

Original Article

Methylprednisolone Pulse Therapy in Severe Covid-19 Pneumonia reduces mortality significantly.

Dr Waseem ud din^{1*}, Dr Sehar Tariq², Dr Zaid Khan³, Dr Shahid Hamid⁴,
Dr Mehwish Mushtaq⁵, Dr. Naveed Nazir Shah⁶

^{1*}Postgraduate Scholar Department of Pulmonary Medicine, Government Medical College Srinagar, India.

²Postgraduate Scholar, SKIMS SOURA, Srinagar, India.

³Postgraduate Scholar Department of Pulmonary Medicine, Government Medical College Srinagar, India.

⁴Postgraduate Scholar Department of Pulmonary Medicine, Government Medical College Srinagar, India.

⁵Postgraduate Scholar Department of Pulmonary Medicine, Government Medical College Srinagar, India.

⁶ Professor, HOD, Department of Pulmonary Medicine, Government Medical College Srinagar, India.

***Corresponding Author:** Dr Waseem ud din

*Postgraduate Scholar Department of Pulmonary Medicine, Government Medical College Srinagar, India. Mail id: drwasemudin@gmail.com

Abstract

Background: COVID-19 disease can manifest as a wide spectrum ranging from asymptomatic patients to severe COVID pneumonia with the latter leading to morbidity and even death. The human physiological response to COVID infection mainly presents as a hyperacute inflammatory reaction which leads to multi organ damage especially of the lungs. Corticosteroids reduce morbidity and mortality in COVID pneumonia by suppressing the inflammatory reaction and minimizing organ damage. High dose corticosteroids delivered early in the form of pulse therapy have shown an enhanced benefit over routine therapeutic doses.

Aim: This study aimed to compare the clinical outcomes in patients with COVID-19 pneumonia with standard therapeutic doses of methylprednisolone (MPPT 1000 mg/day for three days) admitted to an intensive care unit(ICU).

Methods: A profile 318 patients were selected retrospectively for standard corticosteroid dose regimen on the basis of severity of the disease and lab parameters. The patients were divided into two cohorts with one receiving MPPT, Group A (N=192) and the other standard corticosteroid dose Group B (N=126). Data was compiled from the hospital records and compiled in Excel. MPPT was given as 1000mg of the drug daily intravenously for 3 days. In almost all these patients, the drug was given early in the morning in the form of an infusion of 250 ml of Normal Saline over a period of 2 hours. Patient records and electronic data were assessed in the hospital and values related to clinical outcome was compiled.

Results: It was found that there was a significant reduction in mortality as compared to the other group $p < 0.01$. Patients receiving pulse therapy of steroids had markedly higher improvement in clinical parameters as well as a quicker reduction in levels of inflammatory cytokines which translated into much lesser morbidity later on with significant differences among the study groups $p < 0.01$.

Conclusion: Hence this study reaffirms the notion of high dose pulse therapy being beneficial in Severe Covid-19 disease.

Keywords: Covid-19, Pneumoniae, Steroid Pulse Therapy, Methylprednisolone, Intensive Care Unit.

INTRODUCTION:

Covid-19 disease is a systemic illness caused by 2019-nCoV/SARS-CoV-2, a novel β coronavirus of group 2B.¹ The virus was originally described in Wuhan, China in December 2019.² With the passage of time, the virus spread globally to assume pandemic proportions leading to morbidity and mortality in millions.

The virus gains entry into the human body mainly through respiratory passages till it enters the systemic circulation and enters into various cells.³ The virus has direct cytopathic effect, although greater damage is done by the body's hyperacute systemic inflammatory and cytokine response.⁴ This manifests as pneumonia and ARDS in the lungs as well as other morbid conditions including renal function compromise, coagulopathy, superadded infections and sepsis.⁵ The disease typically has three phases in its course including an initial phase of respiratory symptoms followed by lung involvement leading to hypoxemia and finally a state of systemic inflammatory reaction.⁶ The hyper inflammatory state is characterized by high levels of pro inflammatory mediators and cytokines which is responsible for wide spread tissue damage leading to multi organ failure, ARDS and death in a sub-set of patients.⁷

