ORIGINAL ARTICLE

Study of Role of Dexamethasone in Critically Ill COVID-19 Patients at COVID Critical Center

Akshi Goel, Tahleel Mohd Jeelani

Abstract

Background: Coronavirus disease 2019 (COVID-19) is a global pandemic and a substantial proportion of older individuals with COVID-19 develop a respiratory illness requiring intensive care, which can progress to critical illness with hypoxemic respiratory failure requiring prolonged ventilatory support. Corticosteroids reduces systemic inflammation & exudative fluid in the lung tissue and thus prevents further damage to diffuse alveolar tissue, thereby improving the hypoxia and minimizes the risk of respiratory failure. ***Purpose:*** To study clinical characteristics and early outcomes in critically ill patients with COVID-19 receiving dexamethasone. ***Material and Methods:*** In present prospective, interventional study, intravenous dexamethasone was started depending on clinical condition either at admission or when they became hypoxic or when they did not improve with conventional therapy or became critically ill. ***Results:*** Primary outcome was 28-day mortality which was 28%, while secondary outcomes were discharged from hospital within 28 days (82%), invasive mechanical ventilation required (73%), duration of mechanical ventilation (6.3 ± 4.5 days), length of stay in the hospital (13.9 ± 8.4 days). ***Conclusion:*** Intravenous dexamethasone decrease the overall mortality in critically ill COVID 19 patients. Early use of dexamethasone in patients with moderate to severe COVID-19 may prevent progression of disease and improve outcomes.

Key Words

COVID-19, Dexamethasone, Critically ill patients

Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic and a third coronavirus infection in two decades that was originally described in Asia. Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) were the earlier two infections (1).

The majority of COVID-19 infections are either asymptomatic or results in only mild disease. However, a substantial proportion of older individuals with COVID-19 develop a respiratory illness requiring intensive care, which can progress to critical illness with hypoxemic respiratory failure requiring prolonged ventilatory support (2). Complications of COVID-19 seen in critically ill patients, include acute respiratory distress syndrome, myocardial ischemia, myocarditis, acute renal injury, secondary infection, cytokine storm syndrome, pulmonary embolism, and hemorrhagic encephalitis among others (3).

Corticosteroids reduces systemic inflammation and exudative fluid in the lung tissue and thus prevents further damage to diffuse alveolar tissue, thereby improving the hypoxia and minimizes the risk of respiratory failure (4). Earlier based on the experiences in other similar viral

Department of Anaesthesiology and Critical Care, Govt. Medical College, Srinagar (J&K)- India

Correspondence to: Dr. Akshi Goel, Department of Anaesthesiology and Critical Care, Govt. Medical College, Srinagar (J&K). 121/1, Old University Lane Canal Road, Jammu(J&K)

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illness independent reports by Russell *et al*. (5) and Shang *et al*. (6), published in the Lancet commented that corticosteroids should be avoided for the treatment of COVID- 19. Similarly, Word Health Organization (WHO) (7) and COVID-19 Treatment Guidelines Panel (8) also advised against the use of corticosteroids in COVID-19 infection.

Steroids helps to reduce the destructive inflammatory immune response and to treat suspected adrenal insufficiency associated with sepsis, particularly in those with refractory shock. Also, corticosteroids cause immune suppression by impairing the innate immunity, their use has been largely discouraged because of the fear of worsening of viral propagation. However, in patients who are on long term maintenance dose of steroids, there is no increased incidence of development of severe or critical pneumonia in presence of COVID-19 (9).

In the absence of reliable evidence from large-scale randomized clinical trials, there is great uncertainty about the effectiveness of corticosteroids in COVID-19. In present study, we studied clinical characteristics and early outcomes in critically ill patients with COVID-19 receiving dexamethasone.

Material and Methods

Present study was a prospective, interventional study conducted in Department of Anaesthesiology and Critical care, Government Medical College, Srinagar and its associated hospitals. Study duration was 4 months (from April 2020 to July 2020). The Institutional Ethical Committee approval was taken.

