Original Article

Relationship Between Day of Starting Steroid and Clinical Outcome in Hospitalized Covid-19 Patients

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ABSTRACT

Various guidelines recommend steroid in only severe COVID-19 patients. But in hospitals steroids are being rampantly used even at the beginning of symptom onset. Some studies indicate starting steroid only in severe and/or patients on mechanical ventilation while some suggest starting in first 5-7 days to stave off cytokine storm. Hence this study was undertaken with the aim to study the relationship between initiation of steroid therapy and clinical outcome in hospitalized COVID-19 patients. The data for this study was collected from the medical records of patients diagnosed with COVID-19 in a tertiary care hospital. Evaluation of relationship between day of initiating steroid therapy and dose with the clinical outcome was done in terms of all-cause mortality, duration of hospital stay, requirement of assisted ventilation, requirement of ICU and requirement of oxygen therapy. Patients were categorized according to the day of initiating steroid after symptom onset or RTPCR or RAT positivity date, whichever was earlier in 4-7 days group, 8-10 days group and 11-14 days group. And according to dose given of methylprednisolone per day in 40 mg and 80 mg groups. All-cause mortality was significantly less in 8-10 days group (25.78%) compared to 4-7 days (38%) and 11-14 days group (39.68%) and significantly less in 40 mg group (26.67%) compared to 80 mg group (38.46%). Starting steroid between 8-10 days and in low dose (40 mg) is more beneficial in terms of all-cause mortality.

Keywords: COVID-19, mortality, methylprednisolone, steroid.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) wreaked havoc in the form of a global pandemic with India being one of the countries worst hit by this pandemic.[1] Globally, the numbers of COVID-19 cases and deaths have showed decline but spikes in cases are seen frequently indicating that COVID-19 pandemic continues to constitute a Public Health Emergency of International Concern.[2] New variants are continuously being detected indicating the need for optimization of available treatment options.[3] Multiple pharmacological therapies (like low molecular weight heparin, ivermectin, hydroxychloroquine and azithromycin, lopinavir-ritonavir, remdesivir, corticosteroids, tocilizumab) were tried since the emergence of this disease and are still being used despite the lacking, controversial or insignificant evidence of efficacy.[4] Rise in inflammatory biomarkers, cytokines and chemokines is evident in COVID-19 disease.[5] Evidence of intense inflammation associated with COVID-19 disease and paucity of specific effective therapy, propelled the use of potential therapeutic options that target inflammation with the rationale to counter acute inflammation, reduce tissue injury and improve outcomes. Corticosteroids received early heed because of their well-established broad-spectrum anti-inflammatory and immunomodulatory effects. [6] WHO had initially warned against the use of steroids for the treatment of COVID-19 because of lack of survival benefits in patients with SARS and possible harms (avascular necrosis, psychosis, diabetes, and delayed viral clearance). [7] RECOVERY trial observed that dexamethasone treatment improves survival in patients suffering with severe and critical COVID-19. On the basis of this solitary large open label randomized controlled trial (RCT) corticosteroids has been considered worldwide as the most effective COVID-19 therapy. RCT even though is considered to provide high level of evidence for the efficacy of an intervention, observational studies may play a role to test the generalizability of findings. [8,9] After the entry of SARS-CoV-2 into the body, there is an initial phase of viral replication and followed by a phase of adaptive immunity. Influenza-like illness is due to the cytopathic effect of the virus in the replicative phase. Viral levels decline thereafter in the adaptive phase as a result of T-cell dependent immune

response. Dysregulation between protective and altered immune responses is a critical point for disease progression. Thus, the use of antivirals in the early phase, and immunosuppressive agents in the adaptive immunity phase is recommended.[10] A New York-based study conducted with the primary aim to determine the association of early glucocorticoid treatment with mortality or the need for mechanical ventilation did not show favorable results. Rather early glucocorticoid use and initial hs-CRP of less than 10 mg/dL posed patients at risk of mortality or mechanical ventilation usage. In contrast, hs-CRP of 20 mg/dL or higher was associated with a significant reduction.[10,11] In other words if steroid is started in the early viral replicable phase i.e., early symptomatic phase more virus replication is possible. The anti-inflammatory steroid should be initiated early in the pulmonary phase to counter the immune dysregulation.[12] Few authors have also reported the failure of corticosteroids in late phase of disease and that they do not appear to have a role in managing acute respiratory distress syndrome (ARDS) if started beyond the optimum time. Corticosteroids therefore seem to be a double-edged sword if it is to be used as a weapon in war against COVID-19. [13] Several questions need to be addressed and there is a need to optimize the timing of corticosteroid initiation, the dose of a particular steroid and the duration of treatment. Therefore, this retrospective observational study was done with the primary objective of evaluating relationship between timing of corticosteroid therapy and mortality.

