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Case Series

Timing methylprednisolone pulse therapy in COVID-19 infection-finding the sweet spot: a case series

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ABSTRACT

Steroid therapy has been proven beneficial in the treatment of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) in various trials all around the world. However, the dosing and timing of this therapy are crucial and still under debate. Studies exist regarding the use of pulse IV therapy of steroids in this illness, but it has still not been widely used and accepted throughout the world. Here we described four cases of SARS-CoV-2 who presented to a tertiary care center in India within the first week of illness, with moderate to severe disease activity. These patients were treated with pulse doses of intravenous methyl prednisolone. All four patients showed positive outcomes in terms of oxygen requirement and early recovery.

Keywords: Corticosteroid, COVID-19, Methyl prednisolone, SARS-CoV-2

INTRODUCTION

SARS-CoV-2 originally isolated in the Wuhan province of China and subsequently became a global pandemic has posed serious therapeutic challenges for physicians all around the world.[1] This pathogen belongs to the family of coronavirus. Beta-coronaviruses are positive-single strand RNA (+ssRNA) viruses that have historically caused outbreaks of the middle eastern respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) over the past two decades.[2,3] This pathogen and its disease have been extensively researched upon since its emergence.[3] Various treatment modalities have been tried and proven ineffective however steroids have been proven beneficial in many clinical trials all over the world.[3,4] The only shortcoming being the dosing and timing of these steroids in the course of this illness.[5]

Anti-viral and monoclonal antibodies to cytokines have been of equivocal benefits or no benefits at all.[6] The anti-inflammatory doses of steroids find a prominent mention among most national guidelines across the world, however, the time to switch over to pulse therapy in case of worsening disease is not clear in any guideline, though small studies, randomized trials and case reports exist in literature. Pulse IV therapy is used in life-threatening inflammatory diseases like pericarditis, pneumonitis, cerebritis, nephritic syndromes, vasculitis or sight-threatening disorders.[7]

Here we describeD four cases of moderate to severe SARS-CoV-2 which were treated with pulse IV methyl prednisolone therapy, at a tertiary care center in South Western India; leading to favorable outcomes in terms of decreasing oxygen requirement and recovery.

CASE SERIES

Demographic and patients characteristics of patients with moderate COVID infection selected for pulse therapy at our center are presented in Table 1. Three male and one female patient, with an age range of 32 to 54 years, were

part of this case series. Patients presented to our center with chief complaints of fever, cough, dyspnea and body ache of 2 to 4 day duration and were found to be COVID-19 RT PCR positive. Cases 2 and 3 were known cases of hypothyroidism and diabetes, respectively.

Case 1

The patient presented on day three, post symptom onset. Over the next two days, he developed breathing difficulty and was started on supplemental oxygen. The oxygen requirement increased sequentially and was put on non-invasive ventilation support (NIV). His computed tomography (CT) severity score was 19/25, CRP was positive and normal D-dimer levels. The patient was started on pulse IV methyl prednisolone 1 gm intravenous (IV) OD for five days, on day six of admission. His oxygen requirement decreased in the subsequent days and he was discharged on day 22 of admission (Figure 1A).

Table 1: Patient characteristics.

Characteristics	Case 1	Case 2	Case 3	Case 4
Age (in years)	32	41	54	34
Sex	Male	Female	Male	Male
Co-morbidities	None	Hypothyroidism	Diabetes	None
Symptoms at presentation	Anosmia, body ache, weakness	Body ache, cough, fever	Dyspnea, fever, body ache	Cough, dyspnea
Days from the onset of illness to hospitalization	3	3	4	2
Type of oxygen therapy	NIV	NRBM	NIV	NRBM
Dose of methyl prednisolone pulse (in gm IV OD)	1	1	0.5	0.5
Duration of therapy (in days)	5	5	5	5
Timing of pulse (day of illness)	9	7	14	9
Time to event (discharge)	22	31	32	34

IV=intravenous; NIV=non-invasive ventilation support; NRBM=non-rebreather mask.

