypoxemic COVID-19, administration of DXM at a daily dose of 6 mg for up to 10 days resulted in reduced mortality rates within 28 days compared to standard care (rate ratio 0.83; 95% confidence interval [CI]: 0.74–0.92; $p < 0.001$), as demonstrated in the pivotal RECOVERY trial.[3] Furthermore, the recent multicentre randomised placebo-controlled study by Villar et al. provided insights into the long-standing controversy surrounding corticosteroid use in patients with ARDS. The study revealed that patients with moderate to severe ARDS who received DXM had fewer days

of mechanical ventilation and lower overall mortality rates.[14] Glucocorticoids are frequently prescribed for a wide range of medical conditions. However, the selection of the appropriate glucocorticoid is not a one-size-fits-all approach due to their diverse pharmacological properties. MTP, an intermediate-acting glucocorticoid, exhibits superior lung penetration compared to other available options.[15] Consequently, MTP may serve as a more effective anti-inflammatory agent during the pulmonary phase of severe COVID-19 infection, reducing lung injury while minimising undesired side effects associated with prolonged corticosteroid exposure, thanks to its shorter plasma and biological half-life compared to DXM.[16-17]

The prudent use of MTP, a potent glucocorticoid, and higher doses equivalent to DXM is recommended for patients with severe to critical COVID-19 presenting with cytokine storm and ARDS. Achieving therapeutic plasma levels and optimal saturation of glucocorticoid receptors to elicit sufficient anti-inflammatory effects necessitate higher initial loading and subsequent maintenance doses.[18] The efficacy of MTP administration was initially observed in an early retrospective study conducted in Wuhan, China, during the initial phase of the COVID-19 pandemic. Low to medium doses of MTP (25–80 mg/d) were found to prevent disease progression to a severe or critical state in patients aged ≤65 years with COVID-19.[19] Subsequent studies further supported the use of MTP.[5,7] A triple-blinded randomised controlled trial demonstrated that patients treated with MTP exhibited improved clinical status, as measured by the World Health Organization Ordinal Scale for Clinical Improvement (3.909 vs. 4.873, p =0.004), and had a lower requirement for mechanical ventilation (18.2% vs. 38.1%, p=0.040) compared to those treated with DXM.[5] Patients with severe ventilatory failure due to COVID-19 showed more significant improvement in gas exchange when treated with MTP compared to DXM. Similar findings were observed with the administration of MTP at doses of 125–250 mg/d for three consecutive days during the second week of illness in patients with severe disease and elevated inflammatory markers.[6] Both cohorts of patients, particularly those treated with MTP, exhibited improvements in blood inflammatory markers such as CRP and ferritin. Additionally, a cohort study by Pinzón MA et al. reported a significant reduction in CRP, D-dimer, and lactate dehydrogenase values in 216 patients treated with MTP.[7]

The current study demonstrated improvement in gas exchange at 72 hours with the use of MTP. Significant gas exchange improvement was seen even with the smaller cumulative dose of MTP of ≤750 mg. However, despite gas exchange improvement at 72 hours, patients treated with MTP remained in severe respiratory failure with a mean SF ratio of < 235. Hence, we were unable to demonstrate that the use of MTP reduced intubations or ICU admissions in a cohort of severely and critically ill COVID-19 patients with respiratory failure. One of the concern associated with high doses of corticosteroids is the potential risk of secondary infection. The risk of nosocomial infection is undeniably increased with the injudicious use of glucocorticoids although the rate of nosocomial infection for both groups of patients in this study was not statistically different. Similarly, clinicians are reminded that pulse glucocorticoids used in the treatment of many life-threatening autoimmune diseases are associated with an increased risk of infection.[17]

In terms of mortality, the Cruces COVID Study Group reported that MTP at week 2 of disease showed a lower adjusted risk of death and death or intubation.[6] Current study demonstrated no mortality benefit at 28 days with the use of high-dose MTP for severe and critically ill patients. The disparity in results may be explained by patient selection. Patients recruited in this study demonstrated more severe ventilatory failure (overall SF ratio of 141.28 [±43.17]) compared to those reported in the previous study (median SF ratio 380 [160] and overall PF 255 [240–271]).[6-7] Thus, improvement in short-term gas exchange may not translate into overall mortality benefits in patients with severe or critical COVID-19. The findings of our study are in line with those reported by Ngu et al.,[20] although our patient cohort exhibited more severe respiratory failure. This definitive evidence confirms the limited role of high-dose MTP in the management of severe and critically ill patients with COVID-19 pneumonia.

Some limitations identified in the current study include its single-centre and retrospective nature, which can introduce selection bias. The number of patients recruited is limited. The MTP prescription solely based on the physician's clinical judgment might contribute to indication bias. Additionally, heterogeneity in the overall management was anticipated during the height of the pandemic when medical resources were overwhelmed.

CONCLUSION

The use of high-dose methylprednisolone (MTP) in patients with severe or critically ill COVID-19 and severe ventilatory failure may offer short-term improvement in gas exchange but is not associated with improved clinical outcomes. There was no observed mortality benefit compared to standard treatment. However, considering a lower dose of MTP may be a reasonable therapeutic approach for the patients with COVID-19 experiencing mild to moderate ventilatory failure. To validate these findings, larger randomised trials are required.

ACKNOWLEDGMENTS

The authors would like to thank Moli G from Enago for the English language review of this manuscript.

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