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A comparison of the effects of low and high doses of corticosteroids on recovery of the patients with Covid-19

Hamid Reza Samimagham[1], Ladan Hajiabdolrrasouli [2], Ali Salimi Asl [3], Fatemeh Khajavi Mayvan[3] , Elham Boushehri [4], Mohsen Arabi [5] , Mohammad Amin Abbasi [6] Mohammad Reza Moradi [3], Mitra Kazemi Jahromi[2]*

[1] Clinical Research Development Center, Shahid Mohammadi Hospital, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

[2] Endocrinology and Metabolism Research Center, Hormozgan University of Medical Sciences, Bandarabbas, Iran

[3] Student Research Committe, Faculty of Medicie, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

[4] Medical Education Department, Health School, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

[5] Preventive Medicine and Public Health Research Center, Family Medicine Department, Iran University of Medical Sciences, Tehran, Iran

6 Firoozabadi Hospital Clinical Research Development Center, Iran University of Medical Sciences, Tehran, Iran

***Corresponding author:** Mitra Kazemi Jahromi, **Address**: Endocrinology and Metabolism Research Center, Hormozgan University of Medical Sciences, Bandarabbas, Iran, **Email**: mitra.kazemijahromi@gmail.com, **Tel**: +987631281648

Abstract

***Background & Aims*:** SARS-CoV-2 is a new coronavirus type that first appeared in Wuhan, China, and caused a pandemic of respiratory diseases from the end of 2019. Severe infections of this virus can cause incorrect adjustments of cytokine and chemokine responses, which ultimately causes damage to the lung tissue. Corticosteroids are a class of drugs that reduce inflammation and immune system activities in the body. For this reason, many doctors and researchers thought of using corticosteroid treatments to control the cytokine storm.

***Materials & Methods*:** In this retrospective descriptive cross-sectional study, the files of Covid-19 patients who were admitted to Shahid Mohammadi Hospital, Bandar Abbas, Iran, were examined. On the basis of the severity, the patients were grouped into two groups of moderate and severe patients. Patients in each group were then sub-categorized into high dose and low dose, according to the received dose of corticosteroids. Then we investigated the effect of different doses of corticosteroids on the course of recovery of Covid-19 cases.

***Results*:** In the severe group, the patients who received high-dose of corticosteroids had a higher mortality rate as compared to the low-dose group. In both the severe and moderate groups, the LDH level of the patients who received low doses of corticosteroids at the time of discharge were significantly less compared to those who received high doses. In the moderate group, the percentage of lymphocytes in the low-dose corticosteroid group was considerably higher compared to the high-dose corticosteroid group at the time of discharge.

***Conclusion*:** According to the results, in the case of patients with moderate clinical severity, a low dose of corticosteroids improved the disease, but in the case of patients with severe clinical severity, the results were contradictory, which may be caused by interference of other factors such as underlying diseases, the severity of the illness, etc. in the severe group.

***Keywords*:** Corticosteroids, Covid-19, Mortality

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Introduction

SARS-CoV-2 is a new coronavirus type that causes harmful effects on health and body systems and has caused a pandemic of respiratory infections such as severe acute respiratory infection (SARI), pneumonia, COVID-19 disease, and other complications from December 2019 (1-8). This virus first appeared in Wuhan, China, then rapidly spread globally, causing a pandemic and became a public health emergency (9-11). The clinical manifestations of this infection include respiratory symptoms, cough, fever and fatigue, although it may progress to pneumonia, Acute Respiratory Distress Syndrome (ARDS) and even shock (12).

