Original Article

Efficacy and Safety Comparison of Two Different Doses of Dexamethasone in Hospitalized Patients with COVID-19: A Randomized Clinical Trial

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ABSTRACT

Objective: The current study aims to investigate high- versus low-dose dexamethasone administration to control the disease with minor complications. **Methods:** The current multicentric randomized clinical trial was conducted on 119 patients with COVID-19 pneumonia and assigned into two groups of low-dose (8 mg daily intravenous dose for at least 7 days or until discharge) (n = 61) versus high-dose dexamethasone (24 mg for 3 days followed by daily 8 mg for the at least 4 days later or until discharge) (n = 58) during 2020–2021. Oxygen saturation, dyspnea severity based on the Borg scale, and laboratory indices were assessed at 3, 5, and 7 days of corticosteroid therapy. Patients were compared regarding the length of hospitalization, intensive care unit (ICU) admission requirement, and noninvasive or invasive ventilation. The other investigations included corticosteroid-related adverse effects and mortality rates within a month after the medications. **Findings:** Oxygen saturation, Borg scale, and C-reactive protein levels were significantly altered by the time in both the groups ($P < 0.05$). In contrast, the trend of improvements in Borg scale ($P = 0.007$) and lactate dehydrogenase levels ($P = 0.034$) were superior in high-dose treated cases. Drug-related adverse ($P = 0.809$), mortality rate ($P = 0.612$), hospitalization duration ($P = 0.312$), ICU admission requirement ($P = 0.483$), and noninvasive ($P = 0.396$) and invasive ventilation ($P = 0.420$) did not differ between the groups. **Conclusion:** According to this study, low- versus high-dose dexamethasone therapy did not affect the outcomes, so low-dose dexamethasone is recommended for COVID-19 pneumonia to achieve optimal results and prevent potential adverse events.

Keywords: *COVID-19, Dexamethasone, high dose, low dose, viral pneumonia*

Introduction

By the end of 2019, an emergence of a novel viral respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, ignited alarms of a health issue that turned into a pandemic within a few months. The number of deceased patients raised growingly, which required prompt therapeutic reactions.[1,2]

The presentations were primarily initiated by flu-like symptoms such as fever, cough, malaise, headache, sore throat, and headache; however, it can turn to acute respiratory distress syndrome (ARDS) and multi-organ failure in severe or critically ill patients within the next early days.[3]

Therefore, the competition to present effective therapies for COVID-19 has been initiated by different health-care

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systems worldwide; however, in contrast to the promising outcomes, most of them were abandoned due to low or inappropriate efficacy or safety concerns,[4] and coronavirus unrelentingly involved numerous people. Despite the primary considerations, medications such as hydroxychloroquine, protease inhibitors, and interferons were withdrawn regarding the lack of enough evidence in favor of longer use or risks of adverse effects.[5,6] Remdesivir and dexamethasone have led to favorable results in hospitalized patients.[7,8]

Corticosteroid administration has been proposed to subside the cytokine storm in the acute progressive phase of the disease affecting the respiratory system.[9] This theory has been theoretically initiated for treating SARS and Middle East respiratory syndrome (MERS) caused by other types of coronaviruses similar to SARS-CoV-2.[7,10]

The evidence regarding the use of corticosteroids is controversial; however, low-dose dexamethasone has been accompanied by a decreased mortality rate and oxygen supplementation requirement.[7]

Furthermore, high-dose methylprednisolone as pulse therapy led to less mortality in critically ill COVID-19 patients.[11] Nevertheless, considering the ambiguous outcomes following corticosteroid use in COVID-19 and the advantages and disadvantages of corticosteroid therapy in viral infections, the current study aims to determine the optimal dose of dexamethasone for the treatment of noncritical ill patients hospitalized with COVID-19 pneumonia. Two groups of patients were randomly selected, assigned to the intervention groups treated with low- versus high-dose intravenous dexamethasone, and compared regarding laboratory and clinical manifestations.

Methods

As a multicentric investigation, the current randomized clinical trial (RCT) was conducted on 119 patients admitted at Isfahan University of Medical Sciences affiliated hospitals due to COVID-19 infection pneumonia from January 2020 to November 2021.

