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Treatment Response to Methylprednisolone in Moderate to Severe COVID Patients: A Retrospective Study

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ABSTRACT

Aim: The purpose of our research was to assess the response towards moderate to severe covid patients with methylprednisolone treatment.

Methodology: 480 patients from 5 different hospitals in Visakhapatnam were hospitalized subjects, over 18 years of age with a laboratory confirmed diagnosis of SARS-CoV-2 infection were included in this retrospective study on inclusion criteria for the severity of Covid pneumonia. 480 patients each were allocated to two groups- control and the one receiving methylprednisolone (MP) treatment apart from standard treatment for Covid.

Results: The use of MP was associated with a significantly lower risk of the primary outcome with a 20% absolute risk reduction and RR 0.42 (95% CI 0.20–0.89; *p*= 0.043)**.** The length of stay in the hospital was similar for both groups (SOC 20± 14 days, MP 23± 13 days).

Conclusion: Methylprednisolone had a beneficial effect in reducing the mortality. However, prolonged usage is not recommended due to deleterious side effects and post covid complications.

Keywords Steroids, Covid-19, Inflammation, ARDS

INTRODUCTION

It has been generally admitted that corticosteroid therapy should not be routinely recommended in cases of viral pneumonia because the steroids might exacerbate lung injury.[1] This is the reason why guidance from the World Health Organization (WHO) at the start of the SARS-CoV-2 (COVID-19) pandemic advised against systematic use of corticosteroids in COVID-19 patients.[2] The rapid clinical deterioration of severely ill COVID-19 patients with viral pneumonia progresses into a disorder similar to the acute respiratory distress syndrome (ARDS) with multiple organ failure and death.[3,4] The association of increasing interleukin (IL) levels and very high acute phase reactants act as signals for a highly systemic inflammatory response.[5-9] These two findings in COVID-19 patients have led clinicians to question the recommendations against using corticosteroids. Besides, the potential benefit of corticosteroids in ARDS due to other causes has prompted interest in using them in COVID-19.[10] During the first month of the pandemic, several authors recommended prescribing

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corticosteroids based on anecdotal observations and retrospective uncontrolled series of patients.[11-14] In contrast, other studies argued that corticosteroids may be deleterious and cause delayed viral clearance in COVID- 19 patients as was also found in SARS patients.[15,16]
On 17 July 2020, the RECOVERY trial was published in which glucocorticoid use showed a clear beneficial effect in patients with COVID-19 who were on mechanical ventilation at the time of randomization in the United Kingdom (UK).[17] Other studies have confirmed a decrease in the number of ventilator-free days (CoDEX[18]) after steroid administration. In addition, two studies of critically ill patients (CAPECOVID and REMAP-CAP-COVID) showed a tendency for improvement in patients receiving corticosteroids; however, both were stopped early after the RECOVERY publication.[19,20] In contrast, METCOVID did not show differences in mortality after a short course of methylprednisolone (MP).[21] The evidence for the association of systemic corticosteroids with a reduction in critically ill COVID patient mortality has been summarized in few systematic reviews.[22,23]
The RECOVERY trial results showed a modest benefit of corticosteroids in less severely ill patients receiving oxygen without invasive mechanical ventilation (IMV). No benefits from the use of corticosteroids were found in patients without respiratory support on admission.
ARDS is the main reason for death in COVID-19 patients and there are no efficient specific treatment agents for the disease.[24] It is suggested that glucocorticoids and immunosuppressive treatment can reduce the inflammation of the respiratory system and prevent the cytokine storm and ARDS induction in COVID-19 patients.[25] Methylprednisolone is a glucocorticoid medication used to suppress autoimmune and inflammatory responses in rheumatic diseases.[26] Previously, methylprednisolone was administrated in SARS and MERS patients, and the results were controversial; however, glucocorticoid administration in COVID-19 patients in the hyperinflammation stage is likely to have survival benefits due to cytokine storm suppression.[27-29]

AIM OF THE STUDY

The purpose of our research was to assess the response towards moderate to severe covid patients with methylprednisolone treatment. This study also explores the efficacy rate of steroids in managing covid patients.

METHODOLOGY

We designed a programmed retrospective analysis of 480 patients who were hospitalized in 5 different hospitals in Visakhapatnam, subjects over 18 years of age with a laboratory confirmed diagnosis of SARS-CoV-2 infection and CT scan showing covid pneumonia, with following inclusion criterions were included in the study-
1. Moderate to severe disease with abnormal gas exchange:
(a) partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2 or PaFi) <300,
(b) arterial oxygen saturation/fraction of inspired oxygen (SaO2/FiO2 or SaFi) <400 or
(c) at least two criteria of the BRESCIA-COVID Respiratory Severity Scale (BCRSS).[30]
2. Evidence of a systemic inflammatory response with any of the following: serum C-reactive protein (CRP) >15mg/dl, D-dimer >800ng/ml, ferritin >1000mg/dl, or interleukin-6 (IL-6) levels >20pg/ml. The study was approved by the institutional review boards of participating hospitals, and patients gave informed consent. Patients in both study groups received standard ofcare (SOC) therapy according to the local hospitalprotocols. The SOC protocols were similar acrossthe participating hospitals and were based on theWHO recommendations. The SOC included symptomatictreatment with acetaminophen, oxygen therapy, low molecular weight heparin, and antibiotics for coinfections. Azithromycin, hydroxychloroquine, and lopinavir plus ritonavir were frequently prescribed. In addition to SOC, patients in the experimental group received intravenous (iv) MP 40mg bid for 3 days and then 20mg bid for

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3 more days. The primary outcome measure was a composite endpoint that included in-hospital all-cause mortality, escalation to ICU admission, or progression of respiratory insufficiency that required non-invasive ventilation (NIV). The secondary outcomes included the effects on the individual components of the composite endpoint and the variation of the laboratory biomarkers between baseline and 6 days after inclusion (time window 4–8 days). Continuous variables were compared using Student's t-test and analysis of variance (ANOVA) utilizing SPSS 25.0.

