Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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No clinical benefit of high dose corticosteroid administration in patients with COVID-19: A preliminary report of a randomized clinical trial

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ABSTRACT

The aim of this study was to evaluate the clinical effects of dexamethasone administration in patients with mild to moderate acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19). The study included 50 patients who were randomly assigned to the dexamethasone group or control group. Dexamethasone was administered at a dose of 20 mg/day from day 1–5 and then at 10 mg/day from day 6–10. The need for invasive mechanical ventilation, death rate, duration of clinical improvement, length of hospital stay, and radiological changes in the computed tomography scan were assessed. The results revealed that 92% and 96% of patients in the dexamethasone and control groups, respectively, required noninvasive ventilation ($P = 0.500$). Among them, 52% and 44% of patients in the dexamethasone and control groups, respectively, required invasive mechanical ventilation ($P = 0.389$). At the end of the study, 64% of patients in the dexamethasone group and 60% of patients in the control group died ($P = 0.500$); the remaining patients were discharged from the hospital during the 28-day follow-up period. The median length of hospital stay was 11 days in the dexamethasone group and 6 days in the control group ($P = 0.036$) and the median length of hospital stay was 7 days in the dexamethasone group and 3 days in the control group ($P < 0.001$). No significant differences were observed in the other outcomes. This study showed that corticosteroid administration had no clinical benefit in patients with COVID-19-induced mild to moderate ARDS.

1. Introduction

Coronavirus disease 2019 (COVID-19) was first identified in Wuhan City, Hubei province, China. To date, 111,331,450 cases of COVID-19 have been diagnosed and 2,465,515 related deaths have been reported worldwide. The general mortality rate in this epidemic is 4.0%, and the mortality rate among critically ill patients is reported to be approximately 61.5% (Trilla, 2020). In the majority of cases, patients with

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COVID-19 experience mild symptoms or remain asymptomatic; however, some patients may develop severe pneumonia with bilateral lung infiltrates, leading to hospitalization, and may be at high risk of serious complications such as acute respiratory distress syndrome (ARDS), shock, cytokine storm syndrome, and even death (Dastan et al., 2020; Jamaati et al., 2020). Supportive care is the backbone of the management of patients with COVID-19; it includes fluid management, oxygen therapy, and mechanical ventilation (Dong et al., 2020; Rosa and Santos, 2020). Medications such as antiviral agents, interferons, immunoglobulins, corticosteroids, and antimalarial agents, have been administered to patients with COVID-19 (Chatterjee et al., 2020; Chen et al., 2020; Grein et al., 2020). The timeline of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection consists of two phases: the viral replication phase and the inflammatory phase (Mehta et al., 2020). In some patients, an uncontrolled immunologic response to the SARS-CoV-2 virus can induce a cytokine storm and inflammation that can lead to the development of fatal pneumonia. Inhibition of the inflammatory process has been shown to improve outcomes in animal models infected with the viruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (Chan et al., 2015; DeDiego et al., 2014). Owing to their anti-inflammatory properties, corticosteroids can be used to treat severe acute respiratory infections of viral etiology (Sibila et al., 2008). The cytokines with elevated levels in the SARSare IL-6, IL-1β, IFN, and CXCL10. Such cytokines are secreted mostly by dendritic cells and macrophages. Hence, the innate immunity has an essential role in the lethal phase of SARS. CCR4+, CCR6+, and Th17 cells have several chemokine receptors and have a similar mechanism and function in the cell-cell interactions in SARS. Secreted cytokines induce the infiltration and recruitment of pro-inflammatory Th17 cells. Autopsy findings from SARS patients have demonstrated diffuse alveolar damage as a crucial feature. Dexamethasone is a well-known lifesaving drug and commonly used to treat inflammatory and autoimmune diseases. It exhibits pharmacologic effects at any therapeutically relevant dose by classic genomic mechanisms (Tang et al., 2020). Immunosuppressive effects of dexamethasone are based on transactivation, and glucocorticoid induces gene transcription and protein synthesis of NF-κB inhibitors and lipocortin-1. After inhibition of NF-κB signaling, glucocorticoids induce inhibition of synthesis of downstream proteins such as IL-1, IL-6, granulocyte-macrophage colony-stimulating factor, and inducible cyclooxygenase-2 (Masjedi et al., 2017; Rhen and Cidlowski, 2005). Dexamethasone reduces the proliferation, activation, differentiation, and survival of T cells and macrophages. Dexamethasone proffers inhibitory actions on the transcription and action of various cytokines. The Th1 and macrophage-based pro-inflammatory cytokines such as IL-1β, IL-2, IL-6, TNF-α, and IL-17 are inhibited by glucocorticoids. It has a diverse mechanism of action and can therefore affect several body systems. Also, it can hinder B cell-mediated antibody production, reduce the protective function of T cells, and prevent the macrophage-mediated clearance of apoptotic cells. This mechanism leads to higher plasma viral load and an increased risk of secondary infections (Singh et al., 2020).

