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Research Article

The Effect of Dexamethasone on Outcome of Patients with Severe COVID-19. A Retrospective Cross Sectional Study

Carlos Andres Munoz Tello[1], Alyanna Marie B Manego[2], Carol Mfoniso Etudor[3], Joseph A Manuel[2], Fizza Mohsin[4], Levis Abin Joy[5], Purnadeo Persaud[6], Muhammad Umar Farooq Azam[7], Sidra Naz[8], Muhammad Ijaz Khan[9], Muhammad Shah Zaib[10], Muhammad Hanif[11*]

[1]Universidad Catolica de Cuenca, Ecuador

[2]University of Santo Tomas, Muntinlupa City, Philippines

[3]Avalon University School of Medicine, Texas, USA

[4]King Edward Medical University Lahore, Pakistan

[5]Government Medical College, Thiruvananthapuram, India

[6]Kansas City University, MO, USA

[7]Brookdale Hospital, NY, USA

[8]University of Health Sciences Lahore, Pakistan

[9]University Hospital Kerry, Tralee, Ireland

[10]Bay Health Medical Center Dover, DE, USA

[11]Hayatabad Medical Complex, Peshawar, Pakistan

[*]Corresponding author: Muhammad Hanif, Hayatabad Medical Complex, Peshawar, Pakistan

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Abstract

Introduction: Severe manifestation of Coronavirus disease 2019 (COVID-19) appears to be linked to massive inflammatory response. Glucocorticoids may help to prevent respiratory failure and death by modulating inflammation-mediated lung damage. Nonetheless, there is little conclusive evidence that it is effective in COVID-19 patients.The current study was

proposed to see the differences in several outcomes between the severe COVID-19 patients who received usual care plus dexamethasone (the dexamethasone group), The current study was proposed to see the differences in several outcomes between the severe COVID-19 patients who received usual care plus dexamethasone (the dexamethasone group), and those who did not receive dexamethasone (the usual care group).

Methods: This retrospective study was conducted at Hayatabad Medical Complex Peshawar Pakistan (Isolation units for COVID-19). Patients with severe COVID-19 admitted to hospital from March to July 2020 were included in the study. Data was collected using structured format. Mean differences were calculated using independent sample t test whereas Chi square test was used for determination of association.

Results: A total of 193 patients were included in the final analysis. No significant difference in age, gender, respiratory rate, C-reactive protein, and lactate dehydrogenase between the groups was observed. Patients who received usual care plus dexamethasone were discharged earlier from hospital (8.20 ± 1.90 vs. 11.20 ± 2.40, p< 0.001), and had low percentage of mechanical ventilation (MV) requirement (15.10% vs. 28.30%, p = 0.02). Overall mortality was low in dexamethasone group, however no difference in mortality rate between both the two groups was noted (9.80% vs. 19.70%, p = 0.058). Furthermore, in comparison to the usual care group, mortality rate in patients on MV was lower in dexamethasone group (56.50% vs.23.50%, p = 0.03).

Conclusion: Patient who received usual care plus dexamethasone had lower hospitalization days; proportion of patients receiving mechanical ventilation as well as days on MV was lower as compared to usual care group. Similarly, mortality in patients requiring MV was also low in dexamethasone group. Large scale experimental studies are needed to confirm these findings.

Keywords: COVID-19; Dexamethasone; SARS-CoV-2; ARDs; Corticosteroids

1. Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic and a serious public health concern, first case of which was officially reported in Wuhan, China, in December 2019 [1]. COVID-19 mostly affects the pulmonary system. Patients mostly reported vague symptoms such as shortness of breath, fever, and cough. However, various studies indicate that COVID-19 may affect other organs and systems as well [2, 3]. COVID-19 infection may cause various complications; one of them is that it may cause pneumonia [2, 4]. Mortality in severe COVID-19 is mainly attributed to respiratory failure. Overwhelmed inflammation in COVID-19 appears to be linked with severe manifestation of Coronavirus disease [5]. An initial pneumonic phase with significant radiologic opacity and, on autopsy, diffuse alveolar destruction, inflammatory infiltrates, and microvascular thrombosis are the etiologic characteristics of severe COVID-19 [6].

Various treatments are used in COVID-19 pneumonia, including corticosteroids. The use of corticosteroids is considered as routine treatment to reduce the inflame-mation associated with injury [5]. In patients with severe COVID-19, inflammatory organ injury could occur with raised inflammatory markers such ferritin, C-reactive protein, interleukin-1, and interleukin-6 in a subset of individuals. Several treatment strategies have been recommended to reduce inflammatory organ harm in viral pneumonia; however the effectiveness of glucocorticoids has been questioned. Corticosteroids are

indicated as a treatment option for viral pneumonia because they decrease inflammatory mediators. Although studies have indicated that corticosteroids could significantly reduce excessive inflammatory reactions, they also have the potential to impede the virus's clearance and cause severe side effectsn [6, 7]. National clinical guideline for treatment of COVID-19 in Pakistan also suggested use of dexamethasone in severe cases [8]. There are various clinical trials going on globally, however, there is no local data related to efficacy of dexamethasone in improving prognosis in patients with severe COVID-19. The aim of this study is to evaluate the impact of dexamethasone on outcome of patients with severe COVID-19. This study will aid clinician in making decision for use of dexamethasonein patients with severe COVID-19.