MATERIAL AND METHODS

This was an observational retrospective study. Patients' medical records were obtained from Medical Records Department (MRD) of a tertiary care hospital. Records were selected by systematic random sampling from the records of confirmed COVID-19 cases admitted in the hospital between 1st March 2021 and 31st May 2021. Institutional Ethics Committee (IEC) approval was taken before conducting the study. Permission to access medical records was taken from the concerned authorities of medical records section and consent was not required as it was a retrospective study. The collected data included demographic parameters, duration of hospital stay, co-morbidities, all-cause mortality, day of starting steroid, dose of steroid, oxygen requirement, ICU requirement, ventilator requirement, co-medications, inflammatory markers (CRP, LDH, Ferritin), HRCT scores.

Evaluation of relationship between day of initiating steroid therapy and dose with the clinical outcome was done in terms of All-cause mortality, which was our primary outcome measure. Secondary outcomes evaluated were Duration of hospital stay, Requirement of assisted ventilation, Requirement of ICU, Requirement of Oxygen therapy and change in inflammatory markers (CRP, LDH, Ferritin) from baseline.

Patients were categorized in three groups according to the timing of initiation of corticosteroid therapy from onset of first symptom of the disease or Real Time Polymerase Chain reaction/Rapid antigen test (RT-PCR/RAT) positivity date, whichever was earlier. Group 1 included patients who were given steroid therapy after 4-7 days, Group 2 included patients who were given steroid therapy after 8-10 days and Group 3 included patients who were given steroid therapy after 11-14 days of first symptom of flu-like illness or RT-PCR/RAT positivity date, whichever was earlier. Evaluation was also done to look for any relation between clinical outcome and the dose of corticosteroid used methylprednisolone 40mg (MPS 40 Group) or methyl prednisolone 80mg (MPS 80 Group).

Sample size was calculated using PS for Sample Size ver. 3.1.6. Software. Assuming the difference of mortality between two groups of 12% sample size required was 239 in each group to be able to reject the null hypothesis that the exposure rates for case and controls are equal with probability (power) 0.8. Type I error (alpha) was taken as 0.05. Total sample size considering the attrition rate of 10% came out to be 800.

Statistical analysis was done using Graph pad prism version 8.4.2. Descriptive statistics were reported as frequencies, percentage or mean ± standard deviation. Categorical variables were reported as actual numbers and percentage. For dichotomous data Chi-square test and for continuous data t-test, Mann-Whitney test, one-way ANOVA and Kruskal-Wallis test were used to find the significance between the groups. $P<0.05$ was considered as statistically significant difference.

RESULTS AND DISCUSSION

Eight hundred (800) records were drawn by systematic random sampling from all the records of confirmed COVID-19 cases. Out of these 75 records were excluded who were not given steroid or given steroid before 4 days or after 14 days of symptom onset or RTPCR/RAT positivity date, whichever was earlier. Seven hundred twenty-five (725) patients' medical records were analyzed for results. Methylprednisolone was the steroid used at this setup and other medications received by the patients included Low molecular weight heparin, antibiotics, antivirals like remdesivir and favipiravir, antipyretic and ongoing medicines for the co-morbidities.

Patients were compared for demographic and baseline characteristics according to day of starting steroid (Table 1) and according to dose of steroid (Table 2). In both these tables parameters like age, male: female ratio, co-morbidities, levels of inflammatory markers (CRP, LDH, Ferritin) and HRCT scores were compared between the groups and no significant difference was observed except for Ferritin levels and HRCT scores. Ferritin levels were significantly higher in 11-14 days group (Group 3) ($p<0.0001$). It may be due to the fact that patients in that group presented very late to the hospital and Ferritin levels had already increased by that time. HRCT score was also significantly higher in Group 3 ($p<0.05$) and maybe due to the same reason of late presentation to the hospital.