In the absence of high-quality evidence, the application of corticosteroid therapy in patients with COVID-19 is controversial. In this study, we aimed to evaluate the clinical effects of dexamethasone administration in patients with COVID-19 who developed mild to moderate ARDS.

2. Material and methods

This study was a randomized, controlled, clinical trial conducted in March 2020 at Dr. Masih Daneshvari Hospital, Tehran, Iran, a primary referral center for patients with COVID-19. The ethics committee of Shahid Beheshti University of Medical Sciences approved the protocol of study (IR.SBMU.NRITLD.REC.1399.071) and this trial registered in the Iranian Clinical Trial Registry (IRCT20151227025726N17). The inclusion criteria were as follows: (1) age > 18 years; (2) SARS-CoV-2 infection confirmed by a reverse transcription-polymerase chain reaction test; (3) ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen (PaO2/FiO2) between 100 and 300 mmHg; (4) bilateral lung infiltration; and (5) provision of written informed consent by the patient. Patients with (1) chronic kidney diseases; (2) chronic liver diseases; (3) or presenting with hyperglycemia or (4) women were pregnant or breastfeeding were excluded from the study. The selected patients were allocated to either the dexamethasone group or the control group by block randomization. Ten blocks were generated by the Online Randomizer website. Each block included five patients; of these, two patients were assigned to the dexamethasone group and three patients were assigned to the control group or vice versa. Patients in the dexamethasone group received intravenous dexamethasone at a dose of 20 mg/day from day 1–5 and then at 10 mg/day from day 6–10. The recent studies on ARDS have shown that this dose is effective against cytokine cascade. This dose may stop the cytokine cascade, which has destructive effects on lungs (Villar et al., 2020). Patients in the control group did not receive dexamethasone treatment. Patients in both groups received oxygen support (CPAP with pressure of 5–10 cmH2O and FIO2 equal to 60 to achieve SPO2≥90% and the duration was different according to the monitoring of patients' clinical status), fluid support, and lopinavir/ritonavir (200/50 mg, two tablets twice a day) according to the National Iranian Guidelines (Jamaati et al., 2020). The primary outcomes were the need for invasive mechanical ventilation and death rate. Secondary outcomes included duration of clinical improvement, which was defined as weaning from oxygen support or discharge; length of hospital stay; and radiological changes in the computed tomography (CT) scan. Data were extracted from patient records and included age, sex, underlying diseases, symptoms at onset, time from onset of symptoms to hospital admission, laboratory test results during hospitalization, CT findings, and clinical outcomes. This study lasted for 28 days for patients' follow-up. Continuous variables were reported as medians with interquartile ranges (IQR); categorical variables were summarized as frequencies and percentages. Differences between the two groups were evaluated using Fisher's exact tests or Wilcoxon signed-rank tests and Mann–Whitney U tests. Survival analysis was performed using Kaplan-Meier curves. P value of <0.05 was considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences (SPSS, IBM, New York, US), version 25.

