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Ivermectin as a Potential Addition to the Limited Anti-COVID-19 Arsenal: A Double-Blinded Clinical Trial

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Abstract

Background: Addressing the Coronavirus disease 2019 (COVID-19) pandemic remains a significant challenge for healthcare systems globally. Despite the absence of a proven cure, ivermectin has been proposed as a potentially effective agent against it.
Objectives: This study aimed to evaluate the therapeutic effects of ivermectin compared to a placebo group in non-critically ill confirmed COVID-19 patients.
Methods: A double-blind, randomized clinical trial was conducted on 110 patients with moderate-to-severe (non-critical) confirmed COVID-19 infection. The patients were equally divided into two groups, with one group receiving ivermectin tablets (14 mg every 12 hours for three days) and the other group receiving a placebo. The efficacy and safety of ivermectin were assessed in both groups.
Results: A total of 110 patients, including 62 (56.4%) men and 48 (43.6%) women, with an average age of 53.36 ± 15.10 years, were enrolled in our double-blind, randomized clinical trial. The baseline characteristics of the two groups were similar. The findings demonstrated that ivermectin significantly reduced the need for Intensive Care Unit admission (32.7% vs. 5.5%; $P < 0.001$), hospitalization duration (six vs. four days; $P < 0.001$), and median time to symptom resolution period ($P < 0.05$) in COVID-19 patients compared to the placebo group, without any serious side effects ($P > 0.05$).
Conclusions: Ivermectin appears to be a potentially effective and safe medication for COVID-19 patients with moderate disease.

Keywords: COVID-19, Ivermectin, Treatment Efficacy, Drug Safety, Randomized Controlled Trial

1. Background

One of the major global health challenges is the Coronavirus disease 2019 (COVID-19) pandemic. The SARS-CoV-2 virus responsible for this disease belongs to the beta-coronavirus family and is the seventh member of the coronavirus family (1). According to statistics from the World Health Organization (WHO), as of June 18th, 2021, a total of 3 840 223 individuals had lost their lives due to this infection (2). On a positive note, there have been significant advancements in developing effective vaccines against COVID-19, which have

substantially reduced morbidity and mortality rates and instilled hope for disease control (3). Despite numerous studies investigating potential treatments for COVID-19, no confirmed cure for this virus has been found, and proposed treatments have not proven to be efficient (4). Although vaccination has had a significant impact on controlling the COVID-19 pandemic, certain populations, such as older adults and immunosuppressed individuals, still benefit from treatment for this viral infection, especially if they have been vaccinated (5).

Hence, further robust studies are necessary to discover more effective treatments for the virus. Ivermectin has recently emerged as a relatively safe, cost-effective, and readily available treatment option. This medication is a broad-spectrum antiparasitic drug approved by the US Food and Drug Administration (6). In a recent in vitro study by Caly et al., it was demonstrated that the addition of a single dose of ivermectin to Vero-hSLam cells infected with SARS-CoV-2 resulted in a 500-fold decrease in viral RNA levels over 48 hours. Theoretically, it seems that by inhibiting the beta receptor's entry, which serves as a crucial element in transmitting the virus into target cells, as well as its proliferation and resistance to antibiotic agents, this medication possesses potent antiviral properties (4, 7). Additionally, the findings of some recent observational studies have indicated that ivermectin is effective in reducing mortality among patients admitted to the intensive care unit (ICU) with COVID-19 infection (P-value = 0.005, 95% CI = 0.04 - 0.57, OR = 0.15). However, the decrease in mortality rates was insignificant among moderate to severe patients who had not initially been admitted to the ICU (8). A recent review study by Bhowmick et al., which examined 19 clinical trials and observational studies, revealed that none of the investigations could confirm or refute ivermectin as monotherapy or an adjunct therapeutic agent (9).

2. Objectives

Given the discrepancies in the findings of previous studies and the need for more rigorous investigations into the therapeutic approach for the infection, the authors decided to conduct a clinical trial to examine the efficacy and safety of ivermectin among COVID-19 patients.

3. Methods

3.1. Study Design

This study was a double-blind, randomized clinical trial involving 110 patients diagnosed with confirmed COVID-19 infection, who were referred to Razi and Sina Hospital in Ahvaz, Iran, from July 30th, 2020, to June 15th, 2021. Initially, it received approval from the Research Ethics Committee of Ahvaz Jundishapur University of Medical Sciences and the Iran National Committee for Ethics in Biomedical Research. Subsequently, it was registered with the code number IRCT20200404046937N4 at the Iranian Clinical Trial Registry. All participants provided informed written consent, and patients retained the right to discontinue the trial at any time.

