Steroid in the Treatment of Outpatient COVID-19: A Multicenter Randomized Controlled Trial

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Abstract

Background: Early treatment of COVID-19 patients could reduce hospitalization and death. The effect of corticosteroids in the outpatient setting is still unknown. This study aimed to determine the effect of corticosteroids in the prevention of hospitalization of nonsevere cases.

Materials and Methods: This study is a multicenter randomized controlled trial. Seventy five nonsevere COVID-19 patients presented between days 7 and 14 of their symptoms received either prednisolone or placebo. The primary outcome was hospitalization. The study protocol was registered in the Iranian Registry of Clinical Trials on December 2, 2020 (IRCT20171219037964N2).

Results: Although the rate of hospitalization in the prednisolone group was higher than the placebo group (10.8% vs. 7.9%, respectively), it was not statistically significant (*P* value.,6). One patient in each group reported an adverse event and withdrew the medication.

Conclusion: Considering the null effect of corticosteroids in the prevention of hospitalization in outpatient settings, it is suggested not to consider corticosteroids for outpatient treatment.

Keywords: COVID-19, effectiveness, hospitalization, outpatient, steroid

Introduction

In December 2019, some cases of pneumonia appeared in Wuhan City, Hubei Province, China. The clinical manifestations were very similar to viral pneumonia and analysis of lower respiratory tract samples revealed a new coronavirus as the responsible agent, named the novel coronavirus-2019.[1] This new coronavirus causes an acute respiratory disease called COVID-19.[2] Signs and symptoms of COVID-19 include and are not limited to fever, dry cough, fatigue, dyspnea, and lymphopenia. In most people, the symptoms are mild with a good prognosis, but in more severe cases, viral pneumonia infections can lead to acute respiratory syndrome and even death.[3]

As per signs and symptoms, three phases can be recognized in COVID-19 patients.[4] Phase 1 or early infection represented mild and nonspecific symptoms without hypoxia and phase 2 or the pulmonary phase associated with established pulmonary disease with or without hypoxia. In this phase, the virus could activate lung macrophages and also leads to widespread penetration of monocyte-derived macrophages into the small airways.[5,6] After this phase which is usually accompanied by inflammatory cytokine storm, two pathways in probable inflammation may resolve or the patient may develop a systemic hyperinflammation and multiorgan failure which is

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recognized as phase 3 and is usually associated with a poor prognosis and death.[7-10]

Evidence suggests that corticosteroids are effective in reducing mortality in patients with severe COVID-19.[11] They have a wide range of immunosuppressive effects, including reduced synthesis of inflammatory cytokines and leukocyte infiltration to T-cell apoptosis. In addition to the anti-inflammatory effect, they are also effective in stabilizing patients' hemodynamic status with COVID-19.[12] The Association of Thoracic Specialists recommends low dose (1-2 mg/day) and short-term (3-5 days) administration of methylprednisolone in patients with dyspnea, progressive symptoms, increased C-reactive protein, and early signs of cytokine storm.[13] Following the release of the RECOVERY trial, in which 6,245 patients were tested, Oxford scientists found that dexamethasone reduced mortality in 35% of patients who need a ventilator and in 20% of patients who need supportive oxygen. Hence, the use of corticosteroids in the treatment of COVID-19 patients has been recommended for patients with severe disease.[14]

As per the US Centers for Disease Control and Prevention, the World Health Organization, and Iran's national guideline for managing COVID-19 patients, people with nonsevere COVID-19 could receive care at home. In Iran, these patients are followed up by a telephone call by healthcare providers daily and may refer to the hospital in case of progression of symptoms or may continue supportive care at home.[15] A study on the economic burden of COVID-19 in Iran estimates the mean cost per intensive care unit patient at 13267 USD.[16] Early initiation of corticosteroid in the course of COVID-19 disease reduced the mortality rate by 5%, but the intensive care unit admission rate, intubation rate, and the hospitalization duration were not affected.[17] Higher dose of dexamethasone (12 mg vs. 6 mg) in severe hypoxic COVID-19 patients had higher probability of benefit and lower probability of harm.[18]

The use of low-dose prednisolone in outpatient nonsevere COVID-19 may be effective in reducing tissue degradation and preventing the patient from entering the cytokine storm phase and the need for hospitalization. However, because we have no evidence that the virus stops replicating in this phase, it may exacerbate the virus and cause the virus to invade other tissues. Therefore, in this study, we investigate the therapeutic effect of corticosteroids for nonsevere outpatient cases to find evidence to control disease exacerbation in outpatients.

