Brief Report

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Role of systemic corticosteroids in preventing hypoxia among patients with mild COVID-19: An observational study

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SUMMARY Use of systemic corticosteroids is well-established in COVID-19 patients with hypoxia; however, there is scant data on its role in patients with mild disease and prolonged symptoms as a measure to prevent disease progression. The aim of this study is to evaluate the role of systemic corticosteroids in preventing hypoxia ($SpO_2 \leq 93\%$ on room-air) among mild COVID-19 patients. An observational study was conducted among symptomatic COVID-19 patients taking oral corticosteroids and attending institute teleconsultation facility between 10th-30th June 2021. Patients who were already on corticosteroids for other indication or required oxygen supplementation before or within 24-hours of initiation of corticosteroids were excluded. A total of 140 consecutive symptomatic COVID-19 patients were included. Higher baseline C-reactive protein (OR: 1.03, 95% CI: 1.02-1.06, $p < 0.001$) and early systemic corticosteroid (within 7 days) initiation (OR: 6.5, 95% CI: 2.1-20.1, $p = 0.001$) were independent risk factors for developing hypoxia ($SpO_2 \leq 93\%$). Progression to hypoxia was significantly higher in patients who received corticosteroids before day 7 of illness (36.7%, 95% CI, 23.4-51.7%) compared to ≥ 7 of illness (14.3%, 95% CI, 7.8-23.2%) for persistent fever. Systemic corticosteroids within 7 days from symptom-onset were harmful and increased the risk of progression to hypoxia, whereas it may decrease the risk of progression when administered on or beyond 7 days in patients with mild COVID-19 and persistent symptoms. A well-designed randomised controlled trial is required to validate the findings.

Keywords COVID-19, corticosteroids, hypoxia, prolonged fever

1. Introduction

The successive waves of the ongoing pandemic have overwhelmed even the best of healthcare infrastructure globally. While significant evidence has been generated on treatment options for admitted patients with hypoxia; not much progress has been made among non-hypoxic patients barring monoclonal antibodies, the economics of which makes it unlikely to be a game-changer.

Identifying risk factors for targeted intervention and preventing progression to hypoxia requiring hospitalization, is a much-needed lacunae in coronavirus disease-2019 (COVID-19) management which needs more attention. Some observational studies have reported prolonged fever as a risk factor for progression to severe disease (*1*). The randomized controlled trials on corticosteroids used in COVID-19 have not addressed this group of patients. In the RECOVERY trial, corticosteroids were used early in the disease course in non-hypoxic patients (median 6 days), which theoretically is likely to be harmful (*2*).

In April 2021, at the height of the second wave in India, guidelines were issued recommending low-dose corticosteroids in confirmed COVID-19 patients with prolonged fever beyond 7 days on a case-to-case basis (*3*). In this setting, this observational study was carried out to evaluate the role of systemic corticosteroids in preventing hypoxia ($SpO_2 \leq 93\%$ on room-air) among mild COVID-19 patients.

2. Methodology

This was an ambispective observational study approved by the Institute Ethics Committee and carried out between 10^{th}-30^{th} June 2021. Confirmed COVID-19 patients who had availed the teleconsultation facility at our tertiary care hospital in Delhi, India, were contacted. A confirmed case was defined as per the World Health Organization COVID-19 case definition (*4*). Consecutive patients who were symptomatic and

prescribed systemic oral corticosteroids by their treating physician for COVID-19 illness were invited to fill up a pre-designed questionnaire after informed consent. Patients who were already on corticosteroids for other indication or required oxygen supplementation before or within 24-hours of initiation of corticosteroids were excluded. Patients already on other immunosuppressive drugs and pregnant females were also excluded.