3.2. Participants

One hundred ten patients diagnosed with confirmed COVID-19 infection based on real-time PCR results were included in the study. All participants were randomly assigned to two groups using the block randomization method, resulting in 55 patients in the ivermectin arm and 55 patients in the placebo arm (1:1 ratio). The placebo tablets were identical to the ivermectin tablets in appearance and physical properties, including size, shape, color, taste, smell, and packaging. Placebo medications were manufactured by the Pharmacy Faculty of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, and administered to patients in a manner similar to ivermectin.

Both the individuals administering the medication and the participants were unaware of whether they were receiving placebo or ivermectin. The packages were coded before tablet administration, and only the investigators responsible for statistical analysis had access to these codes.

3.3. Inclusion and Exclusion Criteria

The eligibility criteria for participation in the study included confirmation of COVID-19 infection based on PCR results, moderate to severe disease (non-critical illness) (10), age above 18, hospitalization, consent to participate in the study, and no participation in any other investigations in the preceding 28 days. Exclusion

criteria encompassed patients with critical conditions or mild illness, those requiring ICU admission at the outset of the study, a history of sensitivity to ivermectin, severe renal, hepatic, or cardiac disease, pregnancy, intent to become pregnant, or breastfeeding.

Baseline characteristics, such as gender, marital status, occupation, place of residence, height, weight, vaccination status, smoking history, medical history, and medication history, were documented for all participants. Additionally, patients' signs and symptoms, including fever, chills, cough, dyspnea, nausea and vomiting, myalgia, sore throat, diarrhea, vital signs, O_2 saturation, ward or ICU treatment status, level of lung involvement based on chest computed tomography (CT) scan findings, and laboratory data including lactate dehydrogenase (LDH), qualitative C-Reactive Protein (CRP), polymorphonuclear leukocyte (PMN), and lymphocyte cell counts, were recorded at the outset of the study. Clinical evaluation and treatment of all patients involved in the study were conducted by an infectious disease specialist specializing in COVID-19 management.

Adverse medical events assessment was conducted by an objective team of clinicians with expertise in infectious diseases and pharmacology (pre-determined Adjudicating team) to ensure the accuracy and consistency of the clinical truth of each event. They reviewed the provided clinical event information and based their assessment on that data without bias or partiality. Moreover, the Data and Safety Monitoring Board (consisting of specialists in pharmacology, infectious diseases, and pulmonary diseases) was tasked with monitoring the clinical conditions of patients enrolled in these trials. They screened the trial for early detection of efficacy, findings of harm, and futility in obtaining a meaningful outcome. The DSMB members were committed to keeping the scientific and clinical questions under investigation foremost in their minds as they reviewed the collected data.

3.4. Intervention Protocols

In the intervention group, patients were treated with ivermectin (14 mg every 12 hours for three days) in addition to the standard treatment based on Iran's Internal Guidelines (11). In contrast, the second group received standard therapy with a placebo administered once every 12 hours for three days.

Based on Iran's National Guidelines for COVID-19 treatment protocol, dexamethasone 8 mg (IVI) for a maximum of 10 days, Remdesivir 200 mg (IVI) on the first day, and then 100 mg (IVI) daily for five days, enoxaparin 40 mg subcutaneously once daily (for venous thromboembolism prophylaxis), were administered to all participants as standard treatment. Additionally, supplemental oxygen and symptomatic therapy (for fever, pain, cough, malaise, sore throat, etc.) were applied if needed. Both groups measured all cases' signs and symptoms, conducted physical examinations, and assessed laboratory test results daily. Furthermore, a low-dose chest CT-scan without contrast was performed on all patients on admission and discharge day. All findings were recorded in a standard checklist.