MATERIALS AND METHODS

This study was a triple-blind randomized controlled trial conducted between December 5, 2020 and March 31, 2021, in three outpatient centers in Isfahan, Iran. Patients who were a confirmed case of COVID-19, in the second week of symptoms, with O_2 saturation of 93 or more and 18 years or older were included. Pregnant women and those who had a drug history of antiviral drugs such as Favipiravir-based and Ritonavir-based drugs, those who had taken a steroid in

previous two weeks, and immunosuppressive patients were excluded from this study.

Participants were randomly assigned to the intervention and control group using a simple randomization method (1:1 ratio).org. Patients received either steroid that was prednisolone tablet (Iran Hormone, Tehran, Iran), 50 mg/day for five days, or a placebo. The placebo was made by the school of pharmacy of Isfahan University of Medical Sciences and it was the same as prednisolone in size, shape, and color. An independent staff packed prednisolone and placebo in same boxes and labeled them as A or B. The random string was produced by the project manager who was not engaged with patients using randomization.org. For each eligible patient, a specific code was assigned and the project manager matched the code with random string and defined the group for the patient. In this study, the patients, physicians, project manager, outcome evaluator, and data analyzer were blinded. The A and B label were opened at the end of the study.

The variables that were evaluated in this study were demographic data such as age, gender (female, male), job (self-employed, housekeeper or retired, students, employee), education (diploma and lower, higher education), height, weight, history of underlying comorbidities (diabetes, HTN, cardiovascular and pulmonary disease, and cancer), and date of symptoms initiation. We also evaluated the presenting signs and symptoms (fever, cough, headache, dyspnea, gastrointestinal symptoms, sore throat, runny nose, chills, body pain, loss of appetite, loss of smell or taste, and fatigue).

The primary outcome was hospitalization assessed on day 3, 7, 14, 21, and 28 via phone call. The secondary outcome was the evaluation of adverse events.

Considering the outpatient field of study and the compliance of patients, which is an essential determinant of success, especially in outpatient settings, we analyzed data using the intention to treat method. Data were analyzed using SPSS version 22 software (SPSS Inc., IL, USA). To report continuous and categorical variables, mean (standard deviation) and frequency were used, respectively. To compare age between two groups, independent sample *t*-test was used. For other variables, Chi-squared test was used. A significant level was considered at 0.05.

The study protocol was registered in the Iranian Registry of Clinical Trials on December 2, 2020 (IRCT20171219037964N2). We follow the Consolidated Standards for Reporting Trials in reporting the results.

RESULTS

Eighty patients were assessed for eligibility and 75 of them were randomly allocated into two groups, 37 patients in the steroid and 38 patients in the placebo group. Four patients in the steroid group and seven patients in the placebo group did not follow the allocated intervention [Figure 1].
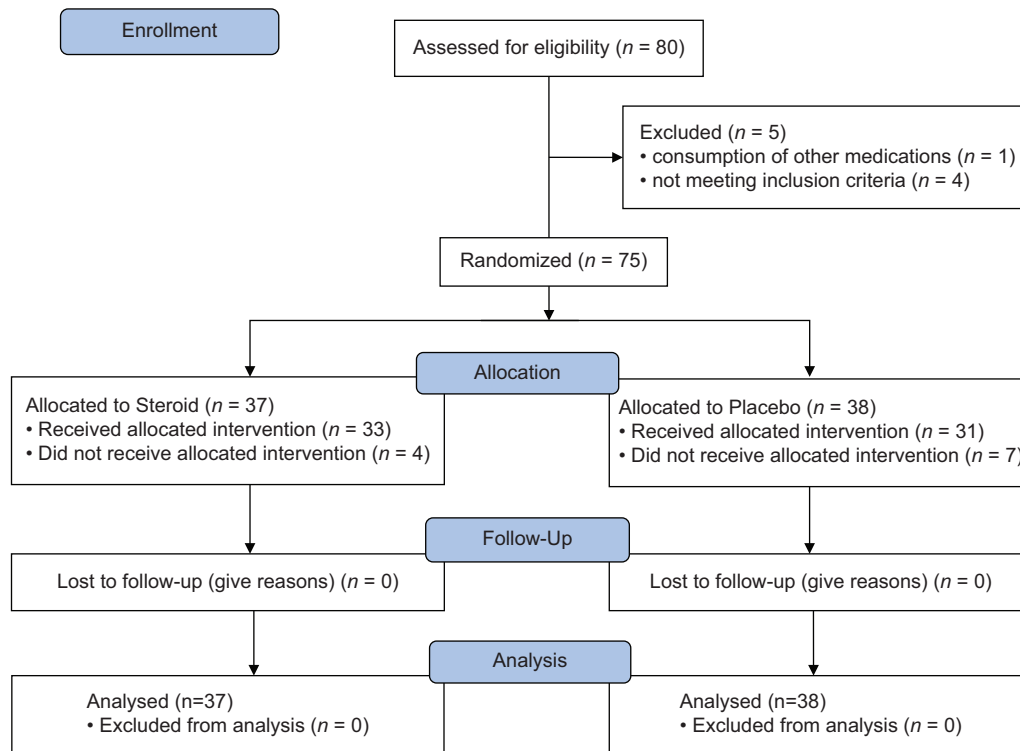
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┌──────────────┐
│  Enrollment  │        ┌─────────────────────────────────────┐
└──────────────┘        │ Assessed for eligibility (n = 80)   │
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                                          ├─────▶│ Excluded (n = 5)                            │
                                          │      │ • consumption of other medications (n = 1)  │
                                          │      │ • not meeting inclusion criteria (n = 4)    │
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                        │ Randomized (n = 75)                 │
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Figure 1 CONSORT flow diagram

