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Original Article

Anaesthesia Section

A Retrospective Evaluation of Combination Therapy of Methylprednisolone and Remdesivir for Severe COVID-19 Patients

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ABSTRACT

Introduction: Severe and threatening complications of Corona Virus Disease-2019 (COVID-19) are caused by direct viral injury as well as excessive and aberrant host immune response induced by the virus. In this context, use of Methylprednisolone (MP) to prevent cytokine storm and Remdesivir to prevent viral replication seems prudent.

Aim: To assess the clinical outcome of combination therapy of Remdesivir and MP pulse therapy in patients with severe COVID-19 in Intensive Care Unit (ICU).

Materials and Methods: The retrospective study was conducted in the COVID-19 ICU, dealing exclusively with 21 severe illness severe illness cases at Safdurjung Hospital, New Delhi, India from June to July 2020. They were given MP pulse therapy (500 mg/day for three days, followed by 1 mg/kg orally once daily, tapered by 10 or 20 mg/day and finishing with 10 mg) along with intravenous Remdesivir. Pre and post-therapy examination of the patients included clinical features, inflammatory markers (Interleukin-6, ferritin and D-dimer), gas parameters like ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) and changes in chest radiograph. Values of PaO_2/FiO_2, inflammatory markers on day 1 and day 3 were expressed as mean±SD and their difference compared using student t-test. Statistical significance was defined as $p<0.05$.

Results: This treatment regimen was associated with significant improvement in PaO_2/FiO_2 ($p<0.001$), significant decrease in inflammatory markers ($p<0.001$) and reversal of radiological changes. Ten patients were discharged within two weeks of treatment while six patients were shifted to high dependency unit for further oxygen requirement. They were all successfully discharged from hospital without oxygen requirement within next two weeks. Five patients developed opportunistic infections and succumbed to death. Side-effects of therapy included hyperglycaemia in nine patients, which was managed by insulin infusion.

Conclusion: Combination therapy of MP pulse and Remdesivir in patients with severe COVID-19 resulted in significant clinical improvement. Given the high efficacy, it could be one of the promising approaches to the management of patients with severe COVID-19.

Keywords: Coronavirus disease-2019, Cytokine storm, Inflammatory markers

INTRODUCTION

The world is in grip of COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The immune response induced by SARS-CoV-2 infection is two phased. During the incubation and early symptomatic stages, viral replication occurs and adaptive immune response is generated that tries to eliminate the virus and prevents disease progression to pulmonary stages. The pulmonary phase is characterised by the development of an organising pneumonia, severe pro-inflammatory state and activation of clotting with macro and microvascular thrombosis and hypoxemia [1]. It has been shown that the severe and threatening complications of COVID-19 are caused by excessive and aberrant host immune response induced by the virus [2-4]. Studies have shown that any intervention which can prevent this catastrophe can also prevent the lung damage and pulmonary thromboembolism [1,5].

In this context, use of immunosuppressive drugs like glucocorticoids, intravenous(iv) immunoglobulin and anticytokine agents (anakinra, tocilizumab) seems prudent for patients with severe COVID-19 to prevent the induction of Cytokine Release Syndrome (CRS) in COVID-19 patients [6-8]. Drugs like tocilizumab and immunoglobulin are expensive and their use in wide-scale epidemics or in less prosperous healthcare systems is not possible. World Health Organisation has recommended systemic corticosteroids for the treatment of patients with severe and critical COVID-19 to dampen the cytokine storm and associated tissue injury [9]. MP is the preferred corticosteroid, in the treatment of COVID-19 as it is a better immunosuppressive agent and helps in improvement of respiratory complications [10]. But, systemic use of corticosteroids has been associated with delayed viral clearance [11]. Therefore, MP should be supplemented with antiviral agent.

Remdesivir inhibits the viral Ribonucleic Acid (RNA) synthesis and has been associated with lesser oxygen requirement and respiratory infection in adults who were hospitalised with COVID-19 infection [12]. Infectious Diseases Society of America (IDSA) has recommended remdesivir in hospitalised COVID-19 patients who require supplemental oxygen. It reduces clinical signs within 12 hours post inoculation, reduces viral replication and severity of lung lesions [13].

There are paucities of studies on safety and efficacy of combination therapy of corticosteroids and remdesivir for the treatment of severe COVID-19 illness. Hence, the study was conducted to analyse the clinical outcome of severe COVID-19 patients admitted in ICU of a tertiary care hospital, who were treated using combination of MP pulse therapy and remdesivir.

MATERIALS AND METHODS

The retrospective study was conducted in the COVID-19 ICU, dealing exclusively with severe illness cases, of Safdarjung Hospital, New Delhi from June to July, 2020. Permission for same was taken from ICU incharge and Head of Department of Anaesthesia and Critical care.