Our primary outcome measure was all-cause in-hospital mortality. Total all-cause mortality was 243 out of 725 patients (33.51%). All-cause mortality was compared between all the groups. It was significantly lower in Group 2 (25.78%) when compared to Group 1 (38%) (p = 0.0022) and Group 3 (39.68%) (p = 0.0420) (Table 3). There was no significant difference in mortality between Group 1 and Group 3 (p = 0.7804). When all-cause mortality was compared according to dose of steroid used it was significantly lower in MPS 40 group (p = 0.0012) (Table 4).

Other parameters that were compared included mean duration of hospital stay in discharged patients, requirement of ventilator in discharged patients, requirement of ICU in all patients, requirement of oxygen therapy in all patients in terms of mean duration and mean oxygen given in L/min. Out of these parameters Requirement of ventilator was significantly less in Group 2 as compared to other 2 groups. ICU requirement was significantly lower in MPS 40 group when compared with MPS 80 group (p = 0.0090) (Table 4) but did not show any significant difference when compared between groups receiving corticosteroids at different time interval (Table 3). Other parameters did not turn out to be significantly different between any of the groups. (Table 3 & 4)

Mean change in levels of inflammatory markers between baseline and after giving steroid therapy was also compared between the groups. Inflammatory markers which were compared included CRP, LDH and Ferritin. Out of these, significant reduction in mean CRP level was seen in Group 3 compared to other 2 groups (p = 0.0063 and p = 0.0047 respectively). (Table 3 & 4).

Table 1: Comparison of baseline parameters in COVID-19 patients according to day of starting steroid (Methylprednisolone)

Parameters	Group 1 4-7 days (n=406)	Group 2 8-10 days (n=256)	Group 3 11-14 days (n=63)	P-Value
Age$	53.46 (15.15)	52.23 (13.13)	51.06 (14.70)	0.4706
Male: Female	1.57:1	1.17:1	1.52:1	0.4157
Co-morbidities (%)	126 (31.03%)	90 (35.16%)	15 (23.81%)	0.1931
CRP in mg/L$	84.9 (65.70)	73.63 (52.30)	76.26 (43.87)	0.6631
LDH in U/L$	732.9 (328.4)	790.5 (308.1)	858.5 (364.6)	0.3592
Ferritin in ng/mL$	415.1 (382)	562.6 (524.9)	1395 (862.4)*	<0.0001
HRCT#	15 (11-19)	13 (9-16)	16 (11-20)	0.0359

CRP = C-reactive protein, LDH = Lactate dehydrogenase, HRCT= High resolution computerized tomography, mg/L = milligram per liter, ng/mL = nanogram per milliliter, U/L = unit per liter, p-value was calculated using chi-square test, one-way ANOVA and Kruskal-Wallis test., **$** values expressed as mean (SD), SD = standard deviation, **#** values expressed as median

Table 2: Comparison of baseline parameters in COVID-19 patients according to dose of steroid (Methylprednisolone)

Parameters	40 mg (n=270)	80 mg (n=455)	P-Value
Age$	54.16 (14.73)	51.79 (14.22)	0.1153
Male: Female	1.19:1	1.57:1	0.2053
Co-morbidities (%)	75 (27.77%)	133 (29.23%)	0.7342
CRP in mg/L$	110.9 (109.3)	117.2 (149.2)	0.6319
Ferritin in ng/mL$	625.6 (645.1)	855.3 (782.7)	0.3385
LDH in U/L$	824.2 (378.2)	753.1 (299.0)	0.3083
HRCT#	15 (9-19)	15 (10-17)	0.2792

CRP = C-reactive protein, LDH = Lactate dehydrogenase, HRCT= High resolution computerized tomography, mg/L = milligram per liter, ng/mL = nanogram per milliliter, U/L = unit per liter, p-value was calculated using chi-square test, one-way ANOVA and Kruskal-Wallis test., **$** values expressed as mean (SD), SD = standard deviation, **#** values expressed as median

Table 3: Comparison of clinical outcomes in COVID-19 patients according to day of starting steroid (Methylprednisolone)