3.5. Outcomes

Primary endpoints included improving the patient's general condition, maintaining O_2 saturation $\geq$ 94% in ambient air without respiratory distress, and being fever-free for at least 72 hours. Secondary endpoints in the study included the requirement for patient transfer to the ICU throughout the study, intubation rate, morbidity and mortality rates, duration of hospitalization, time required for resolution of signs and symptoms, chest CT-scan findings, and laboratory data upon admission and on the last day of the study (at discharge or at the conclusion of the previous chest CT-scan in deceased patients). The Visual Analog Scale was used as a questionnaire to assess the time needed to resolve the patient's signs and symptoms during hospitalization. The time to symptom resolution was defined as the period between the onset of the patients' symptoms and the first day they rated their symptoms as 0 (the lowest possible score) (12). We compared the level of lung involvement in the two groups before and after the trial using chest CT-scan intensity grading (grade 1 = mild, grade 2 = moderate, and grade 3 = severe) as mentioned in the study by Saeed et al. (13). All patients were clinically assessed for side effects, allergies, and possible reactions to ivermectin. Additionally, we measured the six-minute walking distance (6-MWD) as an objective measure for

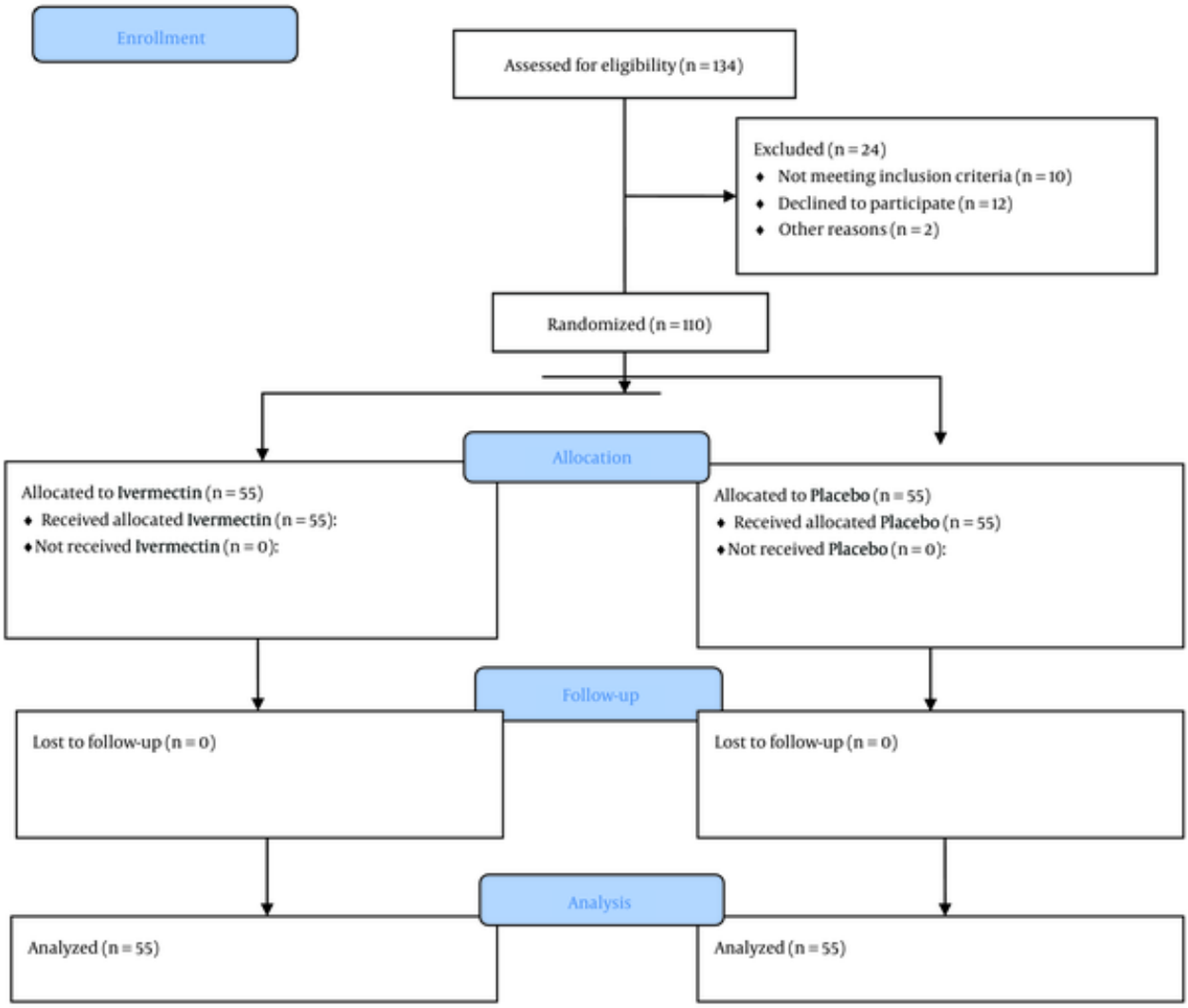

Figure 1. The flowchart of the distribution of participants with Coronavirus disease 2019 (COVID-19) during the study

respiratory recovery in both groups and compared the results (14).

