Original Article

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Biochemistry Section

Effectiveness of Dexamethasone as an Adjunct Drug in Treatment of Critical COVID-19 Patients: An Observational Single Cohort Study

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ABSTRACT

Introduction: Corticosteroids have shown controversial results in severe infections. Limited data is available to prove the efficacy of this drug against Coronavirus Disease 2019 (COVID-19) infection. Such studies have highlighted that steroids such as dexamethasone can be effective against the patients who are exhibiting severe symptoms of COVID-19.

Aim: To determine the effectiveness of dexamethasone as adjunct drug in treatment of critical COVID-19 patients.

Materials and Methods: This observational single cohort study was conducted on 50 COVID-19 positive patients admitted to the tertiary care hospital, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India during August 2020 to October 2020. Critically ill-patients suffering from COVID-19 receiving 6 mg dexamethasone along with standard treatment protocol as prescribed by the Indian Council of Medical Research (ICMR) were included in the present study. Serum interleukin-6, D-dimer, ferritin levels along with Cycle threshold (Ct) values from RT-PCR of nasopharyngeal and oropharyngeal swab were recorded on the day of admission and after 7 days of dexamethasone therapy along with standard treatment protocol of ICMR. The data was analysed using descriptive statistics and paired-t test.

Results: There were 22 males and 28 females enrolled in the study with mean age of males as 55 years and mean age of females as 56 years. The mean weight of males was 68.4 kg, while the mean weight of females was 59.8 kg. Statistically significant decrease in serum levels of interleukin-6, D-dimer, and ferritin after 7 days of dexamethasone treatment along with standard treatment protocol of ICMR was observed. The results were found to be different with p-values=0.001, 0.003 and 0.002, respectively.

Conclusion: Dexamethasone, as an adjunct drug, is an important corticosteroid that is efficient in countering the inflammatory response generated in COVID-19 patients along with standard treatment protocol of ICMR. It reduces the inflammatory markers in patients suffering from COVID-19.

Keywords: Coronavirus disease 2019, Cytokine storm, D-dimer, Ferritin, Inflammation, Interleukin-6, Real time-polymerase chain reaction

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease affecting the respiratory system of an individual [1]. The origin of this viral infection is quite controversial with the majority of evidence highlighting bats as the source of origin [2]. The novel nature of the disease, rapidly increasing positive cases, and its associated mortality acted as a triggering factor for discovering new and improved prevention and treatment modalities [2].

The standard treatment protocol as prescribed by ICMR, India was based on administering hydroxychloroquine to COVID-19 patients with moderate to high severity of infection [3]. This treatment also involved standard care such as treatment of each arising symptoms. Several controversial research findings proved this treatment protocol as statistically inefficient [4,5]. At the same time, countries such as the United States and the United Kingdom prescribed the use of corticosteroid dexamethasone for the treatment of patients with moderate or high severity of disease [6-8]. Dexamethasone is an important steroid that is normally prescribed in patients suffering from different inflammatory diseases such as rheumatoid arthritis, allergies, asthma, pneumonia [9]. Its use in treating critically ill-patients with COVID-19 is still controversial [10].

Though there are different studies that have evaluated the function of some of the markers for diagnosing the severity of COVID-19 [6,11], there are only limited studies that have actually studied all these markers together. Such study could be essential for planning treatment appropriate to patient condition [12,13]. The present study was conducted on COVID-19 patients with severe symptoms, receiving 6 mg of dexamethasone along with standard treatment protocol of ICMR. This study forms a baseline for future studies or future use of this drug for patients suffering from COVID-19.

MATERIALS AND METHODS

This observational single cohort study was conducted out on critically ill COVID-19 positive ill-patients admitted to the tertiary care hospital, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India, from August 2020 to October 2020. The study was conducted after obtaining Ethical Clearance from the Institution (Ethical clearance number Patho:232/2020 dated 24.08.2020). The patients were enrolled in the study after taking prior informed consent.

Inclusion criteria: All the patients who were showing symptoms of severe COVID-19 infection as laid down by the Government of India viz., severe pneumonia with SpO_2 <90%, or acute respiratory distress syndrome were included in the study [14].