Day of starting steroid	4-7 days (n=406)	8-10 days (n=256)	11-14 days (n=63)	p-value
All-cause mortality (%)	152 (38%)	66 (25.78%)*	25 (39.68%)	0.0046
Mean hospital stay in days of discharged pts	11.42 (6.043)	11.49 (5.560)	11.68 (4.639)	0.6847
Ventilator requirement	108 (26.2%)	40 (15.63)*	22 (34.92%)	0.0004
ICU requirement (%)	78 (19.21%)	44 (17.19%)	9 (14.28%)	0.5765
Oxygen requirement in days	8.119 (5.791)	9.217 (5.475)	9.171 (4.748)	0.103
Oxygen requirement in L/min	10.09 (4.351)	10 (4.872)	10.51 (3.543)	0.814
Mean change in CRP level	-81.85 (117.7)	-85.90 (144.8)	-98.28 (153.0)*	0.0041
Mean change in LDH level	-110.6 (390.0)	-190.2 (360.5)	-76.09 (525.9)	0.2675
Mean change in Ferritin level	-54.09 (542.2)	-173.7 (367.4)	-258.2 (847.0)	0.101

CRP = C-reactive protein, LDH = Lactate dehydrogenase, HRCT= High resolution CT, L/min = liter per minute, p-value was calculated using chi-square test, one-way ANOVA and Kruskal-Wallis test.

Table 4: Comparison of clinical outcomes in COVID-19 patients according to dose of steroid (Methylprednisolone)

Dose of steroid	MPS 40 (n=270)	MPS 80 (n=455)	p- value
All-cause mortality (%)	72 (26.67%)*	175 (38.46%)	0.0012
Mean hospital stay in days in discharged pts	11.23(5.77)	11.53(5.75)	0.6586
Ventilator requirement (%)	32 (11.85%)	75 (16.48%)	0.0891
ICU requirement (%)	35 (12.96%)*	94 (20.65%)	0.0090
Oxygen requirement in days	8.36	8.65	0.5246
Oxygen requirement in L/min	10.15	9.97	0.8514
Mean change in CRP level	-88.42 (110.1)	-86.09 (147.7)	0.226
Mean change in LDH level	-191.4 (399.0)	-97.04 (418.8)	0.2379
Mean change in Ferritin level	-198.5 (510.8)	-99.22 (630.4)	0.5994

CRP = C-reactive protein, LDH = Lactate dehydrogenase, HRCT= High resolution computerized tomography, p-value was calculated using chi-square test, one-way ANOVA and Kruskal-Wallis test.

The major findings of our observational study of corticosteroid use in COVID-19 patients are: i)lower mortality when corticosteroid are started between 8-10 days of symptom onset and at a low dose, ii) association of mortality with early (before 7 days) or delayed (after 10 days) use of steroid and also the high dose of steroid, iii) Requirement of ventilatory support in lesser number of patients who received corticosteroids between 8-10 days iv) decreased requirement of ICU in patients who received low dose steroid. These findings were statistically significant after comparing the baseline data for age, gender, comorbidities, serum CRP and LDH levels. Serum Ferritin levels were found to be significantly higher in the Group 3. This could have been the result of delay in receiving any form of treatment owing to the shortage of hospital beds during the struggling times of second wave in India. HRCT score at baseline even though significantly lesser in group 2, was in the same moderate category as the other 2 groups.

The RECOVERY trial reported evidence of decrease in all-cause mortality in patients receiving dexamethasone. The study showed mortality benefit and decreased hospital stay in subgroup of patients requiring respiratory support thus

emphasizing and rationalizing the use of corticosteroids in hospitalized patients of COVID-19. [9] A retrospective study by Chen RC et al. reported that corticosteroids given in critically ill SARS patients resulted in decrease in mortality and a shorter hospitalization stay. [14] Another retrospective study was able to show that treatment with methylprednisolone decreased the risk of death among COVID-19 patients with ARDS. [15] With the limited evidence available, Dexamethasone or other corticosteroids in equivalent doses became a common practice in critically ill COVID-19 patients. Mortality benefit with steroids was blown out of proportion and it was used in all the hospitalized patients of COVID-19 even with no or minimal lung involvement. There was still lack of clarity to use steroids in patients who did not require ventilatory support or who were not critically ill especially if they presented very early with mild respiratory distress requiring only oxygen support. Many questions like optimum timing of initiation of steroids, correct dose and ideal duration still required answers. Our study tried to study one such aspect, the timing of initiation of corticosteroid and its relationship with mortality. To study the influence of corticosteroid on mortality we set the initiation of steroid till 7-day mark as early initiation from the available evidence and some expert opinion. Based on the comparison of survivors vs. non-survivors we found that the onset time for using corticosteroids was clinically relevant, favoring mortality benefit at 8-10 days. [12] According to a data-based study done in England all-cause mortality in COVID-19 hospitalized patient was found to be 31.2 % whereas in an Indian study mortality in hospitalized study was 13%. [16,17] In our study total all-cause mortality was 33.51 % which was on a higher side. Resource limited setting and underwhelming doctor patient ratio in the disastrous second wave of COVID pandemic in India may have been the possible reason for higher hospital mortality rate. But our study could find out the significant difference in the mortality rates according to timing of initiation of corticosteroid therapy (25.78% in Group 2 Vs 38% and 38.68% in other groups).