3.6. Sample Size Calculation

Considering the clinical trial design of the study and the main binary outcomes (survival and ICU admission), assuming alpha = 0.05 and power = 0.8 (β = 0.20), and the proportion of cases exposed to adverse outcomes and good prognosis in each parallel group based on the findings of previous similar studies (12), the following formula was used to calculate the sample size in both parallel groups:

$$N = \frac{\left(z_{\frac{\alpha}{2}} + z_{\beta}\right)^2 (p_1 q_1 + p_2 q_2)}{X^2} \approx 17$$

Considering the effect size (x) of 0.2, the required sample size for each group was at least 17 cases. However, this clinical trial was continued to obtain more accurate

Table 1. Baseline Characteristics of Enrolled Patients [a]

Variables (Demographic Data)	Control	Intervention	P-Value
Age	53.26 ± 14.12	53.56 ± 16.08	0.883
BMI (kg/m ^{2})	25.44 ± 3.06	25.62 ± 2.68	0.745
Gender			> 0.999
Male	31 (56.4)	31 (56.4)	
Female	24 (43.6)	24 (43.6)	
Marital status			0.252
Single	5 (9.1)	9 (16.4)	
Married	50 (90.9)	46 (83.6)	
Education level			0.281
Illiterate	2 (3.6)	0 (0)	
Elementary	14 (25.5)	12 (21.8)	
Diploma	26 (47.36)	23 (41.8)	
University	13 (23.6)	20 (36.4)	
Occupation			0.557
Unemployed	1 (1.8)	4 (7.3)	
Non-governmental	14 (25.5)	12 (21.8)	
Governmental	23 (41.8)	21 (38.2)	
Housewife	17 (30.9)	18 (32.7)	
Living sitting			> 0.999
Urban	46 (83.6)	46 (83.6)	
Rural	9 (16.4)	9 (16.4)	
Baseline medical history			
Positive for an infection history	7 (12.7)	2 (3.6)	0.082
Positive smoking habits	9 (16.4)	8 (14.5)	0.792
Positive past surgical history	18 (33.3)	17 (31.5)	0.837
Past medical history			0.760
Diabetic	8 (14.5)	4 (7.3)	
Hypertension	6 (10.9)	5 (9.1)	
Lung disease	1 (1.8)	0 (0)	
Other	1 (1.8)	3 (5.5)	
Diabetes mellitus and hypertension	2 (3.6)	2 (3.6)	
Diabetes mellitus and other diseases	1 (1.8)	0 (0)	
Hypertension and other diseases	1 (1.8)	1 (1.8)	
Diabetes mellitus disease	1 (1.8)	2 (3.6)	
Baseline symptoms			
Fever	30 (54.5)	20 (36.4)	0.056
Shivering	12 (21.8)	16 (29.1)	0.381
Cough	46 (83.6)	46 (83.6)	> 0.999
Dyspnea	34 (61.8)	38 (69.1)	0.423
Sore throat	7 (12.7)	2 (3.6)	0.161
Nausea	10 (18.2)	10 (18.2)	> 0.999
Diarrhea	11 (20)	4 (7.3)	0.052
Myalgia	29 (52.7)	19 (34.5)	0.055

[a] Values are expressed as No. (%) or mean ± SD.

results until the maximum sample size of eligible patients was fully investigated.

3.7. Statistical Analysis

In this study, continuous variables were reported as mean ± SD or median, and differences between groups were examined using the independent sample *t*-test or the Mann-Whitney test. Categorical variables were reported as number and percentage, and the differences in categorical variables were assessed using the chi-square or Fisher's exact test. Data were analyzed using

Table 2. Comparison of the Need for Intensive Care Unit During Hospitalization and the Duration of Hospitalization in the Study Groups (Fisher Exact Test and Mann-Whitney) [a]

Variables	Control	Intervention	P-Value
Admission in ICU	18 (32.7)	3 (5.5)	< 0.001
Intubation rate	11 (20)	2 (3.63)	< 0.001
Hospital admission length	6 (5 - 6)	4	< 0.001

[a]Values are expressed as No. (%) unless otherwise indicated.

