Use of Pulse Dose Methylprednisolone in a Cohort of very Severe Covid-19 Patients in a resource-limited setting in Myanmar: a retrospective study

ABSTRACT

Aims: This study aims to explore the role of pulse dose methylprednisolone therapy in very severe COVID-19 patients in preventing the need for ICU care and death.
Study design: Retrospective record review study
Place and Duration of Study: Oak-ta-chat-thal-ta-pwint Covid-19 treatment center in Yangon, Myanmar between September 2021 to December 2021.
Methodology: This study included 13 confirmed Covid-19 patients with severe to critical illness, who were treated with pulse dose methylprednisolone therapy. We reviewed the patients' demographics, comorbidities and disease severity before starting pulse dose methylprednisolone therapy and changes in oxygen requirement, chest x ray scores, inflammatory markers, development of significant clinical events and 28 days mortality after therapy.
Results: Before pulse dose methylprednisolone therapy, all 13 patients had very severe disease (mean SPO2/FiO2 = 173mmHg, mean SPO2 = 88.54%, mean CRP =115mg/L, mean ferritin = 1295.5ng/ml and mean Brixia Score = 6.54). They received 3-7 days (mean = 5.5) of pulse dose methylprednisolone. Ten patients (76%) survived in a setting with limited ICU care. High ferritin was a significant predictor of mortality. Improvement in oxygen requirement was noticeable after 1-11 days (mean =5.6g). Hyperglycemia was common and confirmed bacterial infection was found in 3 patients, but all patients received empirical antibiotics therapy.
Conclusion: Pulse dose methylprednisolone therapy may be an effective salvage therapy in a carefully selected subset of very severe covid-19 patients. It might be a feasible alternative to other more expensive immunomodulating agents and organ support treatments in a resource-limited setting.

Keywords: Covid-19, Pulse dose corticosteroid, methylprednisolone, resource-limited settings

1. INTRODUCTION

Coronavirus disease 2019 (Covid-19) is a pandemic disease caused by a novel corona virus SARS-Cov-2. Recently, the world health organization declared an end to covid-19 as a disease of public health emergency. Yet, many mysteries remain about the disease. Since its emergence in 2019, more than six million lives have been lost to this disease [1]. Hypoxic respiratory failure due to ARDS and multisystem failure due to cytokine release syndromes are significant events in critical cases of covid-19. The immunopathology plays a major role in these critical stages of Covid-19 [2].

The use of low to moderate dose dexamethasone therapy in severe covid 19 has been well accepted [3]. In very severe cases, thrombo-inflammation in the lungs and alveolar damages progress despite low dose dexamethasone and antiviral agents, requiring ventilatory support and advanced ICU care. The prognoses in these patients are very poor despite every effort with the use of advanced ICU supports [4,5]. In a resource-limited setting, the advanced life supports are practically almost unavailable during a pandemic crisis and entering a critical stage in covid-19 is usually a one-way downward spiral to death. The pathogenesis in these later stages of disease is mainly due to aberrant and dysfunctional inflammatory response and suppressing the inflammatory response theoretically might benefit.

Coritcosteroids are potent non-specific immunosuppressive and anti-inflammatory agents [6]. They are also widely available in every setting and their use has been familiar to most clinicians for their historical use in severe autoimmune conditions. Various doses of corticosteroids were reportedly used in severe covid-19 and the role of high dose corticosteroids is still uncertain. The studies on high dose corticosteroids in severe covid-19 were mainly retrospective observational studies and success rate has been varied due to the use of various doses of drug and choice of patients [7–19]. There are also concerns for potential harms like delay viral clearance and superimposed infections. Short term use of supra-physiological dose of corticosteroids is believed to act through nongenomic pathway to downregulate immune cells activation and proinflammatory cytokine production [20]. We hypothesized that the high dose corticosteroid would be beneficial if it is given in a critical time window at the start of severe unchecked inflammation.

This study aimed to explore the role of pulse dose methylprednisolone therapy in very severe COVID-19 patients in preventing the need for ICU care and death. The specific objectives were to describe the characteristics of patients treated with high-dose methylprednisolone therapy, ascertain the timing from disease onset and severity status at the initiation of pulse dose therapy, and describe the outcomes and complications of these patients.