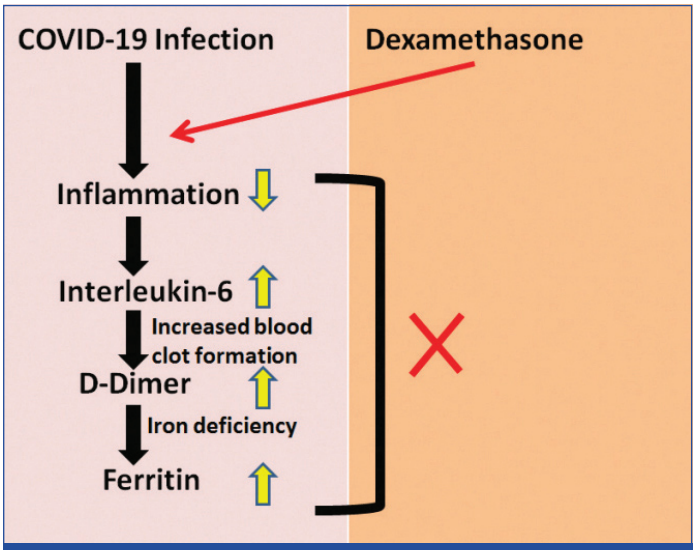
Exclusion criteria: The patients who did not fulfill the severity criteria let down by Ministry of Health and Family Welfare were excluded from the study irrespective of gender or age [14].

During the study period, 58 patients were enrolled in the study out of which eight patients were reported as lost to follow-up. Final sample size was 50 patients. These patients were given 6 mg dexamethasone as treatment protocol as an adjunct along with standard treatment protocol of ICMR.

Procedure

The current observational study was compiled using the data obtained from critically ill-patients suffering from COVID-19. Total 4 mL blood was taken in red vacutainer and the blood was allowed to clot for 30 minutes. It was later centrifuged at 3500 rpm for 17 minutes and the serum was separated for performing biochemical tests. Ferritin and D-dimer was performed on Vitros 5600 using chemiluminescence method, and interleukin-6 was performed using Immulite 2000 Xpi using chemiluminescence method. The Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test was performed using commercially available kit Labgun exofast by Labgenomics, using the protocol provided by the manufacturer. The primers and probes were included in the ready to use mastermix of the kit [15,16].

The mechanism of action of dexamethasone is given in [Table/Fig-1]. The results of ferritin, interleukin-6, D-dimer, and RT-PCR of study participants were recorded on day 0 and day 7 of dexamethasone treatment along with standard treatment protocol of ICMR.



[Table/Fig-1]: Proposed mechanism of action of dexamethasone in COVID-19 patients.

STATISTICAL ANALYSIS

The results obtained from the study were represented as the median and interquartile range on 0 days and 7 days. These results were also analysed using independent student's t-test. The results of 0 days and 7 days were compared using paired t-test. Paired t-test analysis was performed on the selected parameters on results of day 0 and day 7 of treatment. The p-value ≤0.05 is considered as significant, while the p-value ≤0.001 is considered as highly significant. Statistical analysis was performed using the Statistical Package of Social Sciences (SPSS) version 23.0.

RESULTS

The data of 50 patients were compiled for analysis. There were 22 males and 28 females enrolled in the study with mean age of males as 55 years and mean age of females as 56 years. The mean weight of males was 68.4 kg, while the mean weight of females was 59.8 kg [Table/Fig-2].

Parameters	Male	Female
Age (years) Mean±SD	55±4.1	56±2.3
Gender	22	28
Weight (Mean±SD, kg)	68.4±6.2	59.8±7.1

[Table/Fig-2]: Demographic data of patients.

It was observed that the median Ct value of the N gene was 14.8 with an interquartile range of 12.3 to 18.5. The median gradually improved to 19.5 on day 7 with an interquartile range of 18.1 to 23.2. The median Ct value of the RdRp gene was 14.7 with an interquartile range of 12.4 to 18.4. The median Ct value improved to 20.4 on day 7 with an interquartile range of 18.3 to 23.4 [Table/Fig-3].