Table 3. Comparison of Time to Symptom Resolution in the Studied Groups (Tested by Mann-Whitney U)

Symptoms Duration Median (IQR)	Control Days (IQR)	Intervention Days (IQR)	P-Value
Fever	4 (3 - 4)	3 (2 - 3)	< 0.001
Shivering	4 (4 - 5)	3 (2 - 3)	< 0.001
Cough	5 (4 - 6)	3 (2 - 3)	< 0.001
Dyspnea	4 (4 - 5)	3 (2 - 3)	< 0.001
Sore throat	4 (3 - 4)	2.5 (2 - 2.5)	< 0.092
Nausea	4 (3.75 - 4.25)	3 (2.75 - 4)	0.015
Diarrhea	4 (4 - 5)	2.5 (2 - 3)	0.005
Myalgia	5 (4.5 - 5)	3 (2 - 3)	< 0.001

SPSS 21, and P-values < 0.05 were considered statistically significant.

4. Results

Our investigation was conducted from July 2020 to June 2021. During the study period, three disease waves occurred, including 20A (B.1.36), 20B (B.1.1.413), and 20I (B.1.1.7), respectively, in Ahvaz, Iran (1).

In this study, 134 patients infected with COVID-19 were initially assessed for eligibility criteria, and 110 cases were ultimately assigned to two groups receiving either ivermectin or placebo equally (Figure 1).

4.1. CONSORT Flow Diagram

None of the participants were vaccinated. Sixty-two patients (56.4%) were male, and the rest were female. The average age of participants was 53.36 ± 15.10 years. As demonstrated in Table 1, the two groups were similar in basic characteristics, and there was no significant difference between them regarding demographic variables or the severity of illness upon admission. However, lung involvement on chest CT-scans and CRP levels were slightly higher in cases receiving ivermectin (P < 0.05). Additionally, LDH levels were higher in the placebo group at the beginning of the study (P < 0.05).

Primary endpoints (mortality, the need for ICU admission, and the duration of hospitalization):

Fortunately, no deaths occurred in either group during hospitalization. 32.7% of cases receiving placebo and only 5.5% of those administered ivermectin required ICU admission, representing a statistically significant difference between the two groups (P < 0.001). The rate of intubation between the two groups was also significantly different. While only 3.63% of patients in the treatment group were intubated during admission, 20% of participants in the control group were intubated (P < 0.001). Moreover, the median duration of hospitalization in the placebo group was 6 (5 - 6) days, whereas in the group administered ivermectin, it was 4 (4 - 4) days, which also showed a significant difference (P < 0.001) (Table 2).

Secondary endpoints (time to symptom resolution, signs and symptoms, laboratory results, and imaging findings):

Based on Table 3, among those receiving ivermectin, the median time to symptom resolution was 3 (2 - 3) days for fever, shivering, cough, dyspnea, and myalgia, 3 (2.75 - 3) days for nausea, and 2.5 (2 - 3) days for diarrhea, indicating a faster resolution of symptoms compared to the placebo group (P < 0.05). The two groups had no significant difference in the time required to resolve the

Table 4. Comparison of Baseline and Final Para-Clinical Test Results Between Intervention and Control Arms of the Coronavirus Disease 2019 Patients (chi-Square and Fisher Exact Test)

Vital Signs and Laboratory Data, Median (IQR)	Control	Intervention	P-Value
Respiratory rate > 24/minute			
Before trial	11 (20)	14 (25.5)	0.495
On the last day of the trial	0 (0)	0 (0)	> 0.999
Blood oxygen saturation < 94%			
Before trial	36 (65.5)	36 (65.5)	> 0.999
On the last day of the trial	3 (5.5)	4 (7.3)	> 0.999
6MWD			
Before trial	501 (± 75)	493 (± 68)	0.279
On the last day of the trial	510 (± 91)	506 (± 83)	0.405
ESR			
Before trial	53 (40 - 68)	51 (35 - 70)	0.893
On the last day of the trial	40 (30 - 52)	37 (25 - 45)	0.104
Lymphocyte count			
Before trial	1500 (1100 - 1800)	1500 (1300 - 1900)	0.282
On the last day of the trial	1700 (1500 - 1900)	1700 (1400 - 2100)	0.176
PMN cells count			
Before trial	6800 (5000 - 8000)	6000 (5000 - 7200)	0.156
On the last day of the trial	6500 (4800 - 7800)	5500 (4400 - 7000)	0.111
LDH			
Before trial	700 (548 - 840)	560 (423 - 800)	0.026
On the last day of the trial	690 (570 - 870)	466 (400 - 654)	< 0.001
C-reactive protein			
Before trial	2 (2 - 3)	3 (2 - 3)	0.009
On the last day of the trial	1 (1 - 2)	1 (0 - 1)	0.006