Corticosteroids are a group of drugs that reduce inflammation and immune system activities in the body. These drugs are similar in their activity to the cortisol in human body, which is a hormone secreted mainly from the adrenal glands. Any stress, including news of a pandemic, causes severe stress in the people with COVID-19 infection (13). Hydrocortisone, dexamethasone, prednisone, and prednisolone are among synthetic corticosteroids which may be replaced endogenous hormones in the people with cortisol hormone deficiency or any need to it (14). They can also be used to control inflammations and hypersensitivity reactions such as asthma or autoimmune diseases like lupus and systemic sclerosis. Even though corticosteroids are extensively applied to treat various diseases, unfortunately they have side effects depending on the dose and duration of their use. High doses of glucocorticoids may cause hypercortisolism and Cushing's syndrome in the patients receiving corticosteroids including Covid-19 patients. In addition, these drugs may increase the possibility of secondary infections in the patients receiving corticosteroids, causing the conditions the patients unpredictable (15).

Corticosteroids are strong suppressors of the immune system. Serious diseases, traumas, and surgery cause severe stress to the body, which activates the axis of this hormone in the brain, and subsequently the cortisol level is increased (16). Activation of this axis is necessary to cope with stress. It adjusts the body's metabolism and returns it to its normal state (17). In many people, the coronavirus reaches a critical stage and for this, the effect of the immune system in these people is greatly intensified. The severe infection of this virus can cause incorrect regulation of the cytokine and chemokine responses, which ultimately causes damage to organs, including the lung tissue. TNF-a, IL-8, IL-6, IL-12, CCL2 and C-reactive protein are among the molecules that increase after Covid-19 shock. In this way, the infiltration of neutrophil and macrophage cells to the lungs and blood are strongly increased, although the patient has a decrease in CD4 and CD8 T-cells in the peripheral blood sample (18). Deterioration of the Covid-19 disease into acute respiratory distress syndrome may have disastrous effects on a person. Of course, a suitable and definitive treatment has not yet been found. For this reason, many doctors and researchers thought of using corticosteroid treatment to control the cytokine storm. At the beginning of the disease (2020), hospitals strongly avoided corticosteroids due to their immunosuppressive properties (19).

Many studies have been conducted in the last few months on this subject, which sometimes have contradictory conclusions. In this study, we investigated the files of Covid-19 patients who were admitted to Shahid Mohammadi Hospital, Bandar Abbas, Iran, and reviewed the studies conducted on the impact of using low and high dose of corticosteroids on the recovery of Covid-19 patients.

Materials & Methods

The study population of this descriptive-cross-sectional retrospective study consisted of the patients admitted to Shahid Mohammadi Hospital, Bandar Abbas, Iran, from February 2020 to March 2021 with a definite diagnosis of Covid-19 according to PCR test.

The inclusion criteria was a definitive diagnosis of Covid-19 according to a positive PCR result and admission to Shahid Mohammadi Hospital between February 2020 to March 2021; the exclusion criteria

were as following: Patients with an underlying disease such as immunodeficiency, end-stage renal disease, moderate renal failure (creatinine clearance 30-50 ml/min), stage 4 severe chronic kidney disease, the necessity for dialysis (creatinine clearance <30 ml/min), pregnancy, a recent history of myocardial infarction or unstable angina, history of malignancy, diastolic blood pressure above 90 mm Hg, systolic blood pressure above 160 mm Hg, and inadequacy of file information in terms of study variables like age, gender, comorbidities, lymphocyte count, arterial oxygen saturation percentage, hospital stay, intensive care unit stay, pulmonary infiltration, LDH, CRP, and death).

This study is approved under the ethical approval code of IR.HUMS.REC.1399.529. In order to conduct this study, the files of the patients who were admitted to Shahid Mohammadi Hospital were examined, and those with a positive PCR test of Covid-19 were selected for further investigation. Considering the limited number of cases of corticosteroid use at beginning of the Covid-19 pandemic and the downward trend of patients hospitalized from May to September 2020 in Shahid Mohammadi Hospital, Bandar Abbas, Iran, the census method was chosen for sampling. There was no need to determine the sample size due to the entry of all the patients with the eligible criteria in the mentioned time period and also the descriptive nature of the study. On the basis of the severity, the patients were grouped into two groups, moderate and severe.