Inclusion criteria: Patients ≥18 years of age, with severe COVID-19 illness admitted in ICU were included in the study. Patients were considered to have severe illness if they had respiratory rate of ≥30/min, blood oxygen saturation of ≤93%, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2) of less than 300 mm Hg and/or infiltrates in more than 50% of the lung field [14].

Exclusion criteria: Patients who were allergic to any therapeutic agents, pregnant or lactating females, prior uncontrolled Hypertension (HTN), uncontrolled Diabetes Mellitus (DM), history of gastrointestinal bleeding, heart failure and active malignancies were excluded from the study.

Study Procedure

Twenty-two patients with severe COVID-19 illness were admitted in the ICU during the study period. One patient was excluded as she was 28 weeks pregnant.

All patients were started on i.v MP pulse 500 mg/day for three days, followed by 1 mg/kg orally once daily, tapered by 10 or 20 mg/day and finishing with 10 mg [15]. MP was administered as single dosage in morning. 200 mg of injection remdesivir was given iv on first day followed by 100 mg for next 4 days. Patients were also given unfractionated heparin, iv piperacillin/tazobactam along with azithromycin for seven days, vitamin C, B complex and zinc.

Demographical details {age, sex and Body Mass Index (BMI)}, co-morbidities, respiratory variables, X-ray changes, inflammatory markers, mode of ventilation, details of treatment and clinical outcome were recorded.

STATISTICAL ANALYSIS

The data was entered in MS Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 23.0. Age, BMI, number of days from onset of symptoms to ICU, duration of Non invasive Ventilation (NIV), MP intake and total ICU stay was presented as mean±SD. Values of PaO_2:FiO_2, inflammatory markers on day 1 and day 3 were expressed as mean±SD and their difference compared using student t-test. Statistical significance was defined as $p<0.05$.

RESULTS

In the study group, there were 21 patients with 14 males and seven females. Mean age was 58±8.5 years with mean BMI of 26.85±2.3. All patients presented with fever, cough, sore throat and breathlessness, with respiratory rate of 30-32 per minute. Mean time between onset of symptoms and admission in ICU was 7.85±1.45 days. Five patients had Diabetes Mellitus (DM), four had Hypertension (HTN), five patients had both the co-morbidites and two had asthma [Table/Fig-1].

Lung infiltrates occupied more than 50% of lung field on chest radiograph [Table/Fig-2a,3a]. Mean PaO_2/FiO_2 ratio at time of ICU admission was 128.15±10.77. Mean values of inflammatory markers i.e., Interleukin-6 (IL-6), serum ferritin, D-Dimer were 290.2±150.82, 627.4±488.43, 892.83±146.3, respectively [Table/Fig-1]. Patients were ventilated with NIV/High Flow Nasal Canula (HFNC) to maintain saturation ≥92%. Patients were intubated if NIV/HFNC failed to maintain saturation.

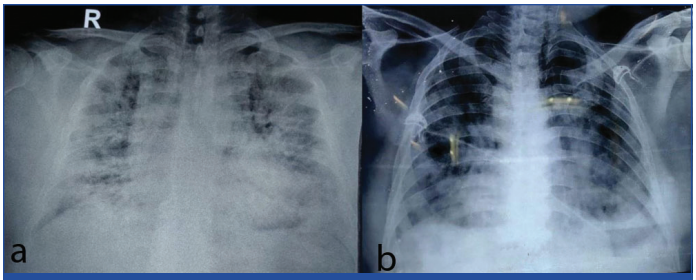
After three days of treatment, mean PaO_2/FiO_2 significantly improved to 214.17±21.86 ($p<0.001$). Mean values of IL-6, ferritin and D-dimer improved significantly to 171.21±118.9, 363.83±350.94 and 461.57±63.42 respectively ($p<0.001$). Infiltrates on chest radiograph were significantly reduced [Table/Fig-2b,3b].

Fourteen patients required NIV and seven were ventilated with HFNC. Later, five patients developed opportunistic infections (two had pseudomonas, one had acinetobacter and two had fungal infections), were started on appropriate treatment and subsequently required intubation but finally succumbed to death. Side-effects included hyperglycaemia, ranging from 200-450 mg/dL, in nine patients which was managed by insulin infusion.