Patients, age more than 40 with a confirmed diagnosis of COVID-19 by RT-PCR, admitted in ICU with critical illness. Critical illness was labelled if patient is having any one of the following:

- Exhibited respiratory failure - High respiratory frequency (RR ≥ 30 bpm) and low oxygen index (arterial partial pressure of oxygen (PaO2)/ fraction of inspired oxygen (FiO2) ≤ 200 mmHg) using oxygen delivery devices.
- Septic shock
- Multiple organ dysfunction/failure

Study was explained in local language and a written informed consent was taken from relatives. As per our institutional protocol all these patients underwent standard laboratory/radiological workup and were initiated on parenteral antibiotics (azithromycin with ceftriaxone/ piperacillin + tazobactam/ meropenem), hydroxychloroquine (400 mg twice daily on day 1 and then 200 mg twice daily), low molecular weight heparin and vitamin C. Intravenous fluids, respiratory support (oxygen by nasal prongs/non-rebreathing mask/non-invasive ventilation/mechanical ventilation), other supportive care was provided as per requirement.

Intravenous dexamethasone 8 mg daily for 10 days followed by tapering dose of 4 mg daily for 5 days & discontinued after 5 days as a part of routine institutional protocol in COVID 19 patients. Intravenous dexamethasone was stared depending on clinical condition either at admission or when they became hypoxic or when they did not improve with conventional therapy or became critically ill. The response to therapy was monitored by change in clinical parameters including fever, oxygen saturation, requirement of respiratory support. Patients were discharged after 2 consecutive RTPCR negative swabs. Follow up was kept for 28 days after admission.

Primary outcome was 28-day mortality while secondary outcomes were discharged from hospital within 28 days, invasive mechanical ventilation required, duration of mechanical ventilation, length of stay in the hospital, morbidities due to steroids (serious hyperglycemia, neuromuscular weakness, gastrointestinal bleeding or superinfection). All details were recorded in a case proforma. Statistical analysis was done using descriptive statistics.

Results

Total 22 patients were studied during study duration. Patients mean age was 67.7 ± 5.8 years. Male to female ratio was 1.75: 1. 45 % patients had 3-5 days duration from onset of symptoms followed by 41 % patients with less than 3 days duration from onset of symptoms. At the time of entry in study, 55 % patients were on invasive mechanical ventilation. Diabetes (32%), cardiovascular disease/ hypertension (27%) & chronic lung disease (18%) were common pre-existing conditions in study patients (*Table 1*). Acute respiratory distress syndrome (77%), septic shock (41%), disseminated intravascular coagulation (36%) & acute kidney injury (27%) were common complications developed during treatment (*Table 2*).

Study outcomes of present study are shown in *Table 3*. Five deaths were noted in study patients. Deaths were noted in patients age more than 60 years, with one or more preexisting morbidities, with early onset of symptoms. 73% patients required mechanical ventilation. 82% survivors were discharged within 28 days of

Table 1: Baseline Characteristics of Patients

Baseline Characteristics	No. of Patients	Percentage
Age (in years)		
< 60	6	27%
61 – 75	13	59%
>75	3	14%
Sex		
Male	14	64%
Female	8	36%
Number of days since symptom onset		
<3	9	41%
3-5	10	45%
>5	2	9%
Respiratory support received		
Oxygen by nasal prongs/ non-rebreathing mask	3	14%
Non-invasive ventilation	7	32%
Invasive mechanical ventilation	12	55%
Pre-existing morbidity		
Diabetes	7	32%
Cardiovascular disease/ Hypertension	6	27%
Chronic lung disease	4	18%
Severe kidney impairment	2	9%
Tuberculosis	1	5%
Severe liver disease	1	5%

Table 2: Complications Developed During Treatment

Complications	No. of Patients	Percentage
Acute Respiratory Distress Syndrome	17	77%
Septic Shock	9	41%
Disseminated Intravascular Coagulation	8	36%
Acute Kidney Injury	6	27%
Myocardial Infarction	3	14%
Liver Failure	2	9%

admission. We did not observe any morbidities due to steroids (serious hyperglycemia, neuromuscular weakness, gastrointestinal bleeding or superinfection)

Discussion

The dexamethasone (synthetic pregnane corticosteroid; a cortisol derivative) is a well-known lifesaving, inexpensive, readily available drug commonly used to treat inflammatory and autoimmune conditions.