2. METHODOLOGY

This is a retrospective medical record review study on a series of severe Covid-19 cases treated with pulse dose methylprednisolone therapy. The study was done in a temporary covid-19 treatment facility in Yangon, Myanmar. The study was conducted from September to December 2021, when the delta B1.617.2 strain of SARS-Cov2 was actively transmitting in the country, coinciding with the later part of the catastrophic "third wave". All patients admitted to the facility during the study period were reviewed for eligibility. There was no sample size calculation and all patients who received the therapy of interest during the study period were included. All adult patients more then 18 years of age with confirmed Covid-19 disease and who received pulse dose methylprednisolone therapy (defined as MP >=250mg or equivalent for at least 3 consecutive days by clinician discretion) were included in the review. The variables of interest were extracted from inpatient medical records of the electronic medical record systems. Outcomes data were extracted from the routine telephone follow-up record of the treatment facility until 28 days from date of admission. Mortality status (death or survive) was final outcome and receiving pulse dose methylprednisolone therapy (PDMPT) was exposure and changes in SPO2/FiO2 status, Brixia Score before and after PDMPT and biochemical makers (CRP, ferritin and lymphocytes) were predictors; age and gender are potential confounders and days of covid 19 and underlying co-morbidity and use of other immunomodulators were effect modifiers.

The age, sex and underlying comorbid conditions were extracted from the initial clinical assessment record by the admitting medical officer. The dose and total duration of high-dose corticosteroid therapy was taken from the highest dose of corticosteroid which the

patient received during admission and the duration of that dose, irrespective of the tapering doses or if-any previous smaller doses. The timing of therapy initiation was measured by days from onset of symptoms and severity of disease at the initiation was measured by oxygen requirement (SaO2/FiO2 ratio estimated from dose of oxygen and pulse oxymetry measurement), chest Xray scores (Brixia score by Borghesi and Maroldi, 2020 [21]) and biochemical markers of inflammation. Any other treatments received were also recorded and they were grouped into antiviral agents, anti-thrombotic, other immunomodulators and antibiotics.

Any event after initiation of therapy until discharged was analyzed as potential complications of therapy. Infection was defined as any event of culture-confirmed or clinically suspected infection, requiring antibiotics therapy. Hyperglycemia was new onset or worsening hyperglycemia requiring any treatment or diet modifications. Clinical severity of disease was classified as asymptomatic, mild, moderate and severe or critical as defined by the Covid-19 treatment guideline by the National Institute of Health [22].

3. RESULTS AND DISCUSSION

Total of 13 patients received 3-7 days course of IV methylprednisolone therapy. Twelve patients received 1 G of methylprednisolone each day while only 1 patient was given 250mg of methylprednisolone therapy. Majority of them (n=11) were also given per oral baricitinib and 9 patients also received two doses of tocilizumab (according to availability). CRP level was the earliest to fall after high dose steroid therapy and improvement in hypoxia was noticeable only after 1-11 days with mean duration 5.6 days.

Table 1: Description of 13 Covid 19 cases under the study in accordance with their final outcomes

Variables	Outcomes		Total	Significant Test *"P"*	Remark
	Alive n(%)	Death n (%)			
Age Group ≤40 years ≥41-60 years >61 years Minimum age – 27 Maximum age -85 Mean (±SD)- 56.63±14.86	 1(100) 5(71.4) 4 (80)	 0(0) 2(28.6) 1(20)	 1(7.7) 7 (53.8) 5 (38.5)	Fisher Exact Test X^2 = 0.795 *"P"* = 1.00	
Gender Male	 4 (57.1)	 3 (42.9)	 7 (53.8)	Fisher exact X^2 = 5.424	

Female	6(100)	0(0)	6 (46.2)	*"P"* = 0.192	
Comorbidity *				X^2 = 0.231	
Yes	8(80)	2 (20)	10(79.9*)	*"P"* = 1.00	
No	2 (66.7)	1 (33.3)	3(23.1*)*		
*Diabetes,Hypertension, IHD, Obesity,Peripheral Vaculopathy					
Risk for Severe Covid				X^2 = 0.231	
Yes	8 (80)	2 (20)	10(76.9*)	*"P"* = 1.00	
(≥61 years± underlying d/s	2(66.6)	1 (33.3)	3 (23.1*)*		
No					
(≤ 60 without underlying d/s)					
Steroid duration (days)				95% CI of the difference	
Minimum days	3	5		lower (-1.19)	
Maximum days	7	5		upper(2.93)	
Mean±SD	5.5(±1.84)	5(±0.0)			
Days from start of steroid to improve in hypoxia				95% CI of the difference	
Minimum days	1	4		lower (-6.09)	
Maximum days	10	11		upper(4.22)	
Mean±SD	5.4(±3.41)	6.33(±4.0 4)			
Additional immunosuppressive				X^2 = 1.501 *"P"* = 0.27	
Baricitinib	3(100)	0 (0)	3 (23.1)		
Nil	1(100)	0 (0)	1 (7.7)		
Tocilizumab, Baricitinib	6(66.6)	3 (33.4)	9 (69.2)		
Symptoms days before admission				X^2 = 0.258 *"P"* = 1.000	
<7 days	5 (83.3)	1(16.7)	6(46.2)		
≥7 days	5 (71.4)	2(28.6)	7 (53.8)		