| Allocation |
Allocated to Steroid (n = 37)	Allocated to Placebo (n = 38)
• Received allocated intervention (n = 33)	• Received allocated intervention (n = 31)
• Did not receive allocated intervention (n = 4)	• Did not receive allocated intervention (n = 7)

| Follow-Up |
| Lost to follow-up (give reasons) (n = 0) | Lost to follow-up (give reasons) (n = 0) |

| Analysis |
| Analysed (n=37) | Analysed (n=38) |
| • Excluded from analysis (n = 0) | • Excluded from analysis (n = 0) |

Figure 1: Consolidated standards of reporting trials (CONSORT) flow diagram

The mean age (± standard deviation) of patients in the steroid and placebo groups were 47.8 (± 13.3) and 44.3 (± 15.2), respectively (*P* value.,3). There was no significant difference between groups in terms of gender, job, and comorbidities. Most of the patients in the intervention and placebo group were female (56.8% vs. 55.3%, respectively; *P* value.,8). About 24% of patients in the intervention group and 23% of patients in the placebo group report previous comorbidities (*P* value.,9). Considering education, 54% of patients in the steroid group had a diploma or less, whereas 68% of patients in the placebo group had higher education (*P* value.,04). Table 1 shows the details of demographic variables in two groups of study.

The most prevalent symptom in the whole study sample was fatigue and cough in 82.7% and 78.7% of patients, respectively. Other prevalent symptoms include dyspnea (53.3%), headache (48.0%), body pain (48.0%), and fever (41.3%). The least prevalent symptom was a runny nose (28.0%). Presenting symptoms were not statistically different between the two groups [Table 2].

The primary end point in this study was the hospitalization rate. In the steroid group, four patients (10.8%) were hospitalized, whereas the hospitalization rate in the placebo group was 7.9% (3 patients). Although the hospitalization rate was higher in the steroid group, this was not significantly different (*P* value.,6) [Table 2]. In the intervention group, one patient was admitted on day 1, one patient on day 2, and two patients on day 3. In the placebo group, all three patients were admitted on day 4. The patients who withdrew the use of steroids or placebo were not hospitalized in the follow-up period.

Table 1: Demographic characteristics of the patients by treatment groups

Characteristics	All patients	Steroid	Placebo	P
Age, year				
Mean (SD)	46.0 (14.35)	47.8 (13.3)	44.3 (15.20)	0.3
Gender				
Male	33 (44.0)	16 (43.2)	17 (44.7)	0.8
Female	42 (56.0)	21 (56.8)	21 (55.3)	
Job				
Self-employed	19 (25.3)	8 (21.6)	11 (28.9)	0.7
Housekeeper or retired	39 (52.0)	21 (56.8)	18 (47.4)	
Students	3 (4.0)	1 (2.7)	2 (5.3)	
Employee	14 (18.7)	7 (18.9)	7 (18.4)	
Education				
Diploma and lower	32 (42.7)	20 (54.1)	12 (31.6)	0.049
Higher education	43 (57.3)	17 (45.9)	26 (68.4)	
Any comorbidities	18 (24.0)	9 (24.3)	9 (23.7)	0.9
BMI ≥25	49 (69.0)	24 (72.7)	25 (65.8)	0.5

Data were reported in *n* (%), otherwise mentioned. Data were analyzed using Chi-square, otherwise mentioned. SD: standard deviation, BMI: body mass index.