3. Results

Twenty-five patients with mild to moderate ARDS due to COVID-19 completed the study in each group. The median age of the patients in the dexamethasone and control groups was 62 (IQR, 52–71) and 62 (IQR, 54–68) years, respectively ($P = 0.846$). There were 18 (72%) male patients in each group. Twenty-three (92%) patients in the dexamethasone group and 17 (68%) patients in the control group had at least one underlying disease ($P = 0.074$). Diabetes was the most prevalent underlying disease in both groups (64% and 44% of patients in the dexamethasone and control groups, respectively). No significant differences were observed between the two groups in terms of underlying diseases. Dyspnea was the dominant symptom at the time of hospital admission in both groups (76% and 80% of patients in the dexamethasone and control groups, respectively). The median time from symptom onset to hospital admission was 8 days. The baseline characteristics of all patients are summarized in Table 1.

The results showed that 23 (92%) patients in the dexamethasone group and 24 (96%) patients in the control group required noninvasive ventilation ($P = 0.500$). Among them, 13 (52%) patients in the dexamethasone group and 11 (44%) patients in the control group required invasive mechanical ventilation ($P = 0.389$). At the end of the study, 16 (64%) patients in the dexamethasone group and 15 (60%) patients in the control group died ($P = 0.500$); the surviving patients were discharged from the hospital during the 28-day follow-up period. The median length of hospital stay was 11 (IQR, 6–16) days in the dexamethasone

Table 1
Baseline patient characteristics.

Characteristic	Dexamethasone group (n = 25)		Control group (n = 25)		P value
	Survivor (n = 9; 36%)	Non-survivor (n = 16; 64%)	Survivor (n = 10; 40%)	Non-survivor (n = 15; 60%)	
Age					
Age (years), median (IQR)	54 (37–63)	63 (55.5–72.5)	61.5 (54–62)	67 (48–73)	0.846
Sex					
Male; n (%)	6 (67)	12 (75)	7 (70)	11 (73)	0.500
Past medical history					
DM; n (%)	5 (56)	11 (69)	4 (40)	7 (47)	0.128
HTN; n (%)	4 (44)	11 (69)	3 (30)	7 (47)	0.129
CVD; n (%)	0	3 (19)	2 (20)	2 (13)	0.500
Pulmonary diseases; n (%)	0	1 (6)	1 (10)	8 (53)	0.005
Symptoms					
Fever; n (%)	6 (67)	10 (63)	5 (50)	13 (87)	0.381
Cough; n (%)	5 (56)	10 (63)	4 (40)	10 (67)	0.500
Dyspnea; n (%)	7 (78)	12 (75)	6 (60)	14 (93)	0.500
Myalgia; n (%)	1 (11)	8 (50)	4 (40)	4 (27)	0.616
Nausea or Vomiting; n (%)	1 (11)	2 (13)	3 (30)	1 (7)	0.500

IQR = interquartile range; DM = diabetes mellitus; HTN = hypertension; CVD = cardiovascular disease.

group and 6 (IQR, 4–9) days in the control group (P = 0.036). The median length of stay in the intensive care unit (ICU) was 7 (IQR, 4–11) days in the dexamethasone group and 3 (IQR, 2–5) days in the control group (P < 0.001). Improvements were observed in the lung CT scan images of 40% of patients in the dexamethasone group and 12% of patients in the control group (Fig. 1). As illustrated in Fig. 1, both groups showed radiological improvement.

The mean Sequential Organ Failure Assessment (SOFA) score was 4.68 ± 1.38 in the dexamethasone group and 4.56 ± 1.36 in the control group (P = 0.758) (Fig. 2). The clinical outcomes of the patients are summarized in Table 2.