Table 2. Comparison of disease severity status before PDMP therapy of 13 Covid-19 cases under study in accordance with final outcomes

Disease severity parameters	Outcomes		Total	Significant Test *"P"*	Remark
	Alive	Death			
SPO2/FiO2 Before Steroid Therapy Minimum Maximum *Mean* (±SE)	96 303 168 (22.2)	100 240 193(±46.67)	96 303 173(±19.46	95% CI of the difference lower (-130.06) upper(79.59) *"P"*= 0.61	
CRP Before Steroid Therapy Minimum Maximum Mean (±SE)	44.3 264.8 117(±24.4)	68.1 151.5 109.9(±46.67)	44.3 264.8 115(±10.16)	95% CI of the difference lower (-96.74) upper(112.13) "P"= 0.87	
Lymphocytes Before Steroid Therapy Minimum Maximum Mean (±SE)	0.37 2.47 0.96(±0.21)	0.63 1.05 0.86(±0.12)	0.37 2.47 0.93(±0.57)	95% CI of the difference lower (-0.76) upper(0.97)	
Ferritin Before Steroid Therapy Minimum Maximum Mean (±SE)	204 1902 944.76(±216.42)	1392 3001 2464.67(±536.3)	204 3001 1295.5 (±268.8)	95% CI of the difference lower (-2854.74)) upper(455.07))	
Lowest SPO2 at Home Minimum days Maximum days Mean±SD	75 93 88.2(±1.718)	88 92 89.67(±1.2)	75 93 88.54(±1.33)	95% CI of the difference lower (-8.7) upper(5.77)	

Table 3. Case Summary of 13 severe Covid-19 patients treated with pulse dose methylprednisolone therapy

Case No	Age	Sex	Comorbidities	SPO2/FiO2	CRP	Lymphocyte	Ferritin	Brixia score	Steroid dose	Steroid duration	Additional immunosuppressives	Events after treatment	Final Outcome
1	60	F	Peripheral vascular disease	95.83	59.86	0.41	326	7	1G	7	tocilizumab, baricitinib	Hypeglycemia	survive
2	43	F	Nil	101.04	73.23	1.01	204	10	1G	7	tocilizumab, baricitinib	Hyperglycemia, Bacterial pneumonia	survive
3	72	F	Hypertension, cardiovascular disease	194.00	264.76	1.09	411.3	2	250 mg	5	tocilizumab, baricitinib	Hyperglycemia, GI bleeding	survive
4	42	M	obesity, hypertension	98.96	108.9	0.37	1621	10	1G	6	tocilizumab, baricitinib	Hyperglycemia, Staphylococus bacteriaemia,	survive

												Fungal infection	
5	55	M	obesity	98.96	75.35	2.47	1902	10	1G	7	tocilizumab, baricitinib	Hyperglycemia, Septicemia	survive
6	61	M	Hypertension, coronary artery disease, obesity	100.00	151.46	0.63	1392	10	1G	5	tocilizumab, baricitinib	GI bleeding, hyperglycemia, Pulmonary oedema	die
7	55	M	hypertension	240.00	110.41	0.9	>3000	8	1G	5	tocilizumab, baricitinib	Hyperglycemia, GI bleeding, CNS thrombosis	die
8	59	M	Nil	240.00	68.1	1.05	>3000	4	1G	5	tocilizumab, baricitinib	Hyperglycemia	die
9	85	M	Hypertension, coronary artery	240.00	99.15	0.43	1539.3	6	1G	7	tocilizumab, baricitinib	Hyperglycemia	survive

			disease										
10	27	F	Nil	194.00	79.07	1.33	1707.7	6	1G	7	baricitinib	Hyperglycemia, GI bleeding	survive
11	65	F	diabetes	165.00	250.43	0.45	885.9	2	1G	3	nil	Hyperglycemia, Septicemic shock	survive
12	46	F	hypertension	303.13	44.3	1.36	253	7	1G	3	baricitinib	Hyperglycemia	survive
13	67	M	Coronary artery disease, benign prostate hypertrophy, renal stones disease	190.00	121.87	0.71	487.4	3	1G	3	baricitinib	Hyperglycemia, shock	survive