2. Materials and Methods

2.1 Study design and population

This retrospective study was conducted in COVID-19 isolation units of Hayatabad Medical Complex, Peshawar Pakistan from March to July 2020. Patients requiring mechanical ventilation on admission were excluded from the study. Patients were classified as having severe COVID-19 based on national clinical guideline, issued by ministry of national health services [8].

2.2 Data collection

Patients were stratified into two groups: those who received usual care plus dexamethasone (the dexamethasone group), and those who did not receive dexamethasone were designated the usual care group. Dexamethasone dose of 6 mg was used via intravenous route in these patients. Gender, age, respiratory rate, oxygen saturation, C-reactive protein, and lactate dehydrogenase were noted in self-structured format. Length of hospital stay, need for mechanical ventilation (MV), number of days on MV, and mortality was also noted and compared for both groups.

2.3 Ethical consideration

The hospital ethical and review board approved the study (Ref.No: 138/HEC/B&PC/21). Written informed consent was waived by the ethical and review board of the hospital.

2.4 Data analysis

The collected data were analyzed using SPSS Version 21.0 (IBM Corp, Armonk, NJ). Mean and standard deviation (SD) were calculated for variable for with continuous nature. Frequency and proportions were calculated for categorical variable. Association was determined using Chi-square test or Fischer exact test where appropriate. Independent t-test was used for mean comparison. P value < 0.05 was taken statistically significant for tests.

3. Results

Out of One hundred and ninety-three patients with severe COVID-19 who were included in the study, 112 (58.03%) received usual care plus dexamethasone and thus considered as dexamethasone group, while 81 (41.97%) did not receive dexamethasone and therefore were classified as usual care group. Fifty seven percent of the patients were male. In terms of age, gender, respiratory rate (Breath per minute), C-reactive protein (CRP), lactate dehydrogenase, and oxygen saturation (%) no statistically significant differences between the two groups were observed as shown in Table 1. Patients who received usual care plus dexamethasone were discharged earlier from hospital (8.20 ± 1.90 vs. 11.20 ± 2.40, $p < 0.001$), and had low percentage of mechanical ventilation (MV) requirement (15.10% vs. 28.30%, $p = 0.02$). Similarly, length of MV was significantly lower in dexamethasone group compared to usual care group ($p < 0.001$). Overall mortality was low in dexamethasone group, however no difference in

mortality rate between both the two groups was noted (9.80% vs. 19.70%, p = 0.058). Furthermore, mortality rate in patients on MV was lower in dexamethasone group (23.50% vs. 56.50%, p = 0.03) compared to the usual care group. The details are given in Table 2.

Characteristics	**Usual care plus Dexamethasone (n=112) Mean ± SD**	**Usual care only (n=81) Mean ± SD**	**p-value**
Age(years)	49.0 ± 11.0	52.0 ± 12.0	0.07
Respiratory rate (BPM)	29.1 ± 5.2	28.3 ± 4.9	0.22
CRP (mg/L)	108.2 ± 16.2	112.8 ± 19.8	0.07
LDH (IU)	305.2 ± 87.2	312.3 ± 90.3	0.58
Oxygen saturation	87.2 ± 4.6	86.1 ± 4.9	0.11

SD; standard deviation

Table 1: Characteristics of the patients with severe COVID-19.

Characteristics	**Usual care plus Dexamethasone (n=112) Mean ± SD**	**Usual care only (n=81) Mean ± SD**	**p-value**
Length of hospital Stay (mean ± SD)	8.20 ± 1.9	11.2 ± 2.4	< 0.001
Mechanical ventilation requirement n (%)	17 (15.1%)	23 (28.3%)	0.02
Length of mechanical ventilation (mean ± SD)	9.1 ± 2.3	12.2 ± 3.6	< 0.001
Overall mortality,n (%)	11 (9.8%)	16 (19.7%)	0.058
Mortality in patients requiring mechanical ventilation, n (%)	4 (23.5%)	13 (56.5%)	0.03

Table 2: Outcomes in patients with severe COVID-19.

4. Discussion

Unfortunately, no definite, effective pharmaceutical treatment, so far, had been revealed to noticeably change the outcome in terms of mortality COVID-19 patients except for dexamethasone. Well-timed identification and determination of potential drug to reduce and deter the world crisis is the utmost need of the present. A number of drugs such as antivirals, antibiotics (azithromycin), and hydroxychloroquine have been tested, however no conclusive result had been reported [9]. In clinical practice, corticosteroids have been used to treat severe pneumonia. However, whether or not corticosteroids should be given in COVID-19 patients was a point of contention. According to some researchers, clinical evidence does not support corticosteroid treatment for COVID-19 [10]. The Chinese management guideline for COVID-19, on the other hand (version 7.0), and a group of Chinese front-line doctors proposed that short-term low-dose corticosteroids can be used safely in COVID-19 patients [11]. As a result, support for the use of corticosteroids in COVID-19 patients is critical.