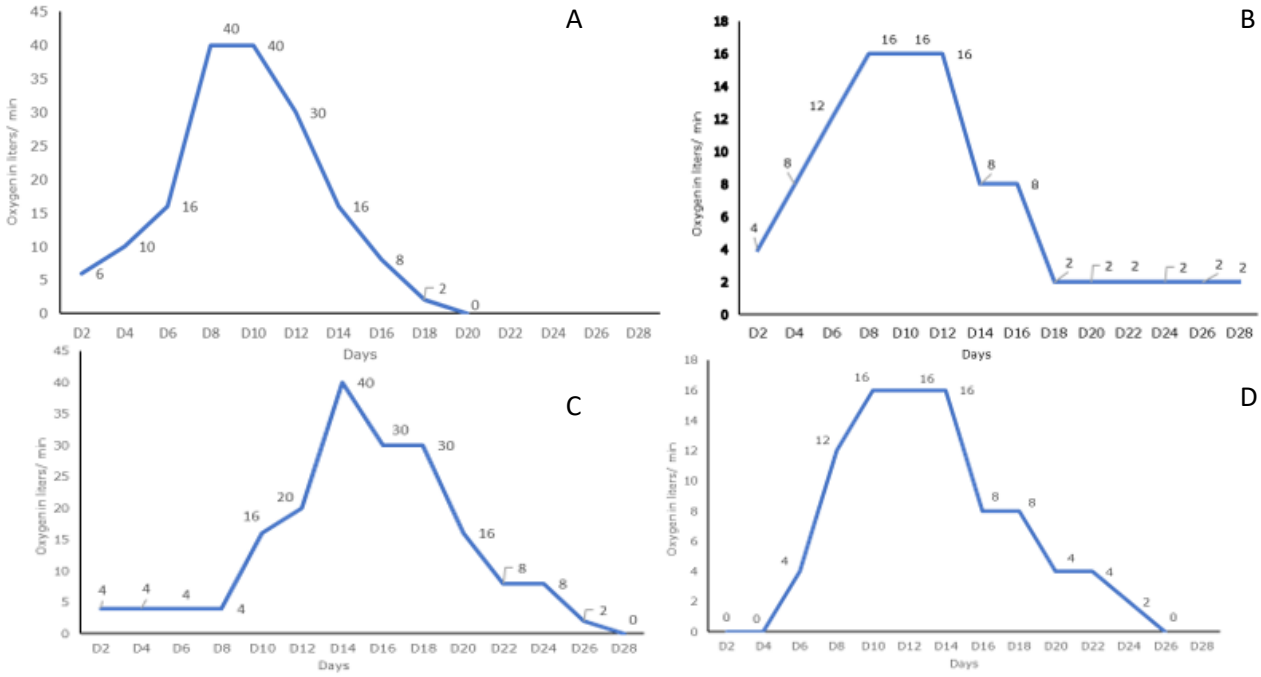

Figure 1: Oxygen requirement; (A) Case 1; (B) Case 2; (C) Case 3; (D) Case 4.

Case 2

The patient was admitted three days after symptom onset and over the next four days went on to have increasing oxygen requirement with raised inflammatory markers. She was administered pulse IV methyl prednisolone 1 gm IV OD for five days, on day four of admission. Over the next eight days, her oxygen requirement decreased and she maintained a saturation level of 2 l/min by nasal prongs (Figure 1B). Due to prolonged oxygen requirement along with tachycardia and dyspnea CT pulmonary angiogram was done which showed a CT severity score of 25/25 and a right posterior basal segment plus sub-segmental arterial pulmonary thromboembolism. She was managed with non-vitamin K oral anticoagulants (NOACs) and discharged on day 28 of admission.