Kaplan-Meier plots for the survival times of patients in both groups are shown in Fig. 3. The log-rank (Mantel-Cox) test showed that there was no statistically significant difference in the time-to-death of patients between the dexamethasone group and the control group (P = 0.425).

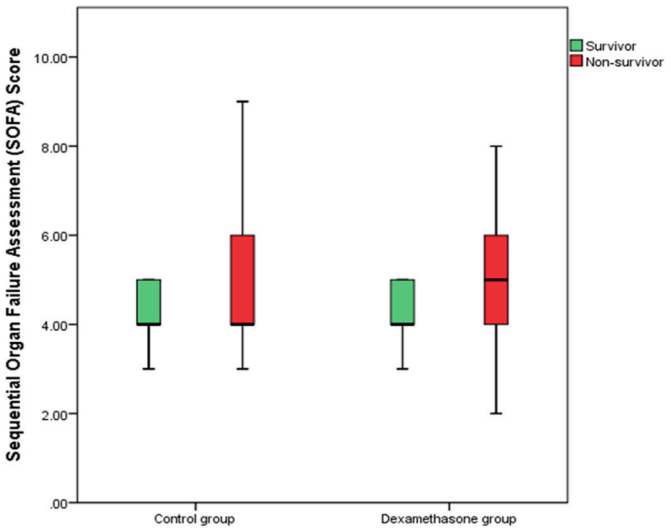

Fig. 2. Mean Sequential Organ Failure Assessment scores in both groups stratified according to clinical outcomes.

Table 2
Clinical outcomes of patients.

Characteristic	Dexamethasone group (n = 25)		Control group (n = 25)		P Value
	Survivor (n = 9; 36%)	Non-survivor (n = 16; 64%)	Survivor (n = 10; 40%)	Non-survivor (n = 15; 60%)	
Hospital stay days; median (IQR)	16 (9-21)	9.5 (5.5-13)	8.5 (5-13)	6 (3-7)	0.036
ICU stay days; median (IQR)	7 (4–12)	7 (4.5–10)	4.5 (3–5)	3 (2–3)	<0.001
Noninvasive ventilation; n (%)	9 (100)	14 (88)	10 (100)	14 (93)	0.500
Invasive mechanical ventilation; n (%)	2 (22)	11 (69)	1 (10)	10 (67)	0.389
SOFA score; median (IQR)	4 (4–5)	5 (4–6)	4 (4–5)	4 (4–6)	0.539

ICU = intensive care unit; IQR = interquartile range; SOFA=Sequential Organ Failure Assessment.