The study proposal was primarily proposed for the Ethics Committee of Isfahan University of Medical Sciences and approved according to code number IR.MUI.MED.REC.1400.160. The study protocol has been signed into the Iranian Registry of Clinical Trials and obtained the code number IRCT20190606043826N2. The study process was explained to the patients or their legal guardians; they were reassured regarding the confidentiality of their information and requested to sign written consent.

Over 18-year-old patients with confirmed COVID-19 infection based on real-time polymerase chain reaction test, pulmonary involvement based on chest computed tomography scan (CT-scan), and oxygen saturation <93% and ≥85% without oxygenation were defined as the inclusion criteria.

Pregnancy or active lactation, immune-compromised, chronic kidney or liver disease, uncontrolled diabetes mellitus with serum glucose above 250 mg/dL, gastrointestinal bleeding (GIB), the presence of any significant psychological disorders, the history of corticosteroid uses within the previous month, and active participation in other RCTs were determined as the unmet criteria.

Reluctance to participate in the study, the incidence of any drug-related adverse effects leading to dexamethasone cessation, and the requirement for noninvasive or invasive mechanical ventilation within the first 24 h of hospital admission were considered exclusion criteria.

The studied population entered the study according to the inclusion criteria. It was assigned to one of the intervention groups using Random Allocation Software (a windows software) that presented a particular random number for each patient. The patients and physicians who filled out the study questionnaire were blinded to the type of therapeutic approach.

The demographic (age, gender, body mass index [BMI], and smoking) and chronic medical characteristics (respiratory disorders, hypertension, and diabetes mellitus) of patients were entered into the study checklist. Furthermore, the COVID-19 infection symptoms on the onset, including fever, cough, dyspnea, myalgia, diarrhea, nausea, vomiting, anosmia, headache, abdominal pain, and pharyngitis, were extracted from the medical records of the patients.

The chest CT scan was obtained from all the patients and categorized as mild, moderate, and severe involvement based on the severity of involvement as ≤49%, 50%–75%, and >75%, respectively.[12]

On-admission laboratory blood samples were taken and sent to assess parameters, including complete blood count and differential count, fasting blood sugar, creatinine, aspartate aminotransferase, alanine aminotransferase, sodium, potassium, calcium, albumin, erythrocytic sedimentation rate, D-dimer, ferritin, and lactate dehydrogenase (LDH). The samples were sent to a reference laboratory to minimize the probable sources of bias.

A quick Sequential Organ Failure Assessment score has been administered to present a septic condition clinically. It

is a bedside clinical score in which if a patient has at least two of the following criteria, including the respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of ≤100 mmHg, they are suspected of sepsis.[13]

The included patients received anti-COVID-19 infection and anticoagulation therapies according to Iran's national guidelines.[14]

The first group was assigned as the high-dose dexamethasone-treated one in which intravenous dexamethasone (Aburaihan Pharmaceutical Co., Iran) was administered in 24 mg dose for 3 days and continued with 8 mg daily for at least 4 days later or until discharge. The low-dose dexamethasone-treated group consisted of patients treated with an 8 mg daily intravenous dose for at least 7 days or until discharge.

The primary outcome of this study was to assess the mortality rate of the patients within a month after the interventions. Hence, the outcomes of admission were assessed using the hospital records or directly from patients or their legal guardians.

The other investigations to evaluate corticosteroid treatment efficacy, including oxygen saturation without supplemental oxygenation and dyspnea severity according to the modified Borg scale,[15] were assessed on days 1, 3, 5, and 7 of corticosteroid administration.

The length of stay in the hospital, the requirements for intensive care unit (ICU) admission, and the requirement for noninvasive or invasive ventilation were also recorded in the study checklist, as well. In addition, medication usage (antibiotic therapy and antifungal therapy), laboratory factors, including C-reactive protein (CRP), LDH, ferritin, lymphocyte proportion (%), and neutrophil-to-lymphocyte ratio were measured on days 1, 3, 5, and 7 during corticosteroid administration. The evaluated adverse effects of corticosteroids included hyperglycemia, secondary infection, psychosis, and GIB was entered into the checklist. Those with hyperglycemia were treated with insulin.