Patient characteristics, clinical details, vaccination, investigations, day, type and dose of corticosteroid at initiation, response to treatment, and progression to hypoxia ($SpO_2 \leq 93\%$ on room-air) requiring oxygen supplementation were recorded. The records and variables were analysed using Statistical Software Stata 16·0 (StataCorp, College Station, TX). Categorical data were expressed as frequency and percentage, quantitative data expressed as mean (SD) and median (IQR). Independent *t*-test was used to compare means, Mann-Whitney *U* test for medians and Chi square/ Fisher's exact test for categorical variables. A binary logistic regression model was developed to assess the impact of different variables (which had $p < 0.2$) on the likelihood of development of hypoxia with the forward conditional method. Kaplan-Meier curves were constructed for the oxygen requirement for the two groups (early corticosteroid intake and late corticosteroid intake) and the difference between the two curves was estimated using the log rank test. For the outcome of oxygen requirement, hazard ratios were computed using a Cox proportional hazards model. Univariate Cox models were initially used to determine significant effects of each covariate, following which these were incorporated into a multivariate Cox model. Statistical significance was considered at *p*-value less than 0.05.

3. Results and Discussion

A total of 145 patients were interviewed among which 5 were excluded as they required oxygen supplementation before or within 24-hours of initiation of corticosteroids. Among the 140 patients included in the study, the mean (SD) age was 45.4 (15.6) years and 87 (62.1%) were males. Patients were divided into two groups: those who received systemic corticosteroids before day 7 of illness (early) and patients who received corticosteroids on or after day 7 (late) for persistent symptoms. Age, gender distribution, presence of overall comorbidities, vaccination status and C-reactive protein (CRP) values were comparable between the groups; however, diabetes was more common in the early corticosteroids group (Table 1). The mean duration of illness at initiation of corticosteroids in the first group was 4.9 ± 1.6 days and 8.6 ± 2.0 days in the second group ($p < 0.001$). There was no significant difference in the type, initial dose or duration of corticosteroid use. Incidence of hypoxia was significantly higher in patients who received corticosteroids before day 7 of illness (36.7%, 95% CI, 23.4-51.7%) compared to patients who received corticosteroids on or after day 7 of illness (14.3%, 95%CI, 7.8-23.2%) with *p*-value < 0.005. We also analysed for risk factors of developing

Table 1. Comparison of patient profile receiving corticosteroids before day 7 of illness and receiving corticosteroids on or after 7 days of illness (*n* = 140)

Items	Corticosteroids before day 7 of illness (*n* = 49), *n* (%)	Corticosteroids on or after day 7 of illness (n = 91), *n* (%)	*p*-value
Age in years[a]	47.98 ± 16.99	43.98 ± 14.71	0.15
Male gender	30 (61.2)	57 (62.6)	1
Comorbidities			
Hypertension	8 (16.3)	17 (18.7)	0.8
Diabetes	13 (26.5)	11 (12.1)	0.04
Coronary artery disease	1 (2)	4 (4.4)	0.66
COPD/Asthma	2 (4.1)	1 (1.1)	0.28
Hypothyroidism	5 (10.2)	2 (2.2)	0.05
Vaccination status			0.3
Unvaccinated	22 (44.9)	51 (56)	
Single dose	19 (38.8)	24 (26.4)	
Both doses	8 (16.3)	16 (17.6)	
First available CRP in mg/dL[b,c]	14 (4-32)	20.5 (9.8-43)	0.07
Duration of illness in days at initiation of corticosteroids[a]	4.9 ± 1.62	8.65 ± 2.04	< 0.001
Type of corticosteroids			
Dexamethasone	22 (44.9)	45 (49.5)	0.7
Methylprednisolone	22 (44.9)	39 (42.8)	0.9
Prednisolone	5 (10.2)	7 (7.7)	0.8
Dose at initiation (Methylprednisolone equivalent in mg/day)[c]	32 (20-60)	32 (30-48)	0.71
Duration of corticosteroids treatment in days[c]	10 (7-13)	7 (5-11)	0.06
Oxygen requirement	18 (36.7)	13 (14.3)	0.005
Duration of illness at oxygen requirement in days	10.94 ± 4.66	11.1 ± 1.3	0.92

[a.] mean ± S.D.; [b.] Available for 41/49 in first group and 74/91 in the second group of patients; [c.] median (IQR).