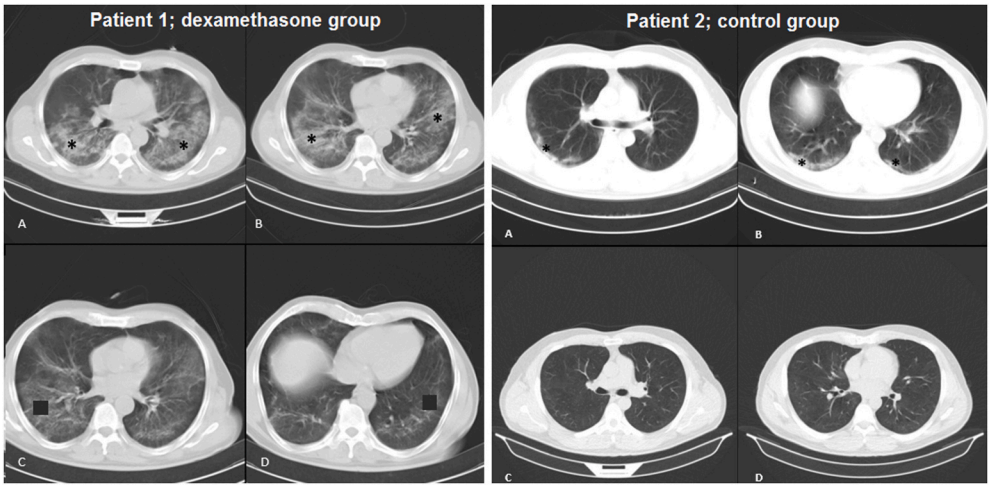

Fig. 1. (Left side, Dexamethasone group) A 48-year-old man with fever, dyspnea and positive RT-PCR for SARS-CoV-2. Initial non-contrast enhanced CT in axial planes (A and B) shows bilateral ground glass opacities and consolidation in subpleural and peri-bronchovascular locations (*). Repeated CT images (C and D) after dexamethasone administration show decrease in the severity of mentioned parenchymal infiltrations bilaterally (■). (Right side, Control group) A 41-year-old man with fever, dyspnea and positive RT-PCR for SARS-CoV-2. Initial non-contrast enhanced CT in axial planes (A and B) shows bilateral ground glass opacities and consolidation in subpleural and Peri-bronchovascular locations (*). Repeated CT images (C and D) shows decrease in the severity of mentioned parenchymal infiltrations bilaterally.

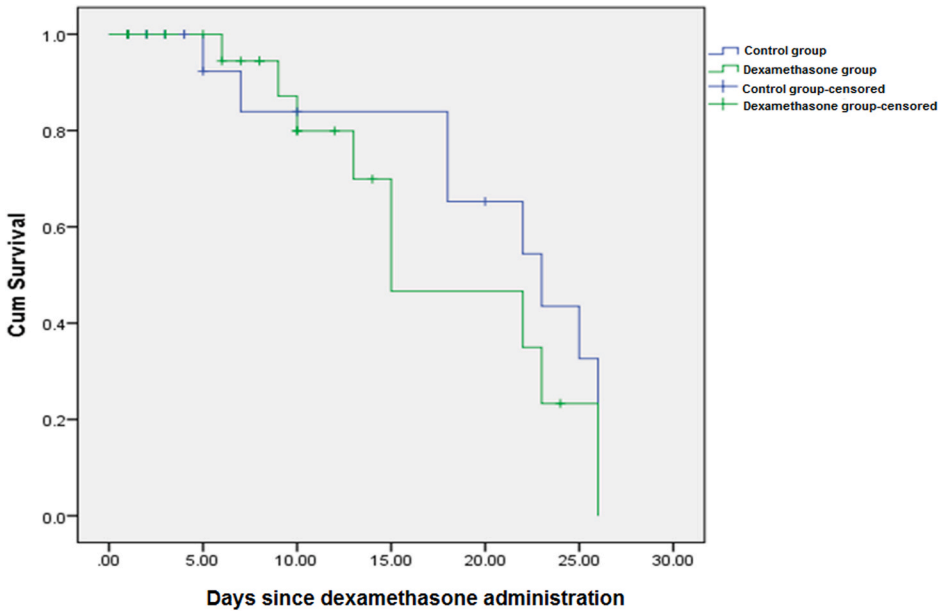

Fig. 3. Cumulative incidence of death from baseline to day 28 stratified according to dexamethasone administration. Fall in lines shows the death event and small vertical lines show the improvement event.

4. Discussion

Our findings show that corticosteroid treatment was associated with higher mortality, but this association was not significant. Dexamethasone therapy failed to improve the oxygen support needs of the patients. The need for noninvasive ventilation was similar in both groups. Additionally, dexamethasone administration couldn't shorten the length of hospital stay, but not the length of ICU stay. No clinical benefits were observed for other outcomes.

Despite the beneficial effects of low to moderate dose of dexamethasone in recent studies, our study showed that the administration of the high dose of dexamethasone may not have any additional benefit in SARS-CoV-2 associated ARDS.

A previous study found that corticosteroid administration increases the risk of mortality in patients with influenza (Lansbury et al., 2019). Another investigation reached a similar conclusion and showed that corticosteroid treatment is not beneficial in patients with viral pneumonia and may worsen their prognosis (Ni et al., 2020).