Patients with one or more of the following symptoms was categorized in severe groups and those without them in moderate group (20).

1- Number of breaths more than 30 per minute

2- arterial oxygen saturation (SaO2) < 93%

3- Lung infiltrates > 50% within 24 to 48 hours

4- The fraction of inspired oxygen (FiO2) < 300 mmHg

Patients in each group were then sub-categorized into high dose and low dose, according to the received dose of corticosteroids as follows:

- **High dose:** standard treatment + 16 mg of dexamethasone or its equivalent of prednisolone (each 5 mg of prednisolone is equivalent to 0.75 mg of dexamethasone).
- **Low dose:** standard treatment + 8 mg of dexamethasone or its equivalent prednisolone (each 5 mg of prednisolone is equal to 0.75 mg of dexamethasone).

The standard medical treatment based on the protocols of the National Committee for Covid-19 was as follows:

1. Hydroxychloroquine/chloroquine phosphate: 200 mg tablets of hydroxychloroquine sulfate or 250 mg tablets of chloroquine phosphate, which were taken as two tablets with an interval of 12 h on the first day, one pill per 12 h for a minimum of one week, and a daily consumption for a maximum of two weeks.

2. One of these two treatments: 1) Clatra tablets (lopinavir/ritonavir) 200 mg in the form of two tablets every 12 hours after meals for a minimum of one and a maximum of two weeks. 2) Atazanavir/ritonavir 300 mg pill daily with food or atazanavir 400 mg for a minimum of one and a maximum of two weeks.

After collecting the desired information, it was entered into SPSS version 25 software. The sample characteristics were explained in the form of the absolute number of cases, percentages, and standard deviation. Student's t-test, Chi-square, and Fisher's exact test was used to analyze continuous variables.

Results

200 Covid-19 patients with positive PCR, hospitalized in Shahid Mohammadi Hospital, were categorized into Moderate (155 people) and Severe (45 people) groups. The average age of the investigated subjects was 53.6 ± 14.8 years. Out of all 200 cases included in the present research, 101 were women, and 99 were men. Demographic information of the studied population is described in Table 1.

Table 1. Distribution of gender variable in the studied population

Sex			Group	
Total	**Female**	**Male**		
37	18	19	H dose	Severe
8	3	5	L dose	
62	31	31	H dose	Moderate
93	49	44	L dose	
200	101	99	Total	

Table 2. Differences in the patients' mortality results in the two studied groups

P-value	Mortality			Group	
	Total	**Yes**	**No**		
0.001	37	7	30	H dose	Severe
	8	0	8	L dose	
0.998	62	0	62	H dose	Moderate
	93	0	93	L dose	
200		7	193	Total	

As seen in Table 2, people who received high-dose corticosteroids in the severe group had a significantly higher mortality rate as compared to the low-dose group. There was, however, no significant difference in the moderate group.

Table 3. Relationship between the level of CRP during discharge and the amount of treatment received by the studied patients

P-value	CRP during discharge			Group	
	Total	**Positive**	**Negative**		
0.054	37	14	23	H dose	Severe
	8	6	2	L dose	
0.871	62	15	47	H dose	Moderate
	93	20	73	L dose	
200		55	145	Total	

According to the information from Table 3, although the CRP levels at the discharge time in both severe and moderate groups were different in individuals who received a high dose of corticosteroids compared to those who had received a low dose of them, but these differences were not statistically significantly.

Table 4. Relationship between LDH level during discharge and the treatment type

P-value	LDH during discharge	Group	
0.005	629±428	H dose	Severe
	395±111	L dose	
0.001	435±97	H dose	Moderate
	359±87	L dose	

As it is clear in Table 4, the LDH levels were significantly lower in both the severe and moderate groups who received low doses of corticosteroids at the time of discharge compared to those who received high doses of them.