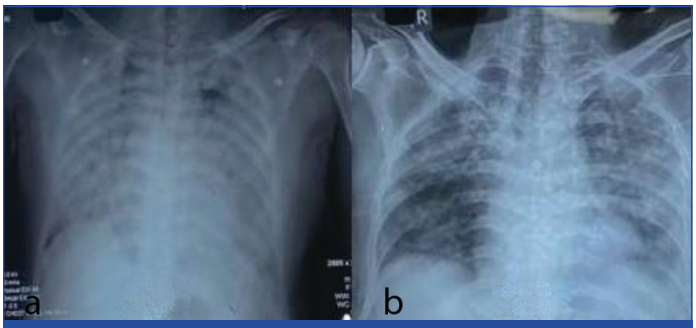
Mean duration of NIV was 5.57±3.59 days. Thereafter, they were shifted on non rebreathing mask, venturi face mask, nasal prongs and then on room air. The mean steroid intake and ICU stay was 11.4±2.44 days and 13.2±2.61 days, respectively. Ten patients were discharged and six patients were shifted to high dependency unit for further oxygen requirement. They were all finally discharged from hospital without oxygen requirement within two-week [Table/Fig-3].

Cases	Age	Sex	BMI	Onset to ICU (days)	Co-morbidities	PaO_2/FiO_2 (Day 1/3)	Inflammatory markers (Day 1/3)			Duration of NIV/HFNC (days)	Total steroid days	Total days in ICU	Outcome
							IL6 (pg/mL)	Ferritin (ng/mL)	D-dimer (ng/mL)				
Case 1	57	F	22.6	9	DM	102.5/194.3	364.4/176.3	888.7/360	1942/508	10	14	15	HDU
Case 2	60	M	30.8	8	HTN	108.75/210	256.2/87.3	742/531.9	1897/1108	10	12	13	HDU
Case 3	44	F	29.3	5	DM, HTN	115/217.2	347.9/202.4	522/435	2693/1078	0	13	13	Died
Case 4	72	M	28	10	DM	137.5/208.6	678.3/560.3	285.5/156.3	1874/524	10	12	13	HDU
Case 5	56	M	26.3	7	DM, HTN	128.75/250	248.5/208	349/120	659/173	0	8	8	Died
Case 6	63	M	30.4	8	HTN	140/236	205.4/151.2	456/159	1435/823	6	14	14	HDU
Case 7	60	F	26.3	7	Asthma	134.6/195.1	95/28	783.3/503.3	734/532	7	12	16	Discharged
Case 8	66	M	26.4	7	Nil	125.5/ 210.6	112/84	563.8/386.3	456/284	6	10	17	Discharged
Case 9	67	M	28.3	8	HTN	127.7/196	243/115	465/207.3	594/456	5	10	16	Discharged
Case 10	54	F	25.4	8	DM, HTN	115.5/250	476.3/306	2587/1744	845/645	0	13	13	Died
Case 11	48	M	26.2	5	Nil	127.9/188	118/94.4	826/524	345/202	5	8	10	Discharged
Case 12	72	M	24	10	DM	134.5/256.2	298.4/108	297.3/173.3	456/268	7	8	12	Discharged
Case 13	54	F	30.7	7	Nil	126.5/190.4	367.4/118.9	643.9/376.2	356/202	10	13	13	HDU
Case 14	47	M	30.3	6	DM, HTN	136/203.4	254.4/165.3	308.3/104.4	934/673	0	8	8	Died
Case 15	66	M	25.3	8	DM	133.8/212.4	135/76.3	573.3/356	456/206	7	7	11	Discharged
Case 16	61	M	24.8	9	DM	112.7/180.6	387.9/189.4	524.3/255.3	345/212	6	12	16	Discharged
Case 17	62	F	25.8	7	Asthma	134.3/206.6	267.7/114.5	298.2/106.3	476/307	9	12	14	HDU
Case 18	58	F	25.5	10	Nil	133/220.4	176.7/38.4	394.7/202.8	398/227	8	15	17	Discharged
Case 19	66	M	25	8	DM, HTN	138.3/202.2	503.5/450.3	823.3/563.4	845/756	0	14	14	Died
Case 20	42	M	26.1	9	HTN	141.3/250.3	435.6/265.3	348.4/167.3	593/307	6	14	15	Discharged
Case 21	53	M	26.5	9	Nil	137.2/219.3	122.7/ 56.3	495.4/208.5	404/202	5	11	11	Discharged

[Table/Fig-1]: Clinical features of patients and their progress.
PaO_2/FiO_2 ratio: a ratio of arterial oxygen partial pressure to fractional inspired oxygen, Normal values of IL-6=0-9.5 pg/mL, Ferritin=0-270 ng/mL (M)/0-160 ng/mL (F), D-dimer=135-250 ng/mL, DM: Diabetes mellitus; HTN: Hypertension; NIV: Non invasive ventilation; HFNC: High flow nasal canula; HDU: High dependency unit; ICU: Intensive care unit



[Table/Fig-2]: a) Lung infiltrates on day 1; b) significant reduction of lung infiltrates on day 3 in chest radiograph.



