Outcomes in severe SARS-CoV-2 patients with liberal oxygenation and steroid therapy - a single centre experience

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Real-world reports on outcomes of SARS-CoV-2 infection using higher oxygenation targets along with steroid therapy are lacking. We conducted a retrospective study of patients requiring oxygen support following targets of oxygenation >95% along with steroid therapy and were divided into 3 groups. Group 1 with oxygenation through a nasal cannula or Hudson mask, Group 2 oxygenation with venturi system, and Group 3 with high flow nasal oxygen, 35-50 litres; non-invasive ventilation; mechanical ventilation. One hundred and eighteen patients (Group 1 74 patients, Group 2 15 patients, and Group 3 29 patients) were studied. The mean age was 55.7 years and most were male (n=77). One hundred and fourteen received dexamethasone or methylprednisolone. Most (88.3%) had at least one pre-existing chronic medical illness. Overall mortality was 22.8% (n=27). Group 3 had the highest mortality (75.9%) followed by Group 2 (26.7%) and Group 1 (1.35%). Our observation raises the query if a higher target of oxygenation for non-mechanical ventilated patients coupled with steroid therapy is beneficial.

Key words: Liberal oxygenation, severe Covid, steroid therapy, non-ventilated patients.

Background

Hypoxia is a critical factor in the outcome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. (1) SARS-CoV-2 binds to the angiotensin converting enzyme 2 (ACE2) receptor in nasopharynx and then after a variable period of time, it induces aberrant immune response in a small proportion of affected individuals resulting in a surge of chemokines and cytokines leading to acute lung injury and a pro-coagulant state leading to morbidity and mortality. (2) Lung histology shows features of bilateral diffuse alveolar damage, hyaline-membrane formation, interstitial mononuclear inflammatory infiltrates, desquamation, and mucus plugs with fibrinous exudates. (3) All these features cause hypoxia, which may be either symptomatic or silent. There is lack of clarity and paucity of data on methods and targets of oxygenation for patients who present with hypoxia due to SARS-CoV-2 infection. Current guidelines suggest oxygenation targets of 92-96%, based on evidence from management of acute respiratory distress syndrome (ARDS) due to non-SARS-CoV-2 etiology. (4) It is known that acutely ill hypoxic patients admitted to intensive care have worse outcomes when peripheral oxygen saturation is less than 90% and most accept a target above 90%. (5-7) Even in conventional ARDS, recently published studies such as LOCO2 which compared conservative (saturation 88-92%) versus liberal therapy (saturation >96%), observed excess deaths in the conservative group (hazard ratio 1.62) and increased incidence of mesenteric ischaemia prompting pre-mature termination of study. (8) On the other end of the spectrum, studies on effect of hyperoxemia in nonhypoxic patients with myocardial infarction and stroke have shown that hy-

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peroxemia can cause vasoconstriction and worsen oxygen delivery to myocardial tissue and marginally increase mortality. (9,10) However, in pneumonias and acute pulmonary conditions managed in ward setting, where monitoring is likely to be less frequent unlike intensive care, recommendations have suggested a higher target saturation of 94-98%. (11)

With regards to drug therapy, steroids are not a standard of care for patients with ARDS in the absence of septic shock requiring high dose of vasopressors. (12) Observations of delayed viral clearance due to corticosteroid administration prevented their use in severe acute respiratory syndrome (2003) and middle east respiratory virus (2012). (12) The RECOVERY-trial emerged as a first major study to identify the beneficial effects of steroids in SARS-CoV-2 infected patients requiring oxygen support resulting in a major shift in treatment protocols across the globe. (13) The benefits were subsequently confirmed in a World Health Organisation (WHO) initiated meta-analysis of 7 randomized trials. (14) Since the pandemic struck India later than Europe and United States, we had the opportunity to utilize steroids earlier compared to other countries. We report outcomes of severe SARS-CoV-2 infection requiring oxygen support when a liberal strategy targeting >95% oxygen saturation along with steroid therapy was used.