Table 5. Relationship between lymphocytes during discharge and the treatment type

P-value	Lymphocytes during discharge	Group	
0.001	15%±8	H dose	Severe
	8%±5	L dose	
0.003	21%±7	H dose	Moderate
	26%±10	L dose	

The information in Table 5 shows that the percentage of lymphocytes was significantly higher in the low-dose corticosteroid group as compared to the high-dose corticosteroid group in the moderate group at the time of discharge. This is while in the severe group, the results were opposite and the percentage of lymphocytes was significantly lower in the low-dose corticosteroid group as compared to the high-dose corticosteroid group. In this way, people receiving low-dose corticosteroids had a lower percentage of lymphocytes than people receiving high-dose corticosteroids.

Discussion

Due to the emergence of the coronavirus and its complications, there is a need for extensive studies in all fields. A corticosteroid can be used as a primary drug to help seriously sick patients with Covid-19. Still, the existence of many contradictions in the results of the studies conducted about the use of corticosteroid as drugs along with the presence of a global challenge to find the proper treatment with the least side effects requires more detailed studies in this field. In this retrospective cross-sectional study, we investigated the impact of these drugs on the recovery of the patients with Covid-19.

According to the results of this study, individuals in the severe group who got high-dose corticosteroids had a significantly higher mortality rate compared to the low-dose group. In the moderate group, however, no significant difference was seen. Furthermore, the CRP level at the discharge time in both severe and moderate groups was not statistically different between people who had gotten a high dosage compared to whom received a low dose. According to the findings, it can be said that the LDH level was significantly lower in both the severe and moderate groups in the patients who received a low dose of corticosteroids at the discharge time. In the moderate group, the percentage of lymphocytes in the low-dose corticosteroid group at the time of discharge was significantly higher as compared to the high-dose corticosteroid group. In contrast, in the severe group, this finding was the opposite. In this way, people receiving low-dose corticosteroids had a lower percentage of lymphocytes compared to the patients who received high-dose corticosteroids.

Xu et al. conducted a controlled study to compare a variety of potential treatments in hospitalized Covid-19 patients. They randomly assigning the patients to two groups receiving oral or intravenous dexamethasone (with doses of 6 mg once daily) for ten days and reported preliminary results. Dexamethasone was administered to 2104 patients, while usual care was administered to 4321 patients. Within 28 days of treatment, 482 patients (22.9 percent) in the dexamethasone group and 1110 patients (25.7 percent) in the standard care group died. The proportionate and absolute difference in mortality rates between groups was significantly different depending on the level of respiratory support the patients received at the randomization time. The mortality rate in the patients receiving invasive mechanical ventilation was lower in the dexamethasone group than the standard care group. Ultimately, their

findings revealed that in individuals hospitalized with Covid-19, the administration of dexamethasone reduced 28-day mortality compared to those who received either invasive mechanical ventilation or oxygen alone. This did not happen to those who did not receive any respiratory support (21).

Quispe-Laime et al. performed an experiment in Miami to determine the relationship between corticosteroid therapy compared to standard care or placebo and 28-day mortality in Covid-19 patients. A total of 1703 patients were examined in this examination. There were 222 deaths among the 678 patients who received corticosteroids and 425 deaths among the 1025 patients who received standard treatment or placebo. This meta-analysis found that systemic corticosteroids are related to lower 28-day mortality compared to standard care or placebo (22).

Tomazini et al. studied whether intravenous dexamethasone improves ventilator-free days in the patients with Covid-19-related ARDS. This multicenter clinical research enrolled the patients with Covid-19 and moderate to severe ARDS in 41 Brazilian intensive care units by a random selection. The intervention was as follows: 20 mg dexamethasone intravenously daily for 5 days, 10 mg dexamethasone intravenously daily for 5 days or till ICU release (151 patients), or standard care alone (148 patients). The findings of this study revealed that among patients with Covid-19 and moderate or severe ARDS, using intravenous dexamethasone in addition to standard care resulted in a statistically significant rise in the number of ventilator-free days (survival days and with no mechanical ventilation) (23).