Corticosteroids suppress the production of harmful pro-inflammatory mediators and the cytokine storm.⁸ These drugs inhibit leucocyte migration to tissues, modify Natural Killer cell activity and limit monocyte activation.⁹ There is an overall down regulating effect on Interleukins, Interferons and Tumor Necrosis Factor which are the main role players in the massive cytokine reaction.¹⁰ The Recovery trial firmly established the effectiveness of Dexamethasone in reducing mortality in severe COVID-19 patients.¹¹ Methylprednisolone was subsequently used in many centers worldwide because it achieves higher lung tissue concentration and based on steroid bio-equivalency, its anti-inflammatory potency is much higher than Dexamethasone.¹²

The effect of steroid therapy is decided by dose of the drug and time from disease onset. Given early in the course of the disease, recovery and survival benefit is maximum as tissue damage is prevented at the earliest. The drug when given, acts on the cytosolic glucocorticoid receptor and forms a complex which acts via the genomic pathway leading to inhibition of production of damaging chemical mediators including IL-1, IL-2, IL-6, IFN-Gamma, Prostaglandins and TNF alpha.¹³ These effects are typically seen at doses of 30-100 mg of Methylprednisolone when given intravenously daily. If higher doses (more than 100 mg) of Methylprednisolone are given daily, the maximum effect of the drug is achieved.¹⁴ This forms the rationale behind Pulse therapy in which supra-physiological doses of Methylprednisolone are given early in the course of the disease for 3-5 days followed by standard doses so as to achieve maximum tissue concentration to arrest the inflammatory process and aim for early recovery.¹⁵

In this study, we compared a group of patients which received Methylprednisolone Pulse Therapy(MPPT) for three days with a group that had received routine dose of the steroid. The groups were compared for differences in clinical parameters, levels of inflammatory markers and survival.

MATERIAL AND METHODS

Study Design

The study was conducted retrospectively from 1 June 2020 to 31st December 2020 in Government Chest Diseases Hospital, an associated hospital of Government medical college Srinagar. Ethical approval was obtained from the ethics committee and proper consent was obtained from all patients who received the drugs.

The patients were divided into two cohorts with one receiving MPPT and the other standard corticosteroid dose. Data was compiled from the in-hospital records and compiled in Excel.

Data Source: In hospital patient records and electronic data was assessed in the hospital and values related to clinical outcome was compiled.

Patients

Patients were diagnosed as COVID-19 positive on the following:

- 1) Positive RAPID ANTIGEN TEST
- 2) Positive RT-PCR report
- 3) CT thorax findings typical of Covid-19 pneumonia including Bilateral Subpleural ground glass opacities, crazy paving pattern, consolidation, lymphadenopathy and parenchymal findings.

On the basis of severity of the disease patients were labeled as Severe COVID-19 pneumonia if they had sPO₂ less than 90% on room air at rest or sPO₂ less than 92% on room air with respiratory rate more than 30 per minute.

Inclusion Criteria

Patients were included in the study if they met the following criteria:

- 1) Age more than 18 years old
- 2) Covid-19 positive based on criteria mentioned above
- 3) Severe COVID-19 pneumonia as described above
- 4) Early phase of the disease i.e. first and second week of the illness
- 5) Those who gave a proper informed consent

Exclusion Criteria

Following patients were excluded from the study:

- 1) Pregnant and lactating females
- 2) Patients allergic to any drug or component of the prescribed regime
- 3) Uncontrolled hypertension or uncontrolled diabetes, bleeding diathesis, heart failure, any malignancy or already receiving any immunosuppressive therapy.

Pulse Therapy Definition

Methylprednisolone Pulse Therapy was defined as patients receiving daily intravenous methylprednisolone at a dose of 500 to 1000 mg for duration of three days continuously preferably early in the morning.

Procedure and outcome

Demographic and clinical parameters of all patients were recorded prior to admission to hospital. Detailed history was taken to ascertain the duration of the illness and severity of the disease besides any treatment received already.

Lab investigations advised on admission included CBC,KFT,LFT,RBS, and the inflammatory cytokines including IL-6, D-Dimer,CRP,Ferritin and LDH. Radiological investigations prescribed included HRCT THORAX besides 12 lead ECG. Vital parameters of all patients were recorded including HR, BP Temperature and sPO2 using standard pulse oximeter. Arterial blood gases (ABG) and VBG were serially measured and correlated with the clinical presentation and overall progress.