Table 2. Comparison of patient profile based on development of hypoxia (*n* = 140)

Items	No hypoxia (*n* = 109) *n* (%)	Hypoxia (*n* = 31) *n* (%)	*p*-value	Multivariate analysis	
				95% CI	*p*-value
Age (in years)[a]	43 ± 13.9	53.9 ± 18.4	0.005		0.1
Male gender	69 (63.3)	18 (58.1)	0.68		
Comorbidities					0.5
Diabetes	17 (15.6)	7 (22.6)	0.42		
Hypertension	18 (16.5)	7 (22.6)	0.43		
Coronary Artery Disease	3 (2.8)	2 (6.5)	0.3		
COPD/Asthma	3 (2.8)	0 (0)	1		
Hypothyroidism	4 (3.7)	3 (9.7)	0.18		
COVID-19 Vaccine status			0.42		
Not vaccinated	60 (55)	13 (41.9)			
1 dose received	31 (28.5)	12 (38.7)			
2 doses received	18 (16.5)	6 (19.4)			
CRP (mg/dL)[b]	14 (5.7-32)	41 (18.9-59.5)	< 0.001	1.03 (1.02-1.06)	< 0.001
Corticosteroids administered			0.005	6.48 (2.1-20.1)	0.001
< 7 days of illness	31 (28.4)	18 (58.1)			
> 7 days of illness	78 (71.6)	13 (41.9)			

[a] mean ± S.D.; [b] median (IQR).

hypoxia by multivariate logistic regression analysis (Table 2). The risk of developing hypoxia was higher in patients with a high baseline CRP (OR: 1.03, 95% CI: 1.02-1.06, $p < 0.001$) and in patients in whom corticosteroids were initiated before day 7 of illness (OR: 6.5, 95% CI: 2.1-20.1, $p = 0.001$) (Table 2).

The Kaplan-Meier curves depicting the probability of oxygen requirement till a follow-up of 30 days between patients with early versus delayed corticosteroid intake is shown in Figure 1. The difference between the survival curves was significant using the log rank test ($\chi^2 = 11.19$, $p = 0.0008$). Oxygen requirement at 30 days was significantly higher in patients with elevated CRP (HR: 1.02, 95% CI = 1.01-1.04, $p < 0.0001$) and in patients with early corticosteroid intake during the course of illness (HR: 4.38, 95% CI = 1.84-10.4, $p = 0.001$).

Out of 140 patients, 63 (45%) patients did not report any adverse events with use of corticosteroids. Among patients who reported adverse events, deranged blood glucose was most common, reported by 33.5% of the participants, followed by gastritis (14.3%) and elevated blood pressures (4.3%).

Initiation of corticosteroids in the early phase of COVID-19 illness (before 7 days from symptom-onset) and higher CRP levels were found to be risk factors for progression to hypoxia. A trend towards decreased incidence of hypoxia was observed among patients with prolonged symptoms who were initiated on corticosteroids on or after 7 days from symptoms-onset.

The pathophysiology of COVID-19 disease comprises three phases: early infection phase, pulmonary phase and hyper-inflammatory phase. The second phase is a transition zone between the viraemic (lasts for around 5-7 days) and the inflammatory phase. End of the pulmonary phase and beginning of hyper-inflammatory

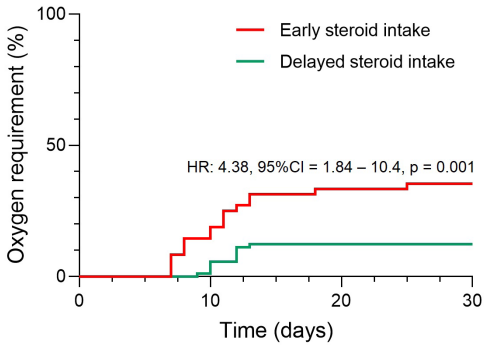

Figure 1. The Kaplan-Meier curves depicting the probability of oxygen requirement between patients with early corticosteroid intake versus delayed corticosteroid intake (*n* = 140).

phase usually marks the onset of respiratory failure. A clinical marker demarcating the onset of immune dysregulation before setting in of respiratory failure would appropriately guide the timing of corticosteroids. A recent systematic review concluded that the virus remains viable only for a short duration. While most studies successfully cultured the virus within the first week of illness, no study reported viable virus beyond day 9 (*5,6*). This may explain the harmful clinical effects of corticosteroids when given in the first week of illness.