Case 3

The patient presented on day four, post symptom onset, with oxygen saturation of 88% on room air at admission. The patient was on 4 l/min supplemental oxygen support for eight days. However, during the next two days, his oxygen requirement increased and he required non-rebreather mask (NRBM) support with 16 l/min oxygen. He was started on pulse IV methyl prednisolone therapy 500 mg IV OD for 5 days on day 10 of admission. His CT severity score was 21/25 with bilateral extensive ground-glass opacities. He had a prolonged hospital stay complicated by acute kidney injury along with metabolic acidosis for which he was managed conservatively. However, he had a serial decline in his oxygen requirement and was off oxygen support on day 28 of admission (Figure 1C). He was discharged three days later.

Case 4

The patient presented on day two, post-onset of symptom and was admitted on the same day. After four days he started having increasing oxygen requirement progressing to 16 l/min by NRBM. He was started on pulse IV methyl prednisolone therapy 500 mg IV OD for five days, on day seven of admission. Following which there was a reduction in his oxygen requirement. He had a CT severity score of 18/25 and had elevated inflammatory markers on admission. On day 32 of admission, he was discharged with no requirement of supplemental oxygen (Figure 1D).

DISCUSSION

Steroids have been proven to have mortality benefits and reduce hospitalization in patients with moderate to severe COVID-19 pneumonia.[8] Their use has been indicated in the national guidelines as a dose of methyl prednisolone 0.5-1 mg/kg in moderate cases and 1-2 mg/kg in severe cases divided into two equivalent doses of their equivalent dose of dexamethasone.[9] Despite various studies all over the world indicating the benefits of pulse therapy as compared to conventional anti-inflammatory doses of steroids, this has not been included in our national guidelines for treatment as of this day. The apoptotic doses of pulse therapy though beneficial in various clinical conditions also conferred significant risk in terms of acute liver failure, cerebrovascular or cardiovascular effects.[10] It was therefore extremely important that patient selection should be such that it took into account this risk-benefit ratio. In our case series patients that were given pulse IV methyl prednisolone doses were all relatively young with a mean age of 40 years. The timing of initiating the therapy was on an average nine days from the onset of symptoms.

Methyl prednisolone pulse has been previously used in MERS and SARS patients and has not shown benefit.[11] However, its use in COVID-19 has led to positive results in terms of hospitalization time and mortality, due to its effect on the hyperinflammatory phase of the disease.[11] COVID-19 disease has 3 phases namely the infectious phase, pulmonary phase and hyperinflammatory phase.[12] The hyperinflammatory phase or the cytokine storm phase caused the organ dysfunction and extrapulmonary feature of this disease.[12] Normally in early disease effective immune response successfully eliminated the virus and halted the progression to the subsequent phases.[13] This led to mild and symptomatic forms of infection.[13] On the other hand, the inability of the immune system to clear the infection led to a severe inflammatory response phase characterized by cytokine storm and elevated inflammatory markers. This led to extensive lung injury-causing ARDS and worsening clinical picture in terms of increasing oxygen requirement.[13] Inflammatory markers like CRP, ferritin, IL-1 and IL-6 helped the clinicians to know about the progression of the disease to the dreaded hyperinflammatory stage.[14] Steroids with both genomic and non-genomic actions helped to control and tide over this hyperinflammatory stage of the disease.[15] It was therefore extremely important to introduce pulse therapy at the right time. In our group of patients, the steroid therapy was started as soon as the patient started having increasing oxygen requirement with a high chance of worsening in subsequent days; along with increasing inflammatory markers suggesting severity of disease, they were subjected to pulse doses of methylprednisolone. This led to positive outcomes in all four patients. All patients received standard treatment protocols for COVID-19 including enoxaparin 1-2 U/kg in divided doses, empirical/culture sensitive antibiotics and other supportive treatment, in addition to steroids. All patients have given signed and written consent for treatment and publication of the results.

CONCLUSION

Pulse steroid therapy through its non-genomic effects is beneficial in terms of reducing oxygen requirement and clinical recovery in these patients. The sweet spot for the timing of this therapy as observed in our patients was the clinical worsening during admission. More exhaustive studies need to be undertaken to confirm the aforementioned findings.

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