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Efficacy and safety of ivermectin in patients with mild and moderate COVID−19: A randomized controlled trial

Alireza Malektojari[1,2#], Sara Ghazizadeh[1,2#], Mohammad Hamed Ersi[1,2✉], Elham Brahimi[3], Soheil Hassanipour[4], Mohammad Fathalipour[5], Mehdi Hassaniazad[3]

[1]Evidence Based Medicine Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

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

[3]Infectious and Tropical Diseases Research Center, Hormozgan Health Institute, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

[4]Gastrointestinal and Liver Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran

[5]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

ABSTRACT

Objective: To evaluate the effectiveness and safety of ivermectin in patients with mild and moderate COVID-19.

Methods: This study was a single-center, randomized, open-label, controlled trial with a 2-arm parallel-group design on 68 patients with COVID-19. According to the 1:1 ratio between the study groups (ivermectin group and standard treatment group), patients were randomly admitted to each intervention arm.

Results: The mean age of the participants in the ivermectin group was (48.37±13.32) years. Eighteen of them were males (54.5%) and the participants in the control group had a mean age of (46.28±14.47) years, with nineteen of them being males (59.4%). As a primary outcome, after 5 days of randomization, there was no significant difference between the ivermectin group and the control group in the length of stay in the hospital (P=0.168). ICU admission (P=0.764), length of stay in ICU (P=0.622), in-hospital mortality (P=0.427), adverse drug reactions, and changes in the mean difference of laboratory data had not any significant difference between the two groups (except for urea change). In addition, the radiologic findings of the two groups of patients were not significantly different. Linear regression analysis showed that for every 10 years increase of age, 0.6 day of hospitalization duration was increased. There was no statistically significant association between other variables and clinical outcomes.

Conclusions: Among adult hospitalized patients with moderate to severe COVID-19, there was no significant relationship between the administration of ivermectin single dose in a five-day course and clinical improvement, and mortality of the participants.

KEYWORDS: COVID-19; Randomized controlled trial; Ivermectin; Hospitalization; Mechanical ventilation; Clinical symptoms

1. Introduction

COVID-19 is a viral infectious disease caused by SARS-Coronavirus-2. COVID-19 was first reported in Wuhan, China in December 2019, and was declared a pandemic by the World Health Organization (WHO) in March 2020[1]. According to the WHO, the disease has affected more than 643 million people worldwide by October 2022, including more than 6.6 million deaths. The most common symptoms include fever, cough, fatigue, sputum production, shortness of breath, joint and muscle pain, nausea, vomiting and diarrhea. SARS-CoV-2 transmission occurs mainly

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Significance

This trial was conducted to assess the efficacy and safety of ivermectin in patients with mild and moderate COVID-19. There was no significant difference between a five-day course of ivermectin and control groups in clinical findings in terms of the length of stay in the hospital and ICU, ICU admission, in-hospital mortality, imaging findings and this study demonstrates that ivermectin cannot improve symptoms and reduce mortality in patients with COVID-19.

[#]These authors contributed equally to the work.
[✉]To whom correspondence may be addressed. E-mail: Hamedersi@gmail.com

after the beginning of the illness and peaks after the severity of the disease[2]. At the start of the illness and especially in the first week of symptoms inspection, the viral load of SARS-CoV-2 in upper respiratory tract samples was the highest and because of that, the risk of pharyngeal virus shedding was quite high in the mentioned duration[3,4]. In addition to the above, COVID-19 is a common disease between humans and animals and its mortality rate is between 2% and 5%. Severity of this disorder may force many patients with pneumonia to temporary oxygen therapy[5,6].