Methods

We conducted a retrospective study of patients hospitalized between 13th May to 31st July 2020 who were aged ≥18 years, confirmed SARS-CoV-2 infection (diagnosed by reverse-transcriptase polymerase chain reaction [RT-PCR] of oropharyngeal or nasopharyngeal swab) and had severe illness defined as peripheral oxygen saturation (SpO2) <94% (15) at admission or during course of hospital stay. All patients were administered supplemental oxygen. We excluded patients who required mechanical ventilation within 24 hours of hospitalization. Details of age, gender, comorbidities, presenting symptoms, peripheral oxygen saturation on admission, type of oxygen support during course of illness, imaging findings, biochemical tests, and medication administered were recorded. Participants were divided as Group 1 (oxygenation through nasal cannula or Hudson mask), Group 2 (oxygenation with venturi system), and Group 3 (high flow nasal oxygen, 35-50 litres; non-invasive ventilation; mechanical ventilation). Complications observed after hospitalization, duration of stay, and outcome were recorded. Primary outcome assessed was death or discharge to home. Statistical analysis was done using unpaired 't' test, chi-square test, Fischer's exact test, and one way ANOVA as appropriate. A 'p' value <0.05 was considered statistically significant. The study was approved with waiver of informed consent by institutional ethics committee of our hospital.

Results

During the study period of 79 days, 118 hospitalized patients (91 ward patients, 9 patients admitted to high dependency unit, 18 admitted in intensive care unit) satisfied the study criteria. Mean age of study population was 55.7±14.8 years and most were male. **Table 1** describes baseline characteristics at admission across groups. Patients presented for hospitalization on day 5 after symptom onset (mean and median). On admission, the mean peripheral oxygen saturation by pulse oximetry was 91.3±7.6%. Mean oxygen saturation prior to initiation of oxygen was 89.4±6.7%. Seventeen patients were mechanically ventilated after 24 hours of admission. The duration of oxygen requirement was 6 days (median) and 8.7 days (mean). Chest X-ray showed features of pneumonia in 106 of 118 patients and computerized tomography (CT) showed features of pneumonia in 34 of 36 patients (mean CT severity score upon 25 was 13.65). Medication administered were dexamethasone or methylprednisolone (n=114), enoxaparin (n=111), and remdesivir (n=12). Mean duration of hospital stay was 12 days (median 11 days). Eleven patients were discharged on request from patient or caretaker before completion of treatment. Overall mortality was 22.8% (n=27). Group 3 had the highest mortality (75.9%, mechanical ventilated 88.2%) followed by Group 2 (26.7%), and Group 1 (1.35%). The mortality among mechanically ventilated was 88.2%, with non-invasive oxygenation was 11.8%. Mean and median day of death was 12.96 and 11. Of the patients who died, 12 (44%) had septicemia (predominantly due to gram negative organisms), 4 (15%) had acute kidney injury, 3 (11%) had thrombosis (2 acute cerebrovascular event and 1 superior mesenteric artery thrombosis).

Discussion

Studies have shown that healthy, nonsmoking adults have an oxygen saturation of 96-98%. (16) These levels change with age and comorbidities and in elderly over 70 years, especially if they have coexistent cardiac or respiratory disease, saturation levels of 94% are considered acceptable. (17) Despite its extensive use as therapy in patients with hypoxia, oxygen as a drug is poorly understood