The secondary infection was diagnosed based on the incidence of fever, leukocytosis, shift to the left, the recurrence of CRP increase, elevated procalcitonin, and positive blood or tracheal secretions culture.[16]

The obtained data were analyzed in the Statistical Package for the Social Sciences (SPSS; version 14.0, SPSS Inc., Chicago, IL, USA). The descriptive data were presented in mean, standard deviation, median, and range for the continuous variable, as well as absolute numbers and percentages for categorical variables. The Chi-square test or Fisher's exact test was used to compare the groups' categorical variables. The continuous variables were compared using a *t*-test. Binary logistic regression analysis was applied to estimate the odds ratio, find the association between the assessed factors and thrombotic events in the crude model, and adjust the model for age and gender. $P < 0.05$ was considered a significant level.

Results

Figure 1 shows the consort flowchart.

Among 145 patients whose eligibility for participation in this investigation was evaluated, 19 cases (14 did not meet the inclusion criteria, and 5 refused to participate) were excluded. Then, the remaining 126 patients were randomly assigned to one of the treatment groups. Two in the low-dose dexamethasone treatment group decided to leave the hospital, and the medical records of the two other ones were incomplete. Three patients withdrew from the treatment in the latter group. The interventions were finally completed by 61 and 58 patients treated with low- versus high-dose dexamethasone, respectively.

The study population consisted of 59 (49.57%) males and 60 females (50.47%), and the mean age of the studied population was 59.06 ± 14.39 years.

The study groups were similar in age, gender distribution, smoking, BMI, the interval between symptoms onset and hospital admission, and chronic medical conditions ($P > 0.05$). Detailed information is presented in Table 1.

Different characteristics related to the course of the disease are presented in Table 2. According to the results of this table, the two studied groups were similar in terms of baseline clinical and medical characteristics ($P > 0.05$). Further information, including laboratory assessments, has revealed no distinct differences ($P > 0.05$).

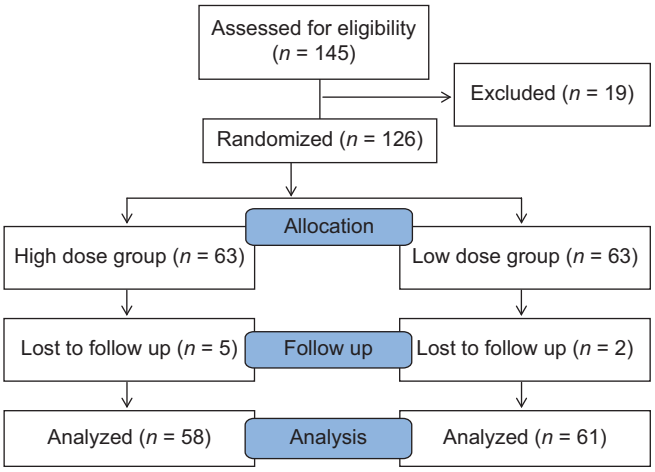

Figure 1: Consort flowchart of the study

Table 3 shows the efficacy of each therapeutic approach on diverse parameters related to the severity of pneumonia. According to this table, oxygen saturation, Borg scale, and CRP levels were significantly altered by the time in both the groups ($P < 0.05$). In addition, considering dexamethasone dosage, the trend of alterations in the Borg scale ($P = 0.007$), lymphocyte count ($P = 0.002$), and LDH levels ($P = 0.034$) were superior in high-dose treated cases.

The mortality rate accounted for a patient (1.6%) in low-dose treatment and two ones (3.4%) in the latter group which revealed an insignificant difference ($P = 0.612$). The other factors, including duration of hospitalization ($P = 0.312$), ICU admission ($P = 0.483$), noninvasive ($P = 0.396$), and invasive ventilation ($P = 0.420$) did not differ between the two studied groups.

Drug-related adverse effects were noted in 26 groups ($P = 0.809$); furthermore, although there was no significant difference between the groups, secondary infections were more common in the high-dose group compared to the low-dose group. The adverse effects related to each intervention are demonstrated in Table 4.