Many vaccines have recently been developed to contain this pandemic, but there is still a need for more efficient drugs to reduce the adverse effects of this disease. Several studies have evaluated the effectiveness of various drugs for the treatment and improvement of clinical results of COVID-19, including hydroxychloroquine[7–9], tocilizumab[10,11], lopinavir-ritonavir[12,13] and dexamethasone[14,15]. The results of these studies were not consistent and there are many differences among the results of the studies. By conducting more studies in this field, drugs such as Paxlovid have shown good effectiveness in improving symptoms and reducing mortality[16]. Paxlovid (unlike other repurposed drugs) is a new drug, developed especially for the treatment of COVID-19. In spite of its existence, the search for drugs that might be repurposed continues to have more debates.

In this research, we tried to evaluate the effectiveness and safety of ivermectin. Ivermectin is an anti-parasitic drug approved by the Food and Drug Administration. Recent *in vitro* studies have reported that this anti-parasitic drug is able to reduce the proliferation of SARS-CoV-2 infected Vero-hSLAM cells by 5 000 times in two days[17]. The aim of this study was to evaluate the efficacy of ivermectin in reducing inflammatory factors, lung imaging findings, improvement of clinical symptoms, and evaluation of toxicity and side effects of this drug in patients with COVID-19. We suspect (our hypothesis is) that prescribing ivermectin as a pharmacotherapy for patients with COVID-19 can reduce the effective viral load, and improve lung imaging findings and clinical symptoms in patients, besides these advantages outweigh the side effects of this drug, which can also be tolerable for sufferers. If positive effects of ivermectin are observed and it responds better than standard treatments, it may be added to this regimen in the future to improve patient clinical signs, as well as laboratory findings and treatment challenges. Consequently, it will lead to a reduction in treatment costs for COVID-19 patients.

This study aimed to investigate the effect of ivermectin on mortality and length of stay in ICU in COVID-19 patients admitted to the acute respiratory syndrome ward of Shahid Mohammadi Hospital in Bandar Abbas, Iran.

2. Subjects and methods

2.1. Study design and participants

This study was a single-center, randomized, open-label, controlled trial with a 2-arm parallel-group design (1:1 ratio) on 68 patients with COVID-19 admitted to the acute respiratory syndrome ward of Shahid Mohammadi Hospital in Bandar Abbas, Iran. Of these 68 patients, 65 eventually entered the final inclusion (33 in the ivermectin group and 32 in the control group).

From the primary sample size (68 people), the number of losses to follow up was 3 people: one of them was due to ICU admission at the beginning and before the intervention, and 2 people were due to non-cooperation in the clinical trial process. Two of these were in the control group and one of them was in the ivermectin group. The follow-up time of the patients was 5 days. Patients were prospectively enrolled and followed up from November 25, 2020.

Inclusion criteria for patients with moderate COVID-19 symptoms were: (1) Having the symptoms of COVID-19; (2) Physician's diagnosis of possible COVID-19 infection; (3) Confirmed infection using PCR; (4) Diagnosed moderate pneumonia using computed tomography and/or chest radiograph (CXR) imaging, requiring hospitalization; (5) Hospitalized ≤ 48 hours; (6) Signing informed consent form.

Exclusion criteria were severe and critical pneumonia due to COVID-19, presence of underlying diseases including AIDS, asthma, loiasis, and severe liver and kidney disease, use of anticoagulants (*e.g.*, warfarin) and angiotensin converting enzyme (ACE) inhibitors (*e.g.*, captopril), pregnancy or breastfeeding and history of ivermectin drug allergy.

2.2. Outcomes

The primary outcome was mortality, improvement of clinical symptoms, the length of hospital stay until discharge, the need for ICU admission until discharge and the need for mechanical ventilation for patients admitted to ICU within five days of randomization.

The secondary outcome was the incidence of serious adverse drug reactions within five days of randomization.

2.3. Recruitment

Two medical students, under the supervision of two infectious disease specialists, performed the admission process according to the inclusion and exclusion criteria. Patients' follow-up days were days 0, 1, 5, and during these days, patients were asked to fill in a pre-designed questionnaire, including the presence or absence of side effects and the patient's general condition (Supplementary materials).