Considering the secondary outcome, one patient in the steroid group reported palpitation and one patient in the placebo group reported aphthous stomatitis.

DISCUSSION

This study was a randomized controlled trial in an outpatient setting to evaluate the effect of corticosteroids in preventing

Table 2: Clinical characteristics and outcome by intervention groups

Characteristics	All patients	Steroid	Placebo	*P*
Signs and symptoms				
Fever	31 (41.3)	16 (43.2)	15 (39.5)	0.7
Cough	59 (78.7)	28 (75.7)	31 (81.6)	0.5
Headache	36 (48.0)	20 (54.1)	16 (42.1)	0.3
Dyspnea	40 (53.3)	22 (59.5)	18 (47.4)	0.2
GI	27 (36.0)	15 (40.5)	12 (31.6)	0.4
Sore throat	22 (29.3)	12 (32.4)	10 (26.3)	0.5
Runny nose	21 (28.0)	12 (32.4)	9 (23.7)	0.3
Chills	35 (46.7)	19 (51.4)	16 (42.1)	0.4
Body pain	36 (48.0)	18 (48.6)	18 (47.4)	0.9
Loss of appetite	33 (44.0)	18 (48.6)	15 (39.5)	0.4
Loss of smell or taste	28 (37.3)	15 (40.5)	13 (34.2)	0.5
Fatigue	62 (82.7)	33 (89.2)	29 (76.3)	0.1
Hospitalization	7 (9.3)	4 (10.8)	3 (7.9)	0.6

hospitalization in nonsevere COVID-19 patients. Seventy five nonsevere COVID-19 patients presented in the second week of symptom initiation were randomly received placebo or prednisolone (50 mg/day) for five days. The result of the study shows no statistical difference in the hospitalization of patients between the two groups.

Early outpatient therapy for COVID-19 patients is vital in the management of resources and reduction of hospitalization. Considering the high transmission rate of COVID-19, home management could also break the transmission chain.[19] Outpatient management of COVID-19 consists of supportive care and reduction of transmission strategies. There is no proven medication in the outpatient setting, and guidelines recommend supportive care.

The use of corticosteroids is supported by valid guidelines for severe patients after the promising results of the RECOVERY study.[14] Studies on hospitalized patients have shown the effect of corticosteroids in reducing the need for mechanical ventilation and length of hospital stay.[20,21] In addition, the early use of corticosteroids is effective in improving the radiographic lesions and also the amount of oxygen support needed.[22]

The severity of response in the second phase of the COVID-19 disease is the determinant of outcome. Phase 2 of COVID-19 is usually accompanied by inflammatory cytokine storm and is supposed to be the proper point for administering corticosteroid, considering its anti-inflammatory and immune system stabilizer effects.[7-10] Keeping in mind the little observation in outpatient settings, the immunosuppressive effects of corticosteroids could potentially deteriorate the clinical outcome.[23] There is also another challenge for the use of corticosteroids considering the clearance time; some studies indicate an increase in virus clearance time[24-26] and some others indicate no significant change.[27-30]

To the best of our knowledge, there is just one study performed on the effect of corticosteroids in outpatient settings but its

result is not published yet.[31] The result of a study on nonsevere hospitalized cases revealed the potential adverse effect of corticosteroids on lung recovery. Also, corticosteroid has not changed the progression to severe disease.[32] This was the same as the result of our study. In our study, the rate of hospitalization did not differ between the two groups.

Our study has some limitations. First, the relatively small sample size which is amplified by the nature of the outpatient setting and noncompliance of patients. Second, data on follow-up polymerase chain reaction are scarce and we cannot come to the proper conclusion on this issue. The result of this study should therefore be interpreted with caution.

Although early treatment with corticosteroids was well tolerated by patients, our preliminary data showed no beneficial effect on hospitalization and disease severity. Although corticosteroids as immunosuppressive drugs can be harmful through the treatment of infection and potentially can increase the viral shedding duration, from the public health viewpoint, restraint and caution are needed.

Conclusion

Considering the potential adverse effects of corticosteroids, along with no effect on prevention from hospitalization, it is recommended to limit the use of corticosteroids for severe cases.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Ethical statement
The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.781). The conduction of the study was as per the Good Practice Guideline; Patients were informed about the study protocol and aims of the study, and they were asked to sign an informed consent before participation.

Conflicts of Interest
The authors declare that they have no conflict of interest.

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