Other studies have suggested that the use of an appropriate dose of glucocorticoids at the early stages could inhibit the elevated secretion of inflammatory cytokines that can occur as a result of the excessive activation of immune cells in response to viral infection, thereby preventing continued exacerbation of lung injury (Kil et al., 2011).

In a study conducted to evaluate the efficacy and safety of corticosteroid administration in the treatment of patients with severe COVID-19 pneumonia, 26 patients received intravenous methylprednisolone at a dose of 1–2 mg/kg/day for 5–7 days (Wang et al., 2020). Oxygen saturation levels improved faster in patients who were treated with methylprednisolone; in contrast, patients who did not receive methylprednisolone required significantly longer supplemental oxygen therapy. This study found that early, low-dose, and short-term administration of corticosteroids was associated with a faster improvement in clinical symptoms and absorption of the lung focus.

An observational investigation assessed the efficacy of corticosteroid treatment in patients with COVID-19 (20). Eleven out of 31 patients received corticosteroid treatment (40 mg methylprednisolone once or twice per day) that was administered within 24 h of hospital admission for a median of 5 days. Overall, outcomes were good among the patients; however, there was no significant association between corticosteroid therapy and patient outcomes. Further, corticosteroid therapy was associated with worse lung CT findings (Zha et al., 2020). CT scan images were evaluated by our hospital radiologist who had more than five years experience in the field of thoracic imaging. She was blinded to lab data and clinical findings. Findings including consolidations and ground glass opacities were assessed with also comparison of initial and follow up images. Improvement and progression of lung infiltration were identified as decrease or increase in the severity of affected lobes, respectively. However, our study noted improved lung CT findings in more patients in the dexamethasone group than in the control groups which may be due to the anti-inflammatory properties of dexamethasone.

The main limitation of the current study was the small sample size. We halted our study because we did not achieve a significant clinical response in fifty patients. Further clinical trials are required to determine the role of dexamethasone in the treatment of patients with COVID-19. Also, it is suggested to study other administration routes such as inhalation of dexamethasone. Measurement of inflammatory markers also was not feasible for us due to limited resources and it may help to improve the future researches.

5. Conclusions

The current study showed that there was no clinical benefit in high dose administration of corticosteroid for the treatment of mild to moderate ARDS in patients with COVID-19. However, dexamethasone administration may shorten the duration of hospitalization.

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None.

CRediT authorship contribution statement

Hamidreza Jamaati: Conceptualization, Validation, Writing - review & editing, Project administration. **Seyed MohammadReza Hashemian:** Conceptualization, Validation, Writing - review & editing. **Behrooz Farzanegan:** Conceptualization, Data curation, Writing - review & editing. **Majid Malekmohammad:** Conceptualization, Data curation, Writing - review & editing. **Payam Tabarsi:** Conceptualization, Data curation, Writing - review & editing. **Majid Marjani:**

Conceptualization, Data curation, Writing - review & editing. **Afshin Moniri:** Conceptualization, Data curation, Writing - review & editing. **Zahra Abtahian:** Conceptualization, Data curation, Writing - review & editing. **Sara Haseli:** Conceptualization, Data curation, Writing - review & editing, Visualization. **Esmaeil Mortaz:** Conceptualization, Writing - review & editing. **Alireza Dastan:** Investigation, Validation, Visualization, Writing - review & editing. **Abdolreza Mohamadnia:** Conceptualization, Writing - review & editing. **Abdolbaset Vahedi:** Conceptualization, Writing - review & editing. **Fatemeh Monjazebi:** Conceptualization, Writing - review & editing. **Fatemeh Yassari:** Conceptualization, Writing - review & editing. **Lida Fadaeizadeh:** Conceptualization, Writing - review & editing. **Ali Saffaei:** Formal analysis, Writing - original draft, Writing - review & editing. **Farzaneh Dastan:** Supervision, Methodology, Investigation, Data curation, Writing - review & editing.

Declaration of competing interest

None.

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