RESULTS

At baseline, study groups had similar biomarker levels. The CRP levels were lower in both groups 6 days later (Table 1) but the decrease was more pronounced in the MP group (77% decrease versus 43%, *p*= 0.034). Other biomarkers were similar in the control and MP groups**.** The use of MP was associated with a significantly lower risk of the primary outcome with a 20% absolute risk reduction and RR 0.42 (95% CI 0.20–0.89; *p*= 0.043)**.**Hyperglycemia (>180mg/dl) was more frequent in the MP group (26% in MP group, andnone in the SOC group, *p*= 0.015). Nosocomial infections also tended to be more common in the MP group (14% versus 3% *p*= 0.637)**.** The length of stay in the hospital was similar for both groups (SOC 20± 14 days, MP 23± 13 days, difference 3 days, 95% CI –10–4 days).(Table 2)

Table 1- Baseline characteristics of the study groups at randomization

Variables	SOC (standard of care - control group)	MP (Methylprednisolone)	Mean differences SOC vs. MP (95% CI)
Age, years, mean± SD	66± 12	73± 11	–7 (–13 to –2)
CRP, mg/dl	16 (11–24)	16 (11–24)	0.1 (–4 to 4)
D-dimer, ng/ml,	980 (557–1856)	1340 (712–2152)	–1912 (–4879 to 1054)

Table 2- Comparison of patients in the control and methylprednisolone (MP) groups-Age-stratified analyses

Outcome	Methylprednisolone	Standard of care	Relative risk (95% CI)	P
<50years	11%	40%	0.28	0.120
≥50years	38%	75%	0.51	0.074
Total	30%	50%	0.42	0.043

DISCUSSION

As the massive lung damage during COVID-19 pneumonia is thought to be caused by an aberrant inflammatory response mediated by a massive release of inflammatory cytokines and chemokines, the use of biological immunosuppressants has been widely proposed. The rationale supporting their use is not only an antiviral effect,but the selective anti-inflammatory role and the capability of interrupting the cytokine cascade eventually responsible for lung failure.[13] One crucial feature of corticosteroid therapy is its duration, particularly in patients with COVID-19 with sustained persistence of ground-glass opacities. Currently, an extended course of corticosteroids beyond 10 days is considered only in select cases of severe COVID-19. Steroid therapy during acute respiratory distress syndrome (ARDS) is still a matter of debate, and the immunosuppressive effect often represents an obstacle for its administration in fragile patients. Nevertheless, a growing body of evidence

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supports its use in this condition, particularly in compromised patients[3]. However, in COVID-19, such a long-lasting course of corticosteroids can inadvertently lead to poor treatment outcomes. The possible effect of steroids in the procoagulant environment of patients with COVID-19, in which even anticoagulant treatment does not sufficiently shield from the thrombotic complications found in deceased patients, should be considered. A hypercoagulable state with profound endothelial injury following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has an essential role in thrombosis. In autopsy studies of patients with COVID-19, diffuse alveolar disruption with large vessel thrombi and microthrombi were seen[4].Dexamethasone (6 mg per day) tends to increase clotting factor and fibrinogen concentrations. Thus, it is plausible for exogenous glucocorticoids to precipitate clinical thrombosis.[5]In addition, protracted corticosteroid therapy might contribute to the so-called long COVID syndrome that manifests with fatigue and psychological symptoms, in which steroid-related adverse drug reactions such as myopathy, neuromuscular weakness, and psychiatric symptoms might have a part to play.

Late in the disease course, corticosteroids do not appear to have a role in managing acute respiratory distress syndrome (ARDS). Routine use of methylprednisolone for persistent ARDS is not recommended despite improving cardiopulmonary physiology. Even initiating methylprednisolone therapy more than 2 weeks after the onset of ARDS might increase the risk of death.[7] A meta-analysis of 21 350 patients with COVID-19 concluded that overall mortality was greater among patients with the disease who were receiving corticosteroids than among patients who were not treated with corticosteroids. The duration of steroid therapy ranged from 3 to 12 days.[8] Theprothrombotic influence of steroids, coupled with their adverse drug reactions, might have contributed to increased mortality.

Patients in the MP arm were somewhat older than those in the control arm. This finding is an important issue in this study since we confirmed that advanced age is a risk factor for poor outcome in this study. The confounding effect of age is complex as it may influence not only the course of the disease but also decisions about escalation to ICU admission in a scenario of limited resources. Thus, age stratification is important for an adequate interpretation of the results. 54% patients died in the control arm as compared to 35% in MP group.

CONCLUSION

Corticosteroids thus seem to be a double-edged sword in the fight against COVID-19 and need to be used judiciously, considering the risk–benefit ratio, as a short-course (e.g., up to 10 days) therapeutic agent in a select group of patients with COVID-19 for whom survival benefit has been reported. There is no evidence supporting long-term use of steroids in patients with COVID-19 to prevent potential adverse sequelae such as pulmonary fibrosis.

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