2.4. Intervention groups

According to the 1:1 ratio between the study groups (ivermectin group and standard treatment group), patients were randomly admitted to each of the intervention arms.

The control group received 200/50 mg lopinavir/ritonavir (Heterd Company, India) twice a day for five days, plus five doses of 44 mcg Interferon beta-1a (CinnaGen, Iran) every other day. Intervention groups received the standard treatment regimen for moderate COVID-19, based on the Iranian Ministry of Health and Medical Education's protocol, along with oral ivermectin (MSD Company, France) at a single dose of 0.2 mg/kg. Dosage of ivermectin was administered stat and two hours before or after meals. We

also statistically tested whether the difference between the drugs administered in the two groups was significant or not.

Other supportive and routine care were the same in both control and intervention groups.

2.5. Randomization and blinding

Patients were randomly divided into treatment and control groups based on block randomization. This trial was an open-label study, and there was no blinding (Figure 1).

2.6. Statistical analysis

SPSS software version 18 was used for statistical analysis. According to the 1:1 distribution between the studied groups, the sample size estimation and power analysis, 24 participants in each group was calculated. The sample volume is considered to be about 20% more due to factors such as the drop of samples. To compare the main indicators of efficacy (reduction of viral load and improvement of clinical symptoms) as the primary outcome and secondary outcome between study groups, *t*-test for continuous quantitative variables with normal distribution or Mann-Whitney *U* test for continuous quantitative variables without normal distribution. The statistical description of qualitative variables was in terms of frequency or percentage of observation and *Chi*-square or Fisher's exact test was used for comparison between groups.

Potential confounder was tested separately in bivariate regression analyses, to investigate association between independent predictors and clinical outcomes. For all statistical tests, $P<0.05$ (bilateral) is considered statistically significant.

2.7. Ethics

Informed consent form was completed and signed by all patients participating in this study. Relevant information remained confidential and none of the personal details of the participants, including first and last name, were entered in the computer and all individuals were given a project code and analysis was performed based on it. The initial information remained with the main executor until the end of the project and the publication of the articles in locked files. At each stage of the plan, patients could leave the plan at their own discretion.

This trial was approved by the Ethics Committee of Hormozgan University of Medical Sciences (Ethics committee reference number: IR.HUMS.REC.1399.410) on November 15, 2020. The investigators declare the trial has received ethical approval from the aforementioned ethical committee as described above.

This clinical trial has been registered in the Iranian Registry of Clinical Trials (IRCT) on November 17, 2020 (IRCT20200506047323N6).

For more information on the methodology of this research work, you can refer to the protocol of this work[18]. The method of this article is written based on CONSORT Statement.

3. Results

3.1. Patient characteristics

From 25 November 2020 to 6 July 2021, 68 participants were evaluated for eligibility and of these 68 patients, 65 eventually entered the final inclusion. Of those enrolled, 33 patients were randomized to the ivermectin group, while 32 were randomized to the control group.

The mean age of the participants in the ivermectin group was 48.37 with a standard deviation equal to 13.32. Eighteen of them were males (54.5%). And the participants in the control group had a mean age of 46.28 and a standard deviation of 14.47, with 19 of them being males (59.4%). Nine participants in the ivermectin group and eight participants in the control group had comorbidities such as diabetes, hypertension, cardiovascular disease, chronic kidney disease, obesity, and cancer. Blood oxygen saturation (SpO_2) was not significantly different between patients in the two groups (Table 1).

Table 1. Demographic characteristics of the participants.

