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The choice of steroids in severe-critical COVID-19 and outcome: A Retrospective Cohort Study from Northern Areas of Pakistan

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ABSTRACT

Background: Covid-19 revealed as global pandemic during year 2020. Until July 2021, the death toll reached 4.15 million. The Recovery trial proved mortality benefit in group of patients who were treated with dexamethasone. However, methylprednisolone has better penetration and half-life in alveoli. There are some internationally published studies showing more beneficial effects in terms of fatality for using high dose methylprednisolone in comparison to dexamethasone. The purpose of this study is to see the difference in efficacy of two steroids i.e. dexamethasone versus methylprednisolone in patients admitted in COVID-ICU Aga Khan Medical Centre Gilgit, Northern Areas of Pakistan with severe-critical COVID.

Methodology: The medical records of all adult patients who were admitted to the ICU at Aga Khan Medical Centre Gilgit, Northern Areas of Pakistan with severe-critical COVID 19 were reviewed from September 2020 till August 2021 over a period of one year. Patients taking chronic steroid therapy, those with mortality within 24 hours of admission and patients with incomplete medical record were exempted.

Results: A total of 89 patients were enrolled during the study time. Along with the standard treatment, 54 patients were given dexamethasone and 27 patients were given methylprednisolone. A 3rd cohort of 8 patients received dexamethasone for the first two days followed by methylprednisolone. There was no significant difference between three groups in terms of demographics and clinical presentation. The overall mortality in this study was 29.2%. No statistical difference in terms of use of inotropic/ vasopressor support, assisted ventilation (invasive & non-invasive) and length of hospital stay were found.

Conclusion: Dexamethasone and methylprednisolone are both equally efficacious in treatment of severe-critical covid-19 disease.

Key words: COVID; Methylprednisolone; Dexamethasone; Mortality

Introduction

COVID emerged as clusters of acute respiratory illnesses. It was initially reported inside Wuhan, Hubei province China during December 2019 and announced as pandemic by World Health Organization (WHO) during March, 2020.[1] Until July 2021, 194 million cases have been reported with 4.15 million deaths globally due to COVID-19.[2]

Corticosteroids are already being utilized to treat many pulmonary diseases such as asthma and COPD. There are studies showing good response of early use of corticosteroids in COVID-19 as they reduce inflammation. A large Michigan study showed good result with prompt brief course of methylprednisolone.[3] Also the RECOVERY trial report published on June 16, 2020 proved mortality benefit in group of patients who received dexamethasone in contrast to the group of patients that had not received it.[4] Following this trial WHO and majority of healthcare institutions regulations have now recommended systemic corticosteroids in the management of COVID-19 meanwhile other trials are being halted.[5,6] However it is not clear so far whether the result was a peculiar outcome of dexamethasone or it was a general corticosteroids group outcome. Hence it was not clearly defined regarding any specific corticosteroid that could be utilized preferentially.

Although it is evident that among corticosteroids methylprednisolone is medically favored due to its more anti-inflammatory property but to achieve its therapeutic effect high dose is required.[7-10] There are internationally published studies showing more beneficial effect in fatality for using high dose methylprednisolone in comparison to dexamethasone.[1,6,11-12] It has also been found in a multicenter study in Pakistan comparing two corticosteroids i.e. methylprednisolone and dexamethasone as uniformly efficacious for management of moderate to severe COVID-19.[12]

The focus of this research intends to find the choice of steroids in management of severe-critical COVID-19 patients by observing the medical consequences of patients who received dexamethasone in comparison to those who received high dose methylprednisolone and those who received combination of both with dexamethasone initially followed by methylprednisolone later on at Aga Khan Medical Centre Gilgit, Northern Areas of Pakistan.

Objectives

To find the difference in efficacy of methylprednisolone versus dexamethasone in the management of severe and critical COVID-19 patients admitted in COVID ICU Aga Khan Medical Centre Gilgit, Northern Areas of Pakistan.