The requirement of oxygen therapy was assessed in terms of flow rates and oxygen delivery devices including nasal prongs, face mask without and with reservoir bag,HFNO and NIV. The need for shifting patients to ICU and invasive mechanical ventilation was recorded with regards to the day of admission and treatment received.

Clinical signs of the patients were recorded daily and in case of patients successfully discharged, the need for domiciliary oxygen support was advised and recorded.

All the data referred to above was compiled in Microsoft Excel sheet in two separate groups. One group included the patients exposed to pulse therapy and the other not exposed. Patients were considered for pulse therapy on the basis of the severity of illness and lack of response to standard corticosteroid steroid dose. It is pertinent to mention that data supporting pulse therapy administration was available to this centre in the latter half of the year 2020 and this was the reason why initially patients received only standard steroid doses. Hence the non-pulse therapy exposed group contains patients admitted to the hospital before the other group. All patients received standard care treatment in both groups as advised by WHO and ICMR guidelines.

Adverse Events

During the course of the study, all adverse events experienced by the patients were recorded irrespective of their link to the corticosteroid administration.

Statistical Analysis

Data was compiled into numerical and nominal values wherever indicated. Statistical analysis was conducted using SPSS software version 2. Statistical significance was expressed as p less than 0.05.

RESULTS

In this retrospective study 318 patients included with mean age **53.52±12.88 in the Group A and 52.45±11** mean age among the Group B. The demographic profile of the study population was comparable (table 1). Most of the studied patients had Comorbidities. Hypertension was the most common Comorbidities among the study population followed by Asthma and COPD reported (Table 2).

Table 1. Demographic profile of the study population (134)

Parameter	Group A	Group B
NO. of patients	192	126
Age	53.52±12.88	52.45±11.38
Male/Female	61.3/38.7	53.8/46.2
Smokers/non smokers	110/81	72/54

Table 2:Co morbidity among the study population

Comorbidity	Group A	Group B
Hypertension	23.4%	24.28%
Diabetes mellitus	10.93%	12.85%
COPD	20.31%	17.14%
Asthma	17.18%	14.28%
Other respiratory diseases	4.68%	7.14%

Ischemic heart disease	6.25%	5.71%
Chronic kidney disease	4.68%	8.57%
Previous TIA/stroke	7.81%	7.14
Liver disease	4.68%	2.85

On admission, the clinical parameters as well as biochemical markers were more severely deranged in the group assigned to pulse therapy as compared to the other group (Table 3).

Table 3: Clinical parameters on admission

Laboratory Data	Group A	Group B	P value
D-dimer ($\mu\text{g/mL}$), median	1.2 (0.7–2.1)	1.5 (0.8–3.6)	0.29
FDP ($\mu\text{g/mL}$), median	3.5 (2.7–4.7)	3.7 (2.8–5.9)	0.71
Lactate dehydrogenase (U/L), median	459(407–582)	441 (365–542)	0.15
IL-6 (U/mL)	389 (276–564)	432 (297–921)	0.51
PCT (ng/mL), median	0.20 (0.10–0.38)	0.15 (0.09–0.34)	0.51
IL-6 (pg/mL), median	92.2 (55.4–126.6)	54.6 (15.3–84.0)	0.03
CRP $\text{mg}\cdot\text{L}^{-1}$	99.1 \pm 80.0	92.6 \pm 70.3	0.707

Patients in the pulse therapy group had a significantly higher improvement in their overall clinical condition and survival. In the pulse therapy group, there was a marked improvement in sPO2 in 64.5% patients as compared to 24.3% in the non-exposed group (Fig 1).