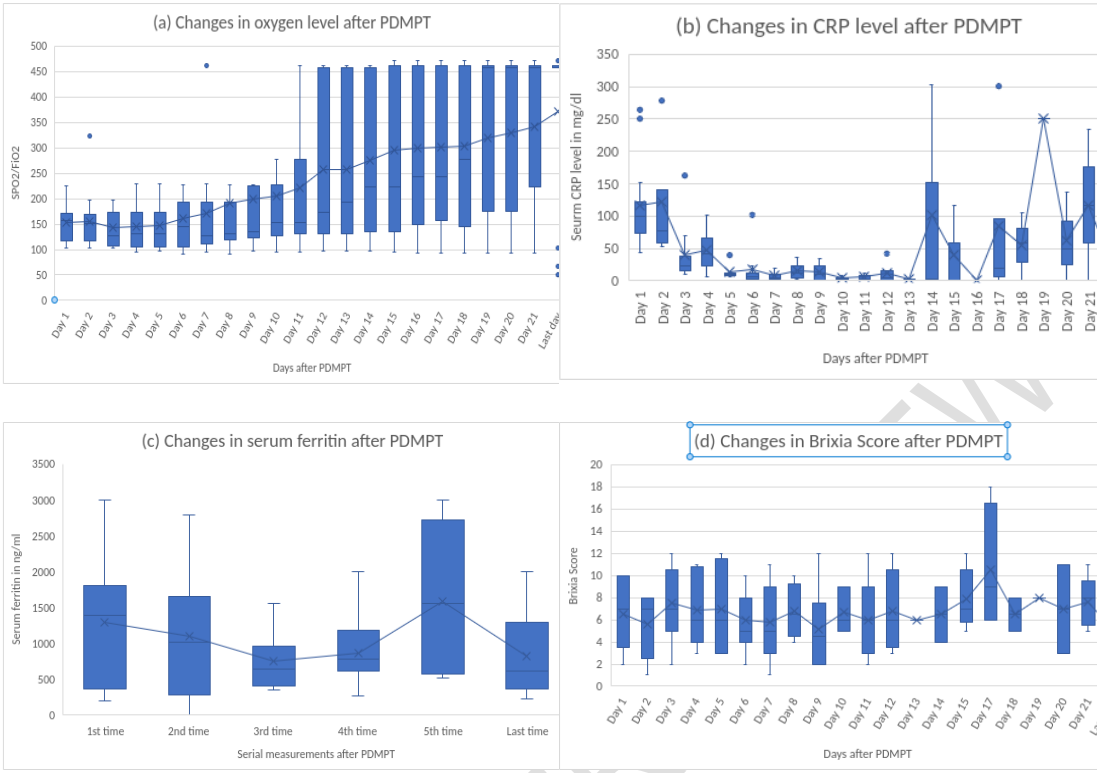

Figure 1. Box plots showing serial changes in disease severity parameters after PDMPT. Day 1 represents the first day of PDMPT. The horizontal line within each box represents the median and the cross represents the mean, the lower and upper border of each box represent the lower and upper quartiles and the T bar represents 1.5 x IQR and the dots are outliers. For measurement of hypoxia, SpO2/FiO2 was used as an estimate of PaO2/FiO2, the value of 200-300 represents mild degree, 100-200 represents moderate degree and <100 represents severe degree of ARDS.

Discussion

In this study, we reported the outcome of 13 very severe covid 19 cases, treated with pulse dose methylprednisolone therapy. These patients were treated in a time of pandemic crisis in a very resource-limited setting where advanced ICU care was practically unavailable. Pule dose methylprednisolone therapy was used as a last resort salvage therapy and we could save 76% of them.

Current treatment guidelines on Covid-19 recommend 6mg of dexamethasone in severe cases requiring oxygen therapy [3]. This recommendation was based on results of clinical trials randomizing all severe patients and lack of statistically significant results in comparison with slightly larger dose of dexamethasone. However, we experienced certain subgroup of patients whose covid-19 related alveolar damage and markers of inflammatory responses were not adequately controlled and who were at imminent risk of progressing into critical stage. In those patients, we tried pulse dose methylprednisolone therapy with the hope that dose-dependent non-specific immunosuppressive and anti-inflammatory effect of corticosteroids might rescue those hopeless patients. There were also reports of successful uses of similarly high doses of corticosteroids. These studies were small retrospective

observational studies. There were also mixed results with different studies using different doses and different criteria for starting high dose corticosteroids.