Abbreviations: 6MWD, 6-Minute walking distance; ESR, erythrocyte sedimentation rate; PMN, polymorphonuclear; LDH, lactate dehydrogenase.

sore throat. Furthermore, a comparison of blood oxygen saturation and respiratory rates at admission and discharge demonstrated substantial improvement in both groups, with no significant difference between the groups regarding these two parameters (P > 0.05).

Regarding laboratory results, qualitative CRP and LDH levels showed significant improvement in patients receiving ivermectin compared to the placebo group (P-value < 0.05). There was no significant improvement in quantitative erythrocyte sedimentation rate (ESR) levels, lymphocyte, and PMN counts (Table 4).

Moreover, there was no significant difference between the two groups regarding the improvement of chest CT-scan findings (P-Value > 0.05) (Table 5). Among those administered ivermectin, there were no reports of sensitivity reactions, adverse effects, or drug-related toxicity. There weren't any differences in the intervention vs control group in this regard (P-Value > 0.05). The 6-MWD was also calculated for both groups before and after the trial but showed no statistically significant difference between the categories, neither before nor following the trial. As it can be seen in the table, the difference between the severity of lung involvement based on CT-scan of the chest between the control and intervention group was not significant.

Table 5 . Comparison of the Improvement of Pulmonary Involvement Based on Chest CT-Scan Intensity Grading Between the Intervention and Control Arms of Coronavirus Disease 2019 Patients (Tested by Fisher Exact Test and Wilcoxon) [a]

Time	Chest CT-Scan Grading Intensity	Control	Intervention	P-Value
Before trial	1	26 (47.3)	12 (21.8)	0.009
	2	29 (52.7)	42 (76.4)	
	3	0 (0)	1 (1.8)	
After trial	1	26 (47.3)	14 (25.5)	0.019
	2	29 (52.7)	39 (70.9)	
	3	0 (0)	2 (3.6)	
P-value		> 0.999	0.564	-

[a] Values are expressed as No. (%).

The pre-determined Adjudicating team, which was responsible for objectively evaluating any probable adverse effect of the medication, reported no serious adverse effects in any of the trial's categories.

5. Discussion

Coronavirus disease 2019 is one of the most important diseases of the last few decades and has created major challenges for healthcare systems worldwide. Although many strategies have been proposed to tackle this infection, none have proven efficient. Despite the development of various vaccines against COVID-19, the SARS-CoV-2 virus undergoes mutations, which lead to changes in its virulence and distribution and possibly reduce the efficacy of vaccines. Therefore, finding effective treatments for patients remains a key component in the strategy to fight COVID-19 (15). One potential therapeutic agent that has recently been investigated in clinical studies is ivermectin, but the results of these studies have been inconclusive (8, 9).

This study was conducted on moderate to severe (non-critical) cases of Covid-19 infection. Based on our findings, ivermectin can be important in shortening the time to resolve symptoms such as fever, shivering, myalgia, cough, dyspnea, vomiting, and diarrhea. A recently conducted case series study has shown that combination therapy with doxycycline and ivermectin can also shorten the time to resolution for some symptoms related to COVID-19 infection in mild to moderate cases (16). In a double-blind clinical trial, Chaccour et al. demonstrated that a single dose of ivermectin (400 mcg/kg) shortened the time to resolution of anosmia/hyposmia and cough among non-critical COVID-19 cases (17). In another clinical trial, Chahla et al. showed that ivermectin reduces the severity of symptoms in COVID-19 outpatients (18). Lopez-Medina et al. conducted a double-blind clinical trial on younger COVID-19 patients with mild disease and compared the time to resolution of symptoms between those administered ivermectin and placebo. Their results showed no significant difference between the two groups, but these findings may be explained by the fact that this study was conducted in young patients with mild illness (19).