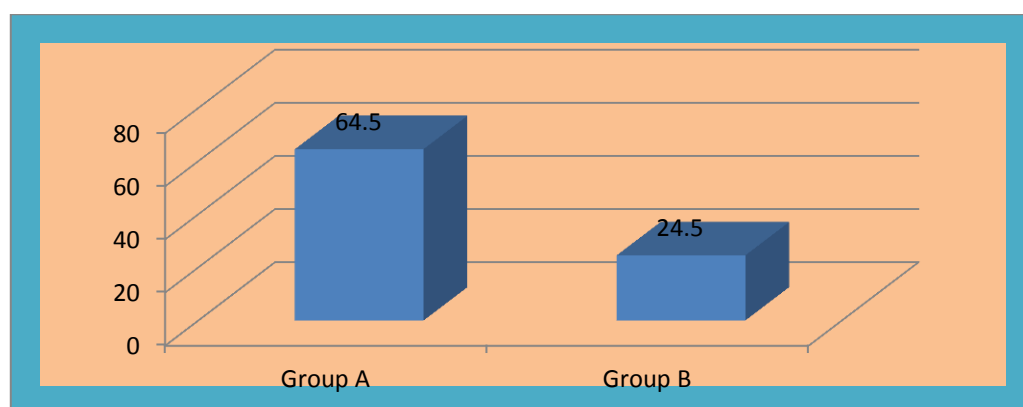


Fig 1

The levels of IL-6 and CRP were significantly lower in the pulse therapy group after treatment as compared to the other group in which there was lesser reduction. Overall hospital stay of less than 10 days in pulse therapy group was lesser(39.8%) as compared to the non-exposed group 68.9% with a p value <0.01 [Fig 2].

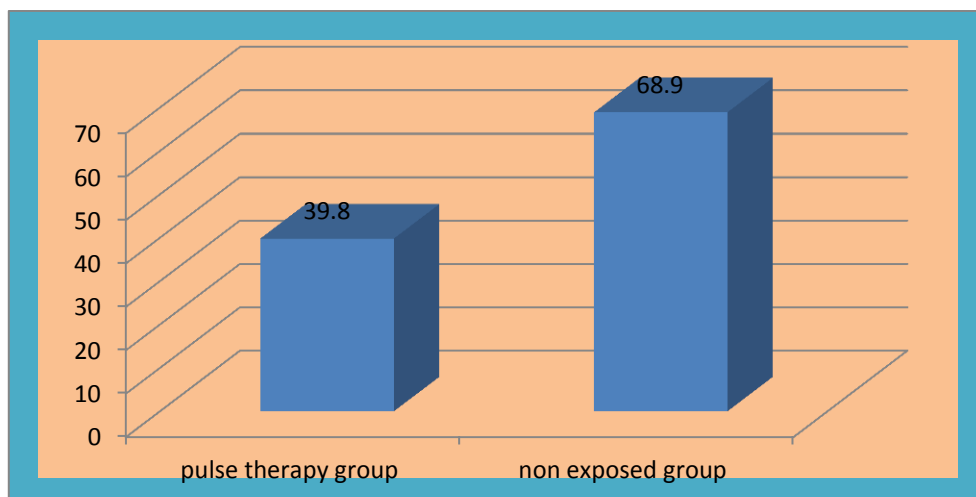


Fig 2

Finally, patients in the methylprednisolone pulse therapy group had a significantly reduced mortality of 16.2% as compared to the non-exposed group of 43.6% which resulted in a p value <0.05 [Fig 3].

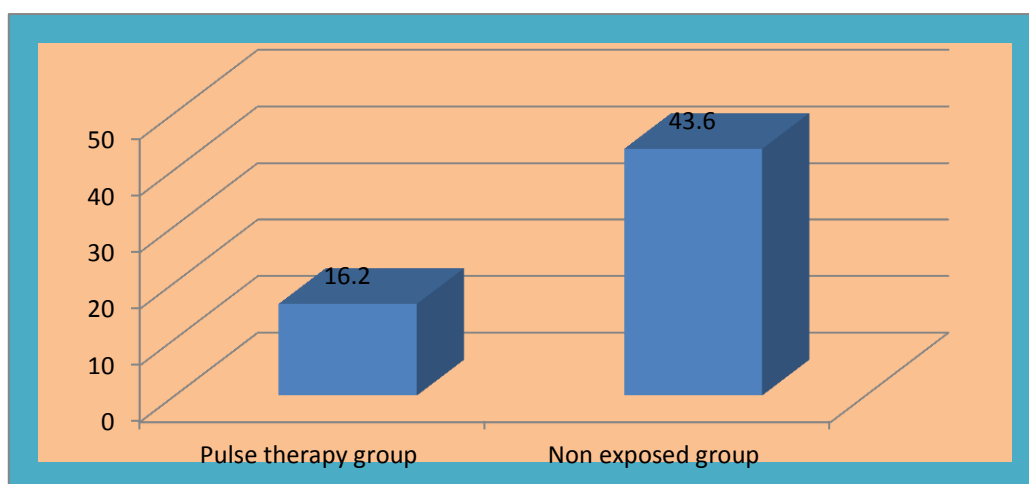


Fig 3

It was observed that fever subsided earlier in the pulse therapy group too. However respiratory rate and need for NIV did not alter significantly in the group that received pulse therapy.