Variable	Ivermectin (*n*=32)	Control (*n*=32)
Age, years, mean ± SD	48.37 ± 13.32	46.28 ± 14.47
20-39	7 (21.9)	11 (34.4)
40-69	22 (68.8)	19 (59.4)
70-99	3 (9.4)	2 (6.3)
Sex, male	18 (54.5)*	19 (59.4)
Comorbidities	*n*=29	
Diabetes	3 (10.3)	2 (6.3)
Hypertension	1 (3.4)	2 (6.3)
Cardiovascular disease	2 (6.9)	0 (0.0)
Chronic kidney disease	1 (3.4)	0 (0.0)
Obesity	2 (6.9)	3 (9.4)
Cancer	0 (0.0)	1 (3.1)
SpO_2, mean ± SD	94.11 ± 3.10	94.07 ± 2.98

Values were presented as *n* (%) unless otherwise specified. *: *n*=33.
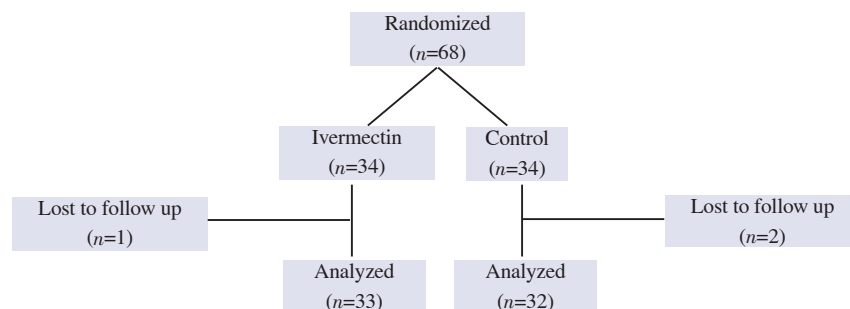Comparison between groups was performed using the *t*-test or the Pearson *Chi*-square test.

Figure 1. Randomization and treatment assignment.

Both groups were comparable in terms of the demographic characteristics, baseline laboratory and imaging findings, and clinical characteristics of the participants (Table 1 and 2, Supplementary Table 1).

Changes in laboratory test result between baseline and day 5 were compared using Mann-Whitney U test between two groups. There was no statistically significant difference between the two groups. Only urea change was statistically significant (P=0.035), in which the urea change was higher in the ivermectin group (Table 3).

The radiologic findings of the patients of the two groups were not significantly different from each other, in terms of pattern and type (Supplementary Table 2).

Logistic regression analyses were performed to investigate the association between the age and sex characteristics, death, mechanical ventilation and ICU admission. There was no statistically significant association between these variables and clinical outcomes (Supplementary Table 3-5). Further linear regression analysis was used to explore the association among sex, age, and duration of hospitalization. This analysis showed that for every 10 years increasing of age, 0.6 day (95% CI 0.08-1.15) hospitalization duration was increased. There was no association between sex and hospitalization duration (Supplementary Table 6).

The mean difference of laboratory findings for each group is reported (Table 3). Comparing administered drugs other than ivermectin between the two groups showed a significant difference only in the administration of atorvastatin, but no other drug had statistically significant difference between groups (Supplementary Table 7).

3.2. Clinical outcomes

As a primary outcome, after 5 days of randomization, there was no significant difference between the ivermectin group and control group in the length of stay in hospital [(6.0 (5.0-9.0) days in the ivermectin group, 6.0 (4.0-7.0) days in the control group, and P=0.168].

ICU admission (24.2% in the ivermectin group, 18.8% in the control group and P=0.764), length of stay in ICU [3.0 (1.8-8.5) days in the ivermectin group, 6.5 (2.5-7.0) days in the control group, and P=0.622] and in-hospital mortality (15.2% in the ivermectin group, 6.3% in the control group and P=0.427), had not any significant difference between 2 groups (Table 4).

Also on day 5, no significant differences were observed between the two groups in the laboratory and clinical symptoms of participants (such as fever, chills, headache, sore throat, diarrhea, cough, dyspnea, fatigue, sputum, nausea or vomiting, myalgia, muscular spasm, chest pain, anorexia, smell change and taste change) (Table 2, Supplementary Table 1).