[Table/Fig-3]: a) Lung infiltrates on day 1; b) significant reduction of lung infiltrates on day 3 in chest radiograph.

DISCUSSION

This study retrospectively analysed 21 patients with severe COVID-19 illness, who were administered MP pulse therapy along with remdesivir, and found the combination resulted in significant clinical improvement. Lung injury in COVID-19 is associated with direct viral injury as well as CRS [1]. MP, a synthetic glucocorticoid is the best choice for the pulmonary phase of COVID-19 because it has better lung penetration [16] and genomic data specific for SARS-CoV-2 [17]. Administration of MP in pulses (500-1000 mg/day), induces apoptotic effects, gives very rapid immunosuppressive and anti-inflammatory effects and completely reverses the cytokine storm [18-21]. Studies have shown that pulse therapy of MP is associated with successful outcomes and decreased risk of death [6,15,21,22].

Sheianov MV et al., had described three cases of severe COVID-19 successfully treated with a combination of MP pulse therapy (1,000 mg/day iv for three consecutive days) and iv immunoglobulin (20 g/day) [6], So C et al., reported a case series of seven mechanically ventilated patients with acute respiratory distress syndrome caused by COVID-19 who received early treatment 1000 or 500 mg/day for three days of MP followed by 1 mg/kg and tapered off. All the patients were extubated within seven days [15]. Saune PM et al., described two cases of severe COVID-19 that were successfully managed with MP pulse therapy (500 mg/day) for three days [21]. Edalatifard M et al., conducted a single-blind, randomised controlled clinical trial involving hospitalised patients with severe COVID-19 at the early pulmonary phase of the illness in Iran. Thirty-four patients received MP pulse therapy (250 mg/day) for three days. The percentage of improved patients was higher and the mortality rate was significantly lower in the MP group ($p<0.001$) [22].

But use of corticosteroids has also been associated with delayed viral clearance, higher mortality rate, longer length of stay, higher rate of bacterial infection and hypokalemia [23]. Therefore, MP pulse should be reserved for patients with severe COVID-19 illness with high inflammatory markers and should be supplemented with antiviral agent to reduce viral replication.

Remdesivir, is a nucleotide analogue and has been reported to inhibit the viral RNA synthesis by a specific mechanism of delayed chain termination for all three coronaviruses (MERS-CoV, SARS-CoV and SARS-CoV-2) and shows promising results [24]. Treatment with remdesivir in COVID-19 is associated with clinical improvement, length of stay, and reduction in serious adverse events. IDSA as well as National Institutes of Health (NIH) guidelines recommend use of remdesivir in hospitalised COVID-19 patients requiring supplemental oxygen. NIH also recommends use of corticosteroid along with Remdesivir for patients who require oxygen through a high flow device or NIV [25].

There is a case report where successful treatment of severe COVID-19 pneumonia patient was done by combination therapy of MP in dose of 1 mg/kg and remdesivir [26]. In the index study, initiation of MP pulse and remdesivir resulted in significant clinical improvement, reduced levels of inflammatory markers, improvement in PaO_2/FiO_2, reversal of radiological changes and led to early weaning of patients. These findings were similar to those reported by other studies [6,15,21,22].

The treatment was found to be generally safe, well tolerated and without any serious side-effects. There was fluctuation of blood sugar levels, which was effectively managed in ICU setting. Other studies also reported changes in blood sugar levels which were managed successfully [6,15,22]. There was no episode of heart rhythm disturbances, uncontrolled HTN and gastrointestinal bleeding. So C et al., reported two cases of delirium while Edalatifard M et al., reported one adverse event [15,22].

In this study, five patients developed opportunistic infections. They failed to maintain oxygen saturation, were intubated and finally succumbed to death. Edalatifard M et al., reported one case of oppurtunistic infection [22]. Stuck et al have shown that higher doses of corticosteroid could probably be associated with concomitant infections [27]. While few previous case reports who have used MP with other drugs have reported zero mortality, study by Edalatifard M et al., reported mortality in two out of 34 patients [6,15,21,22].

Limitation(s)

The limitation of the study is absence of comparative group for this protocol. The study group was not homogenous in terms of age, sex and related co-morbidities. There was no long-term follow-up for the side-effects of corticosteroids. The effectiveness and safety of these components, either separately or in combination, require further evaluation.

CONCLUSION(S)

Methylprednisolone pulse therapy, along with remdesivir resulted in significant clinical improvement with good outcome in patients with severe COVID-19 illness. This line of therapy could be one of the promising approaches to the management of patients with severe COVID-19 illness.

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