and there are controversies regarding methods and targets to be used. We used a higher target of 95-98% based on national guidelines with specific delivery devices, monitoring with peripheral pulse oximetry and up or downregulation based on patient condition (symptoms, breathlessness), and saturation levels. Our study observed a mortality of 11.8% among those needing supplemental oxygen without mechanical ventilation and 88.2% among mechanically ventilated patients. Gram negative sepsis was a major complication that was responsible for increase in mortality in the mechanically ventilated group. The Metcovid trial, which studied the benefit of methylprednisolone observed a mortality of 80% among mechanically ventilated patients and 18.4% among those receiving non-invasive oxygen therapy. (18) The dexamethasone arm of RECOVERY trail observed a mortality of 29.3% in patients requiring mechanical ventilation and 23.3% among those requiring oxygenation without mechanical ventilation. (12) However, the prevalence of at least one preexisting comorbidity was much higher (83.8%) in our study compared to RECOVERY-dexamethasone arm (56%). Further, 18% of patients had 3 comorbidities or more. A metanalysis of 7 trials (n=1703) by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group observed a mortality of 32.7% (222 of 678) among participants who received steroids (hydrocortisone, dexamethasone, or methylprednisolone). (13) The fact that we observed a much lower mortality of 11.8% among non-ventilated patients on oxygen therapy could be attributed to two possible reasons. First, our approach of initiation of oxygen support for a saturation of <94% and targeting a normal saturation could have prevented cellular dysfunction leading to better outcome. Cellular hypoxia upregulates the target receptor, ACE2, for viral entry and could potentially increase severity of SARS-CoV-2 manifestations which is reduced by adequate oxygen administration. (19) Second, less number of patients aged >80 years in our study leading to lowering of age related mortality.

A comparative analysis of oxygen initiation and target policies across 26 countries found a clear association between lower targets of oxygenation and higher case fatality rates. (20) However, the study has not analyzed if the rates differed depending on the need for mechanical ventilation and presence of ARDS. Recent studies discussing oxygen strategies in Covid-19 patients have raised the issue that we may be undertreating hypoxia in these patients due to several differences in the pathophysiology of lung involvement in SARS-CoV-2 compared to ARDS. (19) Multiple clinicopathological processes including effect of ACE2, pulmonary micro-thrombosis and endothelitis, silent hypoxia are all expected to benefit from a strategy of higher target oxygenation.

Limitations of our study include the retrospective design, absence of dynamic recording of fluctuations in oxygen requirement, and use of prone ventilation as decided by treating clinician rather than a practice standard. Further prospective randomized studies on benefits of higher oxygenation targets in patients with diverse risk factors will better inform us on oxygen therapy for the illness.

Conflict of interest

None to declare (all authors).

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None.

Table 1. Comparison of characteristics of study participants

Clinical parameter	Group 1 (n=74)	Group 2 (n=15)	Group 3 (n=29)	p value
Age, years (mean±SD)	51.8±13.6	61.1±16.2	62.9±13.4	0.001
Gender, n (%)				0.75
- Male	48 (65%)	11 (73%)	18 (62%)	
- Female	26 (35%)	4 (27%)	11 (38%)	
Pre-existing illness, n (%)				
- Diabetes mellitus	43 (58%)	12 (80%)	21 (72%)	0.15
- Coronary artery disease	12 (16%)	4 (27%)	7 (24%)	0.49
- Hypertension	31 (42%)	5 (33%)	14 (48%)	0.31
- Chronic lung disease	5 (6%)	1 (7%)	3 (10%)	0.81
- Others	7 (9%)	5 (33%)	10 (34%)	-
Oxygen saturation on admission (%)	93.8±3.9	87.4±9.0	87.0±11.1	0.0005
Investigations				
- Neutrophil-lymphocyte ratio (mean±SD)	4.7±4.07	7.8±3.67	14.33±17.72	0.0005
- D-dimer, mg/l (mean±SD)	0.95±2.51	2.09±2.57	11.28±8.23	0.008
- Serum ferritin, ng/ml (mean±SD)	325±253.9	370±310.3	479±395.1	0.06
- CRP, mg/dl (mean±SD)	7±8.4	9.32±4.58	11.28±8.23	0.07
- Chest X-ray, n (%)				-
- Normal	8 (10.81%)	2 (13.33%)	1 (3.44%)	
- Single lobar opacities	7 (9.45%)	0 (0)	0 (0)	
- Multilobar opacities	59 (79.72%)	13 (86.66%)	28 (96.55%)	

Legend: SD=standard deviation; CRP=C-reactive protein.

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