Table 3: Study Outcomes

Outcome	No. of Patients/ Mean ± SD	Percentage
28-day mortality	5	23%
Discharged from hospital within 28 days (n= 17)	14	82%
Invasive mechanical ventilation	16	73%
Duration of mechanical ventilation (in days)	6.3 ± 4.5	-
Length of stay in the hospital for survivors (in days)	13.9 ± 8.4	-
Time (in days) from treatment initiation to death.	4.6 ± 2.7	-

The mechanism of action of dexamethasone is diverse, with many effects on various body systems. It is widely used for the treatment of rheumatic problems, skin diseases, asthma, many forms of allergies, chronic obstructive lung disease, brain edema, bronchospasm, etc.

"Cytokine Release Syndrome" or CRS is a phenomenon thought to be implicated in serious COVID-19 illness. As evidenced by multiple studies, early identification of hyperinflammation, and its management using existing, approved therapies such as steroids, intravenous immunoglobulins, selective cytokine inhibitors should be done to prevent mortality in serious COVID-19 patients, has been recommended (10). Cytokine storm is a hyperinflammatory state resembles secondary hemophagocytic lymphohistiocytosis (HLH), a major contributing factor in COVID-19-associated mortality. Immunosuppression from corticosteroids has been proposed as a treatment option for such hyperinflammation (10).

Studies in patients with SARS and MERS suggests that receiving corticosteroids did not have an effect on mortality, but rather there is delayed viral clearance. So earlier it was suggested that corticosteroids should be avoided for the treatment of COVID- 19 (11,12). The Surviving Sepsis Campaign COVID-19 recommended against the routine use of systemic corticosteroids in mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS). However, the experts supported a weak recommendation to use low-dose, short-duration systemic corticosteroids in the sickest patients with COVID-19 and ARDS (13).

Later, government of India also recommended IV

methylprednisolone 0.5 to 1 mg/kg OR dexamethasone 0.1 to 0.2 mg/kg for 3 days (preferably within 48 hours of admission or if oxygen requirement is increasing and if inflammatory markers are increased) in clinical management of moderate cases. While for patients with progressive deterioration of oxygenation indicators, rapid worsening on imaging and excessive activation of the body's inflammatory response, they recommended methylprednisolone 1-2 mg/kg/day or dexamethasone 0.2-0.4 mg/kg/day. A precautionary note added, that a larger dose of glucocorticoid will delay the removal of coronavirus due to immunosuppressive effects (14).

In the Randomized Evaluation of COVID-19 therapy (RECOVERY Trial) (15), a prospective multicentric study, significantly lesser number of deaths within 28 days, shorter duration of hospitalization and an earlier likelihood of discharge was noted in dexamethasone cohort compared to the standard of care cohort. Also, positive response to dexamethasone therapy was noted within the first 7 days of dexamethasone therapy. Similar results were noted in present study.

The greater mortality benefit of dexamethasone in patients with COVID-19 who required respiratory support, and among those recruited after the first week of their illness, suggests that at this stage the disease is dominated by immunopathology, with active virus replication playing a secondary role (15). Studies with corticosteroid intervention in patients with mild to moderate COVID 19 not requiring oxygen, did not noted any significant benefit to patients (15,16).

In another similar study, Villar *et al*. (17) studied effects of dexamethasone in patients with moderate-to-severe ARDS receiving lung-protective mechanical ventilation. They noted that treatment with IV dexamethasone 20 mg once daily on day 1-5, followed by 10 mg once daily on days 6-10 resulted in reduced duration of mechanical ventilation and reduced overall mortality compared with conventional treatment alone.

Major limitations of present study were, not blinded study, no placebo/control group, fixed dose of dexamethasone. Further research is needed to define the exact role of corticosteroids in patients with COVID-19 at a high risk of clinical deterioration, identified early in the disease course using prognostic markers or clinical prediction tools.

Conclusion

Intravenous dexamethasone decreases the overall mortality in critically ill COVID 19 patients. Early use of dexamethasone in patients with moderate to severe COVID-19 may prevent progression of disease and improve outcomes.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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