A positive finding associated with use of steroids between 8 to 10 days was less requirement of ventilatory support (15.3%) as compared to other two groups (26.2% and 34.92%). Another finding with use of low dose steroid (40 mg methylprednisolone per day) was lesser ICU requirement as compared to patients receiving higher doses of steroid. Optimum use of corticosteroids is believed to improve compliance and hypoxemia in patients of respiratory distress, reducing the need for ICU admission and ventilatory support. In this regard, initiation of corticosteroid therapy at the right time and dose could be useful in decreasing the load on the Intensive Care Units and decreasing the occupancy of ventilators in times of low resources, as during the stressful COVID-19 pandemic, when ICU and ventilator bed occupancy must be rationalized.[18,19]

A large data base study done by Kam sing Ho found that mean hospital stay was less in patients who were treated with corticosteroids as compared to those who didn't receive any steroids (8.09 vs 9.02 days).[20] Mean duration of hospitalization in our study was 11.4 days which was slightly more but there were no differences between the 3 groups with respect to duration of hospitalization. Many studies have documented that CRP levels are diminished by corticosteroid therapy in comparison to placebo. The effect is postulated to be due to the inhibition of interleukin (IL)-6 synthesis, which is a stimulator for CRP. [21] Our study did document the decrease in CRP levels as well as other inflammatory markers in all the groups but there was no significant difference between the 3 groups.

Though this study throws light on some important aspect of corticosteroid therapy in COVID-19 cases it has some relevant limitations. Firstly, it is retrospective analysis of prospectively collected data from hospital records. Secondly, though the possible covariates were found to be comparable at baseline analysis, covariate analysis or subgroup analysis for the possible confounders was not done. Thirdly, some of the important data like National early warning score (NEWS) and decline in HRCT after repeated HRCT could not be taken into account due to missing data. And finally, this study is a single center study, and the findings might be valid for centers with a similar setup and resources and volume of COVID-19 admissions. Also, the effect of unknown confounding factors cannot be excluded.

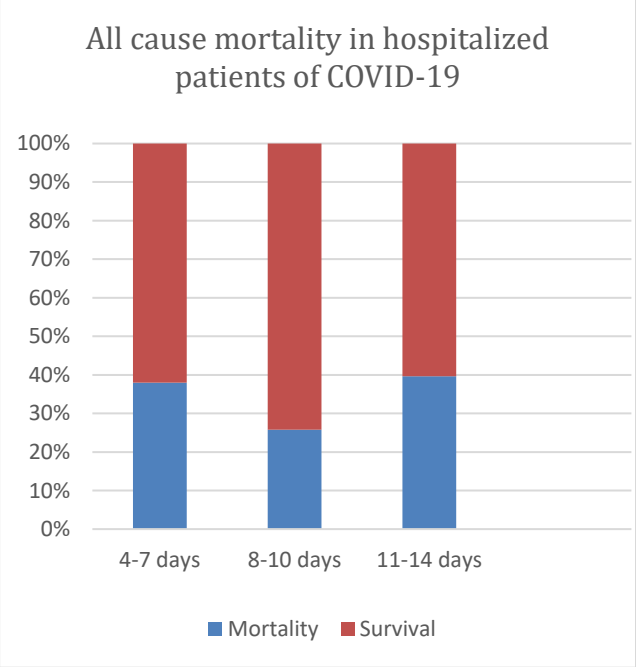

Figure 1: All-cause mortality in hospitalized patients of COVID-19

CONCLUSION

Corticosteroids were found to have the best mortality benefit when given to hospitalized patients of COVID-19 between 8-10 days of symptom onset and in low dose. Secondarily they may have the advantage of decreasing the need of ventilatory support in patients when given between 8-10 days of symptom onset.

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