DISCUSSION:

Corticosteroids have been shown to be beneficial in the treatment of Covid-19 pneumonia. In fact, it is the only class of drugs that reduces mortality as was evidenced by the recovery trial.¹⁶

In the beginning of the pandemic, patients who needed oxygen therapy and hospital admission were given standard doses of steroids. However, over time, several centers globally took the initiative to give the patients with severe disease higher doses of the drug for limited number of days.¹⁷ This mode of admission of Corticosteroids as Pulse Therapy has already been tried in several autoimmune disorders to arrest acute events associated with them.¹⁸

With ample evidence at hand, we tried to expand the benefit of MPPT to our patients so as to see if the globally evidenced benefits could be reproduced in our centre.

The overall results have been quite promising statistically. We observed significant improvement in the clinical condition of our patients. There were several parameters which showed improvement after the therapy. Fever subsided earlier in this group of patients as well as there was marked

increase in sPO₂ levels along with reduction in oxygen consumption and need for shifting back to low flow oxygen delivery devices.

The biochemical markers when compared before and after pulse therapy showed a marked reduction in values especially of CRP and IL-6 which are almost universally taken as indicators of progression of the disease. This also correlated with simultaneous improvement in clinical condition.

Hospital stay was significantly reduced in the pulse therapy group as patients were successful discharged within 10 days of admission and need for oxygen support was much less at home. The biggest advantage of MPPT is evidenced by a significantly lower mortality. The shortening of hospital stay and increased survival benefit underscores the importance of accepting MPPT as an essential tool in management of severe COVID-19 pneumonia patients besides other routine medication and interventions.

The improved advantage of pulse therapy can be attributed to several factors acting at the plasma and cellular levels. It is postulated that maximum doses of methylprednisolone for a short duration of time achieves highest plasma concentrations which leads to the best possible tissue penetration without leading to any significant deleterious effects. Such high doses of the steroid lead to several anti-inflammatory effects which are mediated both via classical genomic pathways and well as non-genomic ones.¹⁹ The overall effect is suppression of the ongoing COVID-19 infected body's self-harming hyper inflammatory response.²⁰ This leads to resolution of lung pathology culminating as improved exchange of gases at the pulmonary endothelial membrane and thus correction of the hypoxemia and end organ hypoxia. Besides this, the multi organ damage is also controlled, giving the body a chance to heal.

The importance of giving MPPT early in the disease is evidenced by the findings that those patients who received the therapy in the early course of the illness (2nd week) got the maximum benefit as compared to those who presented late to the hospital.

In this study we did not find any significant adverse events attributed to the high dose of steroid. Hypertensive patients did not have aggravation of their blood pressure although diabetic patients who were on oral hypoglycemic agents had to be shifted to insulin therapy for better control of blood sugar. Nevertheless, we did not find any significant deterioration of their diabetes and when they were followed for treatment after discharge, almost all of them had switched back to oral drug therapy with acceptable control of plasma glucose.

One undesirable effect of MPPT that was observed was the significant increase in white blood cell counts that was uniform in almost majority of patients. However, this did not necessarily translate into a state of sepsis as corticosteroids are known to cause an initial increase in neutrophil counts.²¹

To prevent patients getting into a septic state, serial blood cultures were taken to culture any pathogenic microorganisms and broad-spectrum antibiotic as well as anti-fungal therapy was given to all patients empirically.

CONCLUSIONS

This study was conducted to compare intravenous MPPT with standard doses of Methylprednisolone in severe Covid-19 pneumonia patients. Our data shows that Methylprednisolone Pulse Therapy of started early in the pulmonary phase of Covid-19 disease gives maximum benefits over and above that of the standard dose of the same drug. This was evidenced by improvement in clinical parameters, decline in inflammatory markers, shortened hospital stay and much lesser mortality in hospital.

Hence, we conclude that steroid pulse therapy significantly improves patient's clinical condition in Severe Covid-19 Pneumonia and markedly reduces mortality.

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