In those studies, benefits of high dose corticosteroids were seen in terms of mortality [7,13]), oxygen requirement [16], ICU admission [13] and inflammatory markers [17]. These benefits were found especially in age less than 70 years of age (7) and if given not too early or too late [16]. Tromp et al (2021) also reported that high dose corticosteroid therapy with methylprednisolone 1000mg/day for 3 days did not increase viral replication [17]. However, recent systematic review and meta-analysis of 12 studies involving 2759 patients reported that high dose corticosteroid was not better than conventional dose corticosteroid [15]. The trials in this meta-analysis used various doses, duration and regimen of high dose corticosteroid, resulting in high heterogeneity. A retrospective cohort study by Yaqoob et al (2022) also found that pulse dose steroid (MP 1G/day) was not better than conventional dose, with higher rate of acute kidney injury [18]. However, this study was done in patients admitted already to ICU, which is different from our patient population who are mostly inaccessible to ICU care. Another cohort study of 573 patients also reported higher mortality with corticosteroid doses higher than 250mg/day [12]. In this study, remdesivir use was one of exclusion criteria and it may be one reason why more intensive immunosuppression resulted in higher mortality due to unchecked viral replication.

In our cohort of patients, we used higher doses of corticosteroids (1 gram of methylprednisolone for 3 to 7 days) and we started this regime as soon as the standard treatment was not apparently working. The criteria for initiation were high oxygen requirement more than 10 litre/minute, more than 50% of parenchymal involvement in chest x rays, and high inflammatory markers in the absence of confirmed or suspected co-infection. Rapid progression of disease severity in terms of oxygen requirement and serial chest x rays was also an important factor in considering the more aggressive treatment. All of our patients were also treated with intravenous remdesivir for 5 days. Intravenous tocilizumab was also given if the patient afforded the cost of drug. However, this therapy was hard to start immediately since it was not readily available at the time. Nine out of 13 patients received tocilizumab therapy while the other 4 did not. The outcome was not significantly associated with the addition of additional immunomodulator therapy like tocilizumab. All 4 patients who could not afford this therapy survive but some treated with tocilizumab were lost.

After initiation of therapy, CRP levels invariably fall after a day or two, but rise again in the 3rd week in some cases (Figure 1.). Superimposed infection was identified in some of those cases and successfully treated. However, improvement in oxygen level was noticeable only after a week. Ferritin level and Chest x ray scores showed no noticeable changes after PDMPT until 3 weeks of follow-up. This can be explained by the facts that serum ferritin was not frequently measured in our cohorts and follow up period was short to detect the usually slow radiological improvements. In two cases of mortality, there was no improvement in hypoxia, CRP level rise again after initial falling. This indicates that inflammatory response was not adequately controlled or smoldering co-infection might have been missed. These cases had very high ferritin and CRP before starting PDMPT. In the third case of mortality, oxygenation and inflammatory markers improved but patient was lost due to a CNS complication, a thrombotic event or infection, which we could not confirmed. High ferritin was only significantly associated with mortality in our cohort.

Generally, the cases we treated with PDMPT were very severe from the outset and failed to respond to standard treatments. Remdesivir and PDMPT (in combination with tocilizumab in some cases) successfully rescued most of them, even in a setting without advanced ICU care. Hyperglycemia was very common after PDMPT as expected and empirical antibiotics therapies were used in all cases but definitive infective infection was proved only in three cases.

We recommend further randomized controlled trials of pulse dose methylprednisolone therapy in very severe covid-19 patients with high oxygen requirement,

diffuse parenchymal involvement in chest x ray or rapidly changing x rays and high markers of inflammation. Since contextual factors like availability of high ends supportive care are varied in different health care settings, defining health care resources settings in future trials might be useful. We observed several limitations of this study. First, we reported the story of a small number of cases and these cases were not randomly selected, limiting the generalizability of the study results. The cases were followed up for only 28 days and we did not study the long-term complications.

4. CONCLUSION

Intravenous Pulse dose methylprednisolone 1 gram per day for 3 to 7 days might be an effective salvage therapy for very severe covid 19 patients. This is especially hopeful for patients in resource-limited setting. Future studies are warranted in carefully selected population of very severe disease.

CONSENT

Written informed consent was obtained from the patient or the next of kin for publication of this case series. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL

All authors hereby declare that this study was approved by the local ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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DEFINITIONS, ACRONYMS, ABBREVIATIONS

ARDS: acute respiratory distress syndrome
Covid-19: Coronavirus disease 2019
CRP: C-reactive protein level in serum
ICU: intensive care unit
PDMPT: pulse dose methylprednisolone therapy
SPO2: peripheral capillary oxygen saturation
SPO2/FiO2: ratio of peripheral capillary oxygen saturation to inspired fraction of oxygen