A study done by Lu et al. looked into mortality in Covid-19 patients with ARDS and the potential role of systemic corticosteroids. According to this study, increased mortality in ARDS caused by Covid-19 necessitates a prompt and aggressive treatment system that involves corticosteroids. The majority of the trials lacked information on the dose regimen of corticosteroid treatment. Nevertheless, low-dose corticosteroids or pulsed corticosteroids can help cases with severe COVID-19 infection (24).

According to a retrospective analysis study done by Arabi et al. on 309 adult MERS patients, half of the cases were given corticosteroids. Ultimately, those who took corticosteroids were found to be significantly more likely to need mechanical ventilation than other cases who received the usual drug (25).

In a study conducted by Nasiri et al. to investigate dexamethasone's effect in the people with Covid-19 and hypoxemia, 156 cases were examined. In this study, some cases who had received dexamethasone at a dose of 12 to 16 mg daily for at least 3 days were chosen randomly, while another group of Covid-19 patients were nearly identical in terms of disease, gender, age, severity, and the pulmonary involvement. According to the findings, the severity of the disease, and the length of the patient's hospitalization following treatment, 28.9 percent died in the intervention group, and 49.4 percent died in the control group. Based on this study, using corticosteroid drugs in treating these cases successfully controls the disease course and decreases its severity (26).

WHO in an article entitled "Corticosteroids for Covid-19", also recommends the use of systemic corticosteroids (oral or intravenous) for severe and critical patients with Covid-19; WHO does not consider corticosteroids necessary in non-critical patients (27).

Tlayjeh et al. investigated the relationship between corticosteroid use and the results of Covid-19 in a systematic review and meta-analysis research. This study showed that the use of corticosteroids is not related to the reduction of mortality and even delays the clearance of the virus. They also stated a large discrepancy between the results of the reviewed observational articles (28).

In an article entitled "Early and Prophylactic Administration of Immunomodulators (Corticosteroids) to Severely Pneumonic Patients with Covid-19,", Lee et al. emphasized that the first dose of immune regulators should be given to the patients at the first times of the respiratory distress (29).

In 2020, Yang et al. examined 15 articles (out of 1685 articles) with a statistical population of 5270

people. They concluded that the patients with severe conditions have a high need for corticosteroids as a treatment. They also mentioned the complications of hypokalemia, hypocalcemia, hyperglycemia, and secondary bacterial infection in these patients (30).

In 2020, Angus et al., performed a clinical trial on 384 patients with an average age of 60 years, investigating three groups for intervention; The shock-dependent dose of hydrocortisone, fixed dose of hydrocortisone, and the group without hydrocortisone as the control. The findings showed that the mortality rate of the patients in the fixed dose and shock-dependent dose groups were respectively 93% and 80% better than the group without hydrocortisone. This clinical trial was stopped prematurely due to the non-compliance of the treatment with the predetermined criteria (31).

As it is clear, there is absolutely contradictory results in the previous studies. As the limited statistical population is one of the limitations of the present work, it is recommended to perform a research with more sample size and in the form of a clinical trial with blinding as well as equalization of the intervention and control groups so that the results can be obtained with more certainty.

Conclusions

This study showed that a low dose of corticosteroids improved the patients with moderate clinical severity. In the patients with severe clinical severity, the results were contradictory, caused by other factors such as underlying diseases, the severity of the disease, etc.

Authors' Contribution

HR.S and M.KJ contributed in conception and design . Other authors contributed in data collection and manuscript drafting. M.KJ supervised the study. All authors approved the final version of the manuscript.

Ethical Approval

The trial was authorized by the Ethical Committee of Hormozgan University of Medical Sciences (IR.HUMS.REC.1399.529 which the webpage of ethical approval code is: https://ethics.research.ac.ir/form/9tjualqoilb0uhis.pdf).

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Conflict of interest

No conflict of interest declaration between the authors.

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