Grade and patterns of fever at admission have been correlated with progression, severity and mortality in COVID-19 (*1,7*). While, very few studies have taken into account the duration of fever, a study from Singapore conducted on 142 patients found that both prolonged (27.8% *vs*. 0.9%; 95% CI 9.7-53.5, $p < 0.01$) and saddleback fever (14.3% *vs*. 0.9%; $p = 0.03$) were associated with hypoxia compared with controls. It also found that patients with prolonged fever were more

likely to require ICU admission (11.1% *vs*. 0.9%; p = 0.05) (*8*). In comparison, our study findings suggest a nearly 50% reduction in the incidence of hypoxia in patients receiving corticosteroids with persistent symptoms (27.8% *vs*. 14.3%) and an increase to 36.7% when given early. However, definitive conclusions about the benefit of corticosteroids cannot be drawn given the small sample size, wide confidence intervals and lack of a control group.

A recent trial compared the effect of 6 mg *vs*. 12 mg dexamethasone in COVID-19 patients with severe hypoxemia, where no statistically significant difference was seen at 28 days in the days alive without life support. However non-hypoxemic patients were not included in this study (*9*). The RECOVERY collaboration group found dexamethasone use with lower 28-day mortality than the usual care group when used in patients with invasive and non-invasive oxygenation, but not in the "not hypoxic" group (RR: 0.95, 95% CI 0.84-1.07) (*2*). Although the investigators report an overall benefit with dexamethasone when given after 7 days from onset of illness, it was not sub-analysed in non-hypoxic patients. Rather, Bahl *et al*. reported mortality benefit in patients when corticosteroids were initiated after 7 days of symptom onset (HR: 0.56, 95% CI 0.33-0.95; p = 0.03). The same was not reported for patients requiring oxygen therapy other than invasive mechanical ventilation (*10*).

A recent systematic review reaffirmed the role of corticosteroids in prevention of disease progression (RR: 0.77; 95% CI: 0.64-0.92; p = 0.005). However, progression was mostly defined as requiring mechanical ventilation/ICU transfer/death, and none of the studies looked at progression from absence of hypoxia to development of hypoxia (*11*).

Numerous studies and meta-analyses have not only shown a strong association between disease severity and mortality with CRP values but also with disease progression (*12,13*). Similarly, in our study high CRP levels at baseline was found to be a predictor of disease progression. However, being a retrospective study, due to limitation of the tests performed an ROC curve could not be generated to get a cut-off value. Diabetes being a known risk factor for COVID-19 severity, it may be a potential confounder. However, on multivariate regression analysis diabetes was not found to be a significant independent risk factor for developing hypoxia in the present study.

The study was limited by a small sample size and lack of a control group of patients with prolonged symptoms not receiving systemic corticosteroids. After the guidelines were notified, most of such patients were initiated on corticosteroids by their treating physicians. Selection bias may have occurred as ours is a tertiary care hospital, more symptomatic patients may have availed the teleconsultation facility. Since this was an interview-based study, as such it is subject to recall bias. The study design may have precluded inclusion of more severe patients and thus missed on patients with poor outcomes.

4. Conclusions

Systemic corticosteroids before day 7 from symptom-onset are harmful and increase the risk of progression to hypoxia in symptomatic patients with mild COVID-19. Corticosteroids given for prolonged symptoms on or beyond day 7 may decrease the risk of progression to hypoxia. A well-designed randomized controlled trial (RCT) is urgently required to address this issue.

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