Table 1: The demographic, medical, and clinical characteristics of the studied population

	Low-dose Dexamethasone (*n*=61), *n* (%)	High-dose Dexamethasone (*n*=58), *n* (%)	*P*
Sex (male)	25 (41.0)	34 (58.6)	0.054*
Age (years), mean±SD	60.77±14.96	57.28±13.80	0.189#
Smoking (yes)	6 (9.8)	7 (12.1)	0.696*
Body mass index (kg/m^2), mean±SD	27.07±3.24	27.00±2.26	0.892#
The interval between symptoms onset to hospital admission (days)	8.13±2.93	8.84±2.27	0.141#
Chronic medical conditions			
Respiratory disorders	8 (13.1)	3 (5.2)	0.135*
Hypertension	21 (34.4)	19 (32.8)	0.847*
Diabetes mellitus	13 (21.3)	9 (15.5)	0.416*

*Chi square, **Fisher's exact test, #*t*-test. SD=Standard deviation

Discussion

The results of this study showed that regardless of the dosage, 10 days of treatment with intravenous dexamethasone could lead to remarkable improvement in the parameters related to the severity of COVID-19

Table 2: COVID-19-related characteristics

	Low-dose Dexamethasone (*n*=61), *n* (%)	High-dose Dexamethasone (*n*=58), *n* (%)	*P*
Symptoms on onset			
Fever	43 (70.5)	48 (82.8)	0.115*
Cough	45 (73.8)	46 (79.3)	0.476*
Dyspnea	39 (63.9)	46 (79.3)	0.063*
Diarrhea	13 (21.3)	20 (34.5)	0.109*
Nausea and vomiting	21 (34.4)	18 (31.0)	0.696*
Anosmia	6 (9.8)	10 (17.2)	0.237*
Headache	26 (42.6)	21 (36.2)	0.474*
Abdominal pain	2 (3.3)	0	0.496**
On-admission oxygen saturation without supplementation, mean±SD	85.52±3.72	85.55±3.29	0.967
The administered medications concurrent with dexamethasone therapy			
Remdesivir	53 (86.9)	51 (87.9)	0.864*
The severity of pulmonary involvement based on CT scans score			
Mild	21 (34.4)	19 (32.8)	0.833*
Moderate	30 (49.2)	27 (46.6)	
Sever	10 (16.4)	12 (20.7)	
On-admission qSOFA			
0	20 (32.8)	22 (37.9)	0.809**
1	38 (62.3)	34 (58.6)	
2	3 (4.9)	2 (3.4)	
3	0	0	
Borg scale, mean±SD	4.03±1.49	4.55±1.55	0.065

*Chi square, **Fisher's exact test, #*t*-test. CT scan=Computed tomography scan, qSOFA=quick Sequential Organ Failure Assessment

Table 3: The efficacy of high-dose versus low-dose Dexamethasone on clinical and laboratory parameters

Time variable	Group	Mean±SD				*P*1	*P*2
		Day 0	Day 3	Day 5	Day 7		
O_2 saturation without oxygen supplementation	Low-dose dexamethasone	85.52±3.72	88.26±5.02	90.94±4.42	91.13±3.95	<0.001	0.850
	High-dose dexamethasone	85.55±3.29	88.98±3.80	91.77±4.66	91.00±2.83	<0.001	
P		0.967	0.381	0.351	0.929		
Borg scale	Low-dose dexamethasone	4.03±1.49	2.20±1.39	1.03±0.96	0.66±0.98	<0.001	0.007
	High-dose dexamethasone	4.55±1.55	2.75±1.47	1.35±1.14	1.10±0.52	<0.001	
P		0.065	0.039	0.123	0.200		
WBC count	Low-dose dexamethasone	6621.31±7463.69	10,518.03±14173.63	9207.69±2901.71	10,917.65±2702.14	0.086	0.658
	High-dose dexamethasone	7712.93±11,294.57	8358.62±2325.45	11,702.83±14718.71	11,700.00±1713.35	0.150	
P		0.533	0.254	0.233	0.420		
Lymphocyte	Low-dose dexamethasone	17.45±9.10	13.68±6.66	13.73±10.94	20.77±47.17	0.248	0.002
	High-dose dexamethasone	14.53±8.22	11.85±6.75	10.68±6.09	8.53±6.44	0.008	
P		0.70	0.139	0.082	0.426		
Neutrophil	Low-dose dexamethasone	73.57±12.23	81.29±9.34	81.66±7.66	82.73±7.61	<0.001	0.316
	High-dose dexamethasone	77.83±13.44	81.69±12.94	81.78±12.46	83.73±8.27	0.233	
P		0.073	0.847	0.952	0.752		
CRP	Low-dose dexamethasone	79.59±19.45	49.90±18.88	25.10±14.26	23.46±17.42	<0.001	0.215
	High-dose dexamethasone	82.43±19.06	49.57±21.99	25.19±19.93	32.35±32.34	<0.001	
P		0.423	0.930	0.982	0.318		
LDH	Low-dose dexamethasone	716.98±184.16	571.97±169.70	475.17±185.08	551.24±170.02	<0.001	0.034
	High-dose dexamethasone	773.26±168.75	659.90±169.40	675.78±852.19	550.60±197.05	0.255	
P		0.085	0.006	0.122	0.992		
Ferritin	Low-dose dexamethasone	748.79±396.08	675.12±376.06	555.00±378.14	610.35±438.69	0.071	0.32
	High-dose dexamethasone	738.14±440.09	677.26±412.81	636.34±388.89	721.20±412.35	0.599	
P		0.890	0.977	0.296	0.434		