5.1. The Effect of Ivermectin on the Length of Hospital Stay and Intensive Care Unit Requirement

According to our results, 32.7% of the placebo group and only 5.5% of those administered ivermectin required ICU admission during hospitalization, which showed a significant difference ($P < 0.001$). Furthermore, the median periods of hospitalization in the placebo group and the group treated with ivermectin were 6 (5 - 6) days and 4 (4 - 4) days, respectively, which showed that the duration of hospitalization was significantly higher in the placebo group. In agreement with our results, Gorial et al. indicated that hydroxychloroquine, azithromycin, and ivermectin, in addition to the COVID-19 treatment regimen, had a significantly lower duration of hospitalization than those treated with hydroxychloroquine and azithromycin without ivermectin (20). Similar to our findings, in a preprint study, Soto-Becerra et al. demonstrated that ivermectin reduced the need for ICU admission among patients with COVID-19 infection (21). Khan et al. reported that ivermectin improved the prognosis of COVID-19 patients and reduced the duration of hospitalization and the time of viral clearance compared to the control group (22). However, in another study, Ahmed et al. found that although the duration of hospitalization in ivermectin recipients with or without doxycycline was shorter than in the placebo group, the difference was insignificant (23). Furthermore, Karale et al. demonstrated that ivermectin is associated with reduced mortality and the need for ICU admission (24).

5.2. Ivermectin's Effects on Laboratory Parameters

Our findings demonstrated that ivermectin significantly improved the qualitative CRP and LDH levels compared to placebo at discharge. These findings agree with those reported by Ahmed et al., who assessed the effects of a 5-day therapeutic regimen consisting of ivermectin on CRP and LDH levels, representing the severity of the inflammatory phase of the illness (23). In addition to its direct antiviral effect, this medication activates inhibitory pathways involved in the inflammatory process, such as TNF-alpha, interleukin-8, and LL-37. Subsequently, there is an indirect activation of interleukin-1 beta and interleukin-18, which results in a decrease in neutrophilic and eosinophilic chemotaxis and improvement in the signs and symptoms, shortening of the course of the illness, and faster resolution of abnormal laboratory findings.

5.3. Ivermectin's Side Effect Profile

In combination with the standard of care, Ivermectin was safe, easily tolerated by the participants in our study, and without serious adverse effects, which was aligned with the findings of other studies. This safety profile can increase adherence to ivermectin (17, 23, 25).

5.4. Conclusions

The present study demonstrates that ivermectin is an effective medication for reducing the length of ICU admission, decreasing the symptomatic period for most acute symptoms, and also declining in some laboratory markers such as CRP and LDH. Moreover, no serious adverse effects of this medication have been observed among the drug arm participants. Therefore, it seems this medication should be considered as a potential treatment for COVID-19, and more investigation should be done on it in the future.

5.5. Limitations

Our study has certain limitations. The sample size was small, PCR was not performed at discharge, and participants were not critically ill; therefore, the results of this study cannot be generalized. To resolve these issues, the authors would advocate conducting clinical trials with larger samples of patients with various levels of disease severity.

Another limitation of the present study was the study of unvaccinated populations, which can reduce the generalizability of the results to vaccinated populations. However, since COVID-19 vaccination is associated with milder forms of the disease (26), Ivermectin is expected to be effective as a potential candidate in treating these patients.

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Footnotes

Authors' Contribution: Study concept and design: M.V., M.D., P.N., K.H., F.A., R.J.; acquisition of data: N.G., S.A., M.D.; analysis and interpretation of data: N.V., K.H., S.K.; drafting of the manuscript: P.N., E.B., S.M., P.E.; critical revision of the manuscript for important intellectual content: M.V., M.D.; statistical analysis: S.A., M.D.; administrative, technical, and material support: M.V., M.D., P.N., K.H., F.A., R.J.; study supervision: N.G., S.A., M.D.

Clinical Trial Registration Code: Code: IRCT20200404046937N4.

Conflict of Interests Statement: The authors declared no conflict of interest.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: It was initially approved by the Research Ethics Committee of Ahvaz Jundishapur University of Medical Sciences and the Iran National Committee for Ethics in Biomedical Research. It was then registered with the code number IRCT20200404046937N4 at the Iranian Clinical Trial Registry.

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