The median ferritin value on day 0 was 747.5 with an interquartile range of 486.5 to 1286.2, while the median value on day 7 was 310 with an interquartile range of 210 to 422.5. The median interleukin-6 and D-dimer value on day 0 were 62.4 (interquartile range 28.7 to 181.7) and 4.5 (interquartile range 1.4 to 7.3), respectively. The median values of these parameters were gradually reduced to 17.5 (interquartile range 12.6 to 27.8) and 0.3 (0.2 to 0.5) on day 7 of dexamethasone administration along with standard treatment protocol of ICMR [Table/Fig-3].

Parameters	Median (Interquartile range) at Baseline values	Median (Interquartile range) at day 7	p-value
N gene	14.8 (12.3-18.5)	19.5 (18.1-23.2)	**0.002**
RdRp gene	14.7 (12.4-18.4)	20.4 (18.3-23.4)	**0.001**
Ferritin (µg/L)	747.5 (486.5-1286.2)	310 (210-422.5)	**0.002**
Interleukin-6 (pg/mL)	62.4 (28.7-181.7)	17.5 (12.6-27.8)	**0.001**
D-Dimer (µg/mL)	4.5 (1.4-7.3)	0.3 (0.2-0.5)	**0.003**

[Table/Fig-3]: Median and interquartile range of different parameters on days 0 and days 7 of administration of dexamethasone along with standard treatment protocol of ICMR.
(p-value <0.05 was considered as statistically significant, paired t-test)

Wilcoxon-Signed rank test was analysed on different parameters by comparing data of day 0 with data of day 7. It was observed that the Ct value of the N gene and the RdRp gene was significantly different between day 0 and day 7 with p-value ≤0.001. Similarly, ferritin, interleukin-6, and D-dimer were also different between day 0 and day 7 with p-value ≤0.002, ≤0.001, and ≤0.003, respectively [Table/Fig-3].

DISCUSSION

The current study involved the study of interleukin-6, D-dimer and ferritin levels in the severe COVID-19 positive patients. These parameters were chosen as they were considered as strong predictors of severity of the disease [17-19]. In the present study, it was observed that serum interleukin-6 levels were increased in all patients at the time of admission. This finding was in accordance with the study by Bhandari S et al., who observed a similar increase in interleukin-6 in patients who were critically ill [20]. This could be because of heightened inflammatory response due to COVID-19 infection. It was further observed that there was a statistically significant decrease in serum interleukin-6 levels after 7 day treatment with 6 mg dexamethasone. This was also reported in studies by Giles AJ et al., and Bronicki RA et al., [21,22].

The serum D-dimer and serum ferritin levels were found to be increased in these patients at the time of admission and showed a statistically significant decline in levels after 7 day treatment with 6 mg dexamethasone along with standard treatment protocol of ICMR. This decline could be due to dexamethasone countering cytokine storm, reducing the formation of the blood clots, and maintaining the normal iron level [23-25]. Similar results were also observed by Burugu HR et al., [26].

The Ct value of the N gene and the RdRp gene remained positive in RT-PCR results. Though the change in Ct values was significant, the majority of patients did not attain negative nucleic acid status. Previous research findings have confirmed the increased duration of viral shedding after treatment with dexamethasone [27].

The present study showed that the use of dexamethasone helped in countering the inflammatory response generated due to infection of COVID-19 as an adjunct drug along with standard treatment protocol of ICMR. The gradual reduction of immune response against the disease helped in reducing the ferritin, D-dimer, and

interleukin-6 levels in the patient. The study by Rubio-Rivas M et al., has highlighted the importance of corticosteroids such as dexamethasone in countering the cytokine storm and normalising these parameters [28].

Limitation(s)

The limitations of the present study were that the sample size was small. The follow-up period could have been increased to confirm the duration of viral shedding in patients after dexamethasone treatment along with standard treatment protocol of ICMR.

CONCLUSION(S)

The current study highlighted the importance of dexamethasone as an adjunct drug along with standard treatment protocol of ICMR, in treating patients with COVID-19 with severe symptoms of infection. The treatment of patients with dexamethasone helped in reducing the different blood markers such as ferritin, D-dimer, and interleukin-6.

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