P=*t*-test, *P*1=GEE within the group, *P*2=GEE between the groups. WBC=White blood cells, CRP=C-reactive protein, LDH=Lactate dehydrogenase, SD=Standard deviation, GEE=Generalized estimating equations

pneumonia infections. Further evaluations regarding the dosage of intravenous dexamethasone by which optimal outcomes could be achieved revealed negligible superiority of low-dose treatment with dexamethasone over the high-dose regimen. The severity of dyspnea complaint assessed was the only significant difference between the groups in which low-dose-treated patients presented better condition.

The remarkable experiences with corticosteroid therapy in former coronavirus epidemics, including MERS and SARS, paved the way to be included in the treatment of COVID-19. High-dose corticosteroids in the treatment of SARS led to significantly less requirement for oxygen supplementation. In agreement, these patients' hospital stay and mortality improved.[17,18]

One of the concerns regarding corticosteroid use in viral infections is the postponement of viral clearance, which has been presented in some studies on MERS.[19] This point has not been markedly noted in the corticosteroid-treated patients with SARS-CoV-2 and seems to be particularly related to the age and the severity of the disease in its initiation rather than

Table 4: The comparison of adverse effects and mortality following corticosteroid treatment between groups

Variables	Low-dose Dexamethasone (*n*=61), *n* (%)	High-dose Dexamethasone (*n*=58), *n* (%)	*P*
The incidence of drug-related side effect (yes)	26 (42.6)	26 (44.8)	0.809*
Hospital admission duration (days), mean±SD	6.26±2.66	6.76±2.67	0.312#
Intensive care unit admission requirement (yes)	5 (8.2)	7 (12.1)	0.483*
Supplemental oxygenation requirement			
Noninvasive ventilation	9 (14.8)	12 (20.7)	0.396*
Intubation and mechanical ventilation	3 (4.9)	5 (8.6)	0.420**
Corticosteroid-related adverse effects			0.934**
Gastrointestinal bleeding	4 (15.4)	5 (19.2)	
Hyperglycemia	21 (34.4)	20 (34.4)	
Mortality rate within a month			0.612**
Alive	60 (98.4)	56 (96.6)	
Death	1 (1.6)	2 (3.4)	

*Chi square, **Fisher's exact test, #Independent *t*-test. SD=Standard deviation

treatment with corticosteroids.[20-22] Nevertheless, the association between viral shedding and clearance in COVID-19 was dose-dependent in the previous studies.[23,24] However, we have not evaluated this issue; it is in line with our findings as favorable outcomes accompanied low-dose dexamethasone.

In contrast to the general findings of this study, an observational report stated discouraging outcomes in corticosteroid use for COVID-19 in which more patients in the corticosteroid group progressed to the severe form of the disease. Furthermore, a therapeutic approach containing corticosteroids delayed the resolution of fever and viral clearance.[25]

Considering the life-threatening potential adverse effects of corticosteroids such as GIB or secondary infection, treatment with 10 days of low-dose dexamethasone (8 mg/day) is favored. This inference has been supported by the Randomized Evaluation of COVID-19 Therapy, in which an even lower dose of dexamethasone (6 mg/day for 10 days) significantly reduced hospital stay and 28-day mortality in COVID-19.[26] Similar promising data have been presented for the patients with ARDS regardless of the underlying etiology[27] and those with on-admission PaO2/FiO2 ratio.[28]