Currently, the guidance of corticosteroids is primarily

taken from their use as part of potential life-saving treatment during the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks [12]. In the recent past, a number of studies have investigated the usefulness of corticosteroids. One study claimed that COVID-19 and ARDS patients treated with methylprednisolone have reported lower risk of mortality [13]. Similar, results have been reported from Spain [14]. Besides, a study on hospitalized patients in Wuhan the epicenter of COVID-19 supplemented the use of corticosteroids in reduction of the duration of supplementary oxygenation [15]. On the other hand, various studies have cautioned against the use of steroids in early in the disease course of COVID-19, referring to their likely immunosuppressive nature as demonstrated by their use in the earlier pandemics [10]. In MERS-CoV individuals on a corticosteroid treatment, for example, virus elimination from the respiratory system was delayed [16]. Likewise, in SARS-CoV-1, the steroid group had considerably decreased hematologic viral RNA elimination; however the result was not measured [17]. As a result, the effectiveness of corticosteroids in the treatment of non-severe COVID-19 infection is unknown. This retrospective study analyzed the differences in several outcomes between the severe COVID-19 patients who received usual care plus dexamethasone (the dexamethasone group), and those who did not receive dexamethasone (the usual care group). There are no significant differences in age, gender, respiratory rate, CRP, LDH and oxygen saturation. Keeping in view the CRP and LDH levels both groups were likely to be in a similar inflammatory condition.

In this study, patients who had received dexamethasone plus usual care were discharged earlier, compared to those who had not received dexamethasone. Similarly, those patients' who required mechanical ventilation and their duration was significantly lower in patients who had received dexamethasone plus usual care, compared to those who had not received dexamethasone. In COVID-19 patients on mechanical ventilation, dexamethasone reduced mortality; however, there was no significant difference in mortality rates between the two groups. In COVID-19 associated pneumonia, there is secretion of inflammatory chemokines such as tumor necrosis factor-alpha (TNF-α). These chemokines are released by neutrophils, which results in fluid accumulation [18]. This fluid accumulation eventually causes ARDS, which is major reason and contributor for mortality in patients with COVID-19 [18]. Dexamethasone inhibits the release of inflammatory chemokines by immune cells [19]. The increase in inflammatory chemokines in COVID-19 and dexamethasone ability to inhibit them is the rationale behind using dexamethasone in patients with COIVD-19, as it may reduce inflammation in lungs and improve prognosis [19]. Interim data of RECOVERY trial was published in June 2020, based on these results it is recommended to use dexamethasone in COVID-19 positive patients receiving respiratory support in the United Kingdom [20]. Our results showed low overall mortality in dexamethasone group; however no difference in mortality rate between both the two groups was noted. Likewise, mortality rate in patients on MV was lower in dexamethasone group compared to the usual care group. This is consistent with the results of RECOVERY trial, where dexamethasone was associated with reduced deaths in mechanically ventilated patients. In RECOVERY trial, dexamethasone was found to reduce deaths by one-third in COVID-19 ventilated patients, and by one fifth in otherCOVID-19 patients receiving oxygen only.

However, dexamethasone showed no benefits among patients who did not required respiratory support [6]. In a retrospective study in March 2020 conducted by Wu C

et al. found that in patients who had progressed to ARDS, mortality was higher in patients who have not received methylprednisolone in comparison to other who received methylprednisolone [2]. Glucocorticoids have been previously used in other disease that resembles COVID-19 such as Severe Acute Respiratory Syndrome (SARS), Middle East respiratory syndrome (MERS), severe influenza, and community-acquired pneumonia. However, the evidence was weak [16, 21-23]. These studies also found that glucocorticoids may impair host ability to produce response to delayed viral clearance, which has reinforced concerns that corticosteroids may impair host response to viruses [16, 21-23]. So far no published study is available from this part of the world, and perhaps this is the first one from Pakistan to explore the impact of dexamethasoneon outcome in patients with severe COVID-19. The study had its limitation as well. The worth mentioning limitation is the respective study design hence pertinent information in terms of clinical parameters collected and analyzed and hence data is limited. Another limitation is lack of diversity of sample due to the single study center. More over selection bias cannot be overruled due to some fatal case exclusion. As the COVID-19 spread across the world, clinicians are struggling to weigh the potential benefits of corticosteroids against the much potential harm associated with these drugs. Further large-scale multicenter trials should be conducted to determine the efficacy with urgency, given the nature of situation.

5. Conclusions

In this study, dexamethasone reduced mortality in patients on mechanical ventilation; however, there was no significant difference in mortality rates between the two groups. There was reduced hospital stay, requirement of mechanical ventilation and number of days on mechanical ventilation. There is contradictory data available related to use of corticosteroids in COVID-19 and similar infections. It is important that large scale multicenter clinical trials should be conducted in local level to assess the efficacy and address the concerns associated with dexamethasone in COVID-19.

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