Methodology

It was a retrospective cohort study. Data was collected from the medical record system, Hospital Information Management System (HIMS) of the Aga Khan Medical Centre Gilgit, Northern Areas of Pakistan. All COVID-19 PCR positive patients of age 18 years and above presented to intensive care unit (ICU), Aga khan Medical

Table 1. Baseline demographic characteristics and comorbidities of study participant

Characteristics	Dexamethasone	Methylprednisolone	Combination	P-Value
Age (median)	64.50	72	64	0.217
Gender				
Male	38 (62.3%)	17 (27.9%)	6 (9.8%)	
Female	16 (57.1%)	10 (35.7%)	2 (7.1%)	0.764
Comorbidities	27 (56.2%)	15 (31.2)	6 (12.5%)	0.472
Addiction	2 (33.3%)	3 (50.0%)	1 (16.7%)	0.308
Severity of Covid				
Severe	14 (53.8%)	7 (26.9%)	5 (19.9%)	0.110
Critical	40 (63.5%)	20 (31.7%)	3 (4.8%)	
APACHE SCORE (median)	8	9	8	0.753
Use of Oxygen/Ventilatory Support				
Non-Rebreathing Mask	15 (62.5%)	5 (20.8%)	4 (16.7%)	0.20
Non-Invasive Ventilation	31 (59.6%)	19 (36.5%)	2 (3.8%)	0.071
Invasive Ventilation	8 (61.5%)	3 (23.1%)	2 (15.4%)	0.619

APACHE= acute physiological assessment and chronic health evaluation; NRM= Non-Rebreather mask; NIV= Non-invasive ventilation

Centre Gilgit from 1st September, 2020 to 31st August, 2021 with the diagnosis of severe and critical COVID-19 according to WHO guidelines on management of COVID-19 were reviewed. Patients with mild or moderate COVID-19 according to WHO definition of severity, those having incomplete medical record, patients on chronic steroid therapy, patients with immunosuppressive disorders, patients having any contraindication for steroids use, and those who died within 24 hours of admission were exempted from the study. Data collector reviewed patients' files and filled the study proforma after obtaining permission from ethics review committee Aga Khan Health Service Pakistan (AKHSP) Gilgit with approval number AKMCG/2022/1001. No identifier of the patients was recorded. Patients' demographic variables including age, gender, co-morbid conditions, addiction history and acute physiological assessment and chronic health evaluation II (APACHE II) score were collected. In addition, data regarding use of type of steroid and relevant outcomes, including vasopressor and ionotropic requirement and duration, type of ventilation, number of days on mechanical ventilation (MV), length of hospital admission and deaths of patients during hospital stay were collected. The data were categorized by the type of steroid use (i.e. Dexamethasone, methylprednisolone, combination of dexamethasone and methylprednisolone). The included patients were followed for the measurement of intended outcomes.

R Studio 4.1.2. (R Foundation for Statistical Computing) was used to perform analyses. Descriptive analyses are presented as median estimates for quantitative variables (age, ICU admission APACHE score, etc.), while qualitative variables (gender, history of addiction etc.) are presented as frequencies with percentages. All variables were studied using stratification analysis to compare steroid groups. The Shapiro-Wilk test was used to test the assumption of normality for the numerical variables. Analysis of variance (ANOVA) was used to determine whether there was a statistically significant difference between steroid groups based on the normality assumption. Furthermore, the z-score proportion test was used to compare each category of qualitative variables under each steroid group. P-value less than 0.05 was considered the significant threshold.

Results

Total 89 subjects were enrolled in this study. Out of those, 54 patients were given dexamethasone along with standard treatment, 27 patients were given methylprednisolone along with standard treatment and 8 patients received both dexamethasone initially and methylprednisolone later on along with standard treatment. The baseline statistics in this study is shown in table 1. As demonstrated in table 1, there were no significant differences between three groups regarding demographic features, presence of comorbidities, history of addiction, disease severity and APACHE score at admission and use of oxygen support.