Despite the efforts made to assess the pros and cons of corticosteroid therapy in COVID-19, a paucity of knowledge is available about the best dosage and period of treatment, albeit different types of corticosteroids, doses, and periods of treatment have been examined in the patients with diverse severity of COVID-19 infection.[29-31]

Numerous studies have applied high-dose corticosteroids to patients with severe courses of COVID-19 or critically ill patients. They have presented promising outcomes in terms of survival rate, ARDS, and respiratory failure. The investigations on the inflammatory markers revealed consistent outcomes, as well.[11,32-35] Nevertheless, little knowledge is available about low-dose corticosteroids, and further RCTs are required to generalize the results.

Corticosteroids in low doses have been examined as well. An observational study by Li *et al.* tried to investigate the efficacy of 40–80 mg daily methylprednisolone for a week and presented a significant increase in mechanical ventilation-free days among patients with considerable lung involvement. However, secondary bacterial infection was the most notifying complication of corticosteroid treatment.[36] CoDEX trial is the other study in which dexamethasone was prescribed in a 20 mg daily dose for 5 days followed by a daily dose of 10 mg for another 5 days or until ICU discharge. Reduced mechanical ventilation requirements and prolonged survival were the outcomes in favor of this therapeutic strategy. Furthermore, the comparison of the control group with dexamethasone-treated patients revealed insignificant differences in terms of secondary infection incidence and hyperglycemia needing insulin therapy.[37] In agreement, Fadel *et al*. presented a significant decrease in mortality rate and the necessity of hospitalization in patients who were treated with 1 mg/kg/day of methylprednisolone for 3 days in the early stage of the infection. As safety is the most significant concern, this study's low rate of secondary infection and hyperglycemia incidence strongly indicated that corticosteroid therapy could be considered safe.[38]

Limited studies have compared different types or doses of corticosteroids. Ko *et al*. compared methylprednisolone and the equivalent dose of dexamethasone in mechanically ventilated patients in a study that revealed the superiority of methylprednisolone considering the mortality rate.[39] Similarly, Ranjbar *et al.* presented significant superiority of methylprednisolone in 2 mg/kg/day to the equivalent dose of dexamethasone in terms of clinical status and oxygenation support.[40]

Comparing different doses of dexamethasone (8 mg twice daily vs. 8 mg twice daily) for 10 days

resulted in outcomes in line with our study. They not only presented a failure to improve the efficacy of dexamethasone therapy in high doses but also the number of adverse events and decreased patients increased in those treated with daily 24 mg of dexamethasone.[30] In contrast, Taboada *et al.* supported the administration of high- rather than low-dose dexamethasone according to the requirement for supplemental oxygenation.[41] Similarly, Maskin *et al*. found fewer days required to liberate the patients from mechanical ventilation among those treated with high doses of dexamethasone (16 mg for 5 days followed by 8 mg for other 5 days) in comparison to 6 mg daily dexamethasone for 10 days. However, the number of ventilator-free days did not differ.[42]

Hyperglycemia and secondary infection are the most significant concerns related to corticosteroid therapy. We found no difference in the incidence of these two complications; however, the previous investigations have presented the range of 3.1%–4.7% of infection incidence during the hospitalization course following corticosteroid therapy.[43] The latter complication seems to be dose-dependent;[44] therefore, guidelines have generally recommended low doses of corticosteroid treatment for COVID-19.[45-46]

According to the findings of this study, a high versus low dose of dexamethasone therapy did not affect the outcomes, including clinical and paraclinical parameters, hospitalization duration, and mortality rate, significantly. The incidence of major adverse effects was similar. Hence, we recommend low-dose dexamethasone for COVID-19 pneumonia to achieve optimal results and prevent potential adverse events.

Authors' Contribution

Marzieh Mollaei Ardestani designed the study. Somayeh Sadeghi did the definition of intellectual content and literature search. Experimental studies were done by Nima Arezoomandi. Data acquisition was done by Mohammad Emami Ardestani. Ziba Farajzadegan did data analysis and statistical analysis. Manuscript preparation was done by Farzin Ghiasi. Manuscript editing was done by Somayeh Sadeghi.

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Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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