Discussion

Corticosteroids are a group of anti-inflammatory medicines used for the treatment of a wide range of conditions. They have got prime focus for the treatment of covid-19 especially after the largest UK trial, the RECOVERY trial. This is evident that subjects having COVID-19 produce high amount of cytokines and autopsy findings of alveolar damage have been demonstrated in these patients. Cytokines are considered steroid sensitive. Studies have been published showing good clinical outcome and beneficial effects in terms of mortality by using corticosteroids in

Table 2. Secondary outcome variables of the study participants

Characteristics	Dexamethasone	Methylprednisolone	Combination	P-value
Ionotropic support	4 (66.7%)	1 (16.7%)	1 (16.7%)	0.411
Vasopressor support	4 (57.1%)	2 (28.6%)	1 (14.3%)	0.696
Use of NIV	31 (59.6%)	19 (36.5%)	2 (3.8%)	0.071
Use of IV	8 (61.5%)	3 (23.1%)	2 (15.4%)	0.619
NIV days (median)	7	7	11.50	0.928
IV days (median)	3.5	10	12.5	0.647
Length of hospital stay				
< 7 days	10 (62.5%)	6 (37.5%)	0	0.351
7 -14 days	28 (59.6%)	15 (31.9%)	4 (8.5%)	0.938
>14 days	16 (61.5%)	6 (23.1%)	4 (15.4%)	0.314

IV= Invasive ventilation; NIV= Non-invasive ventilation

COVID-19. The largest trial, RECOVERY trial, was a multicenter, randomized controlled trial which concluded mortality benefit in patients using dexamethasone 6 mg once daily for a duration of 10 days. The effects were more pronounced in subjects on mechanical ventilation. Multiple retrospective analyses have been published showing mortality benefit and better clinical outcome in patients using methylprednisolone in COVID subjects.[3,13-16]

In this study we compared two types of steroids (dexamethasone, methylprednisolone, combination of dexamethasone initially and methylprednisolone later) with baseline claim that the methylprednisolone has more anti-inflammatory activity and good lung penetration and half-life. Also researchers had suggested better outcome in patients taking methylprednisolone for the management of covid-19 along with improvement in terms of respiratory complications.[16] Although the patients in the dexamethasone group had more comorbidities, the difference in outcome in both groups was not statistically significant in our study.

Studies have been conducted to see the difference in efficacy of methylprednisolone versus dexamethasone in subjects with COVID-19 with variable results. Study by Ranjbar K et al showed that those patients who received methylprednisolone had better results and lesser need of invasive mechanical ventilation as compared to patients who received dexamethasone.[1] Although the study had a number of limitations like small sample size and limited information regarding complications, test reports and CT findings, the researchers were able to demonstrate this important finding. Similarly study by Pinzo`n MA et al concluded that managing severe COVID-19 patients by using heavy dose methylprednisolone for three days followed by oral prednisolone for next 14 days had statistically significant reduced healing time, less need for transfer to intensive care facility and low level of severity markers including C reactive protein, D-Dimers and lactate dehydrogenase.[6] Similar results were of Ko JJ et al who demonstrated decreased mortality rate with sufficient doses of methylprednisolone as compared to dexamethasone.[11]

Our study results coincide with a multicenter study by Fatima SA et al conducted in Pakistan to see the efficiency and safety of dexamethasone and methylprednisolone in patients with moderate to severe COVID disease.[12] They reported that both drugs have same efficacy in treating moderate to severe COVID-19. There were total 100 patients enrolled in their study, out of those 35 subjects were enrolled in dexamethasone group and 65 were in the methylprednisolone group. Mean age was 57.91 years. Like in our study the patients who received dexamethasone in this study were sicker as they had comorbidities and therefore had required more intensive care facility and mechanical ventilation apart from oxygen inhalation. Statistically there was no significant difference in terms of primary and secondary outcomes between two groups. Limitations of their study included unequal number of patients in both groups and non-inclusion of control group.

Our study has several limitations. First, it was a retrospective study and data was collected from hospital medical record compared with prospective studies that require individual patient consent. Second, number of patients is not equal in each study group. Third, it is a single centered study conducted on subjects of a specific locality hence its results cannot be generalized for a wider population around the globe.

Conclusion

Both dexamethasone and methylprednisolone have same efficacy in the treatment of severe-critical COVID-19 disease. There is no difference in mortality and morbidity associated with both types of corticosteroids. Large scale randomized controlled trials are recommended to compare the efficacy of both steroids in patients with severe critical COVID.

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