3.3. Safety

As a secondary outcome, none of the patients (either in the

Table 2. Laboratory findings of the participants.

Characteristics		Ivermectin group (n=33)	Control group (n=32)	Critical values	P-value
Hematologic, ×10⁹/L					
Hematocrit	Baseline	37.97 ± 4.67	37.70 ± 4.70	-0.229	0.819
	Day 5	38.02 ± 4.17	36.84 ± 5.44	-0.914	0.365
Hemoglobin	Baseline	12.4 (11.8-14.3)	12.4 (11.3-13.7)	-0.197	0.844*
	Day 5	12.62 ± 1.68	12.34 ± 1.74	-0.604	0.548
White blood cells	Baseline	5.4 (4.1-7.1)	5.7 (4.2-7.0)	-0.493	0.622*
	Day 5	8.84 ± 3.49	9.95 ± 4.53	1.037	0.304
Neutrophil	Baseline	72.87 ± 10.46	73.70 ± 11.23	1.024	0.767
	Day 5	82.7 (78.5-85.3)	83.2 (77.1-87.8)	-0.493	0.622*
Lymphocytes	Baseline	19.48 ± 7.63	19.47 ± 9.30	-0.006	0.955
	Day 5	11.8 (7.0-16.9)	11.7 (6.6-16.6)	-0.304	0.761*
Platelets	Baseline	181.0 (133.0-258.0)	172.0 (159.0-290.0)	-0.669	0.504*
	Day 5	221.5 (185.2-362.0)	250.0 (192.0-333.7)	-0.123	0.902*
Biochemical					
Urea, mg/dL	Baseline	27.0 (22.0-33.0)	32.0 (28.0-37.0)	-2.269	0.023*
	Day 5	37.5 (31.0-47.2)	34.0 (29.0-48.0)	-0.236	0.813*
Creatinine, mg/dL	Baseline	1.1 (0.9-1.2)	1.0 (0.8-1.1)	-1.345	0.179*
	Day 5	1.10 (0.90-1.15)	1.0 (0.9-1.1)	-0.316	0.752*
Lactate dehydrogenase, units/L	Baseline	510.0 (450.5-657.0)	560.0 (473.0-669.0)	-0.385	0.701*
	Day 5	503.0 (435.5-638.5)	518.0 (436.0-720.0)	-0.566	0.572*
Ferritin, ng/mL	Baseline	336.7 (220.4-1 036.2)	427.7 (139.0-842.0)	-0.252	0.801*
	Day 5	332.9 (192.9-778.5)	477.4 (221.5-1 146.8)	-0.549	0.583*
C-reactive protein, mg/dL	Baseline	39.22 ± 25.48	29.47 ± 22.31	-1.554	0.126
	Day 5	6.81 (4.03-14.51)	8.60 (3.90-12.92)	-0.262	0.794*
Potassium, mmol/L	Baseline	4.29 ± 0.48	4.45 ± 0.48	1.311	0.195
	Day 5	4.36 ± 0.63	4.54 ± 0.80	0.963	0.340
Sodium, mEq/L	Baseline	139.0 (137.0-140.0)	137.0 (136.0-139.0)	-1.327	0.185*
	Day 5	139.0 (136.5-141.0)	139.0 (137.0-141.0)	-0.074	0.941*

Comparison between groups was performed using either t test for variables with normal distribution presented as mean ± SD or Mann-Whitney U test for variables without normal distribution presented as median (IQR). *Mann-Whitney U test was carried out, and others were performed by student t test.

Table 3. Mean difference of changes in laboratory findings between baseline and day 5.

Characteristics	Ivermectin group (n=33)	Control group (n=32)	Critical values	P-value
Hematologic, ×10^9/L				
Hematocrit	-0.6 (-1.6-2.0)	0.45 (-2.80-1.40)	-0.633	0.527
Hemoglobin	-0.30 (-0.72-0.25)	-0.05 (-0.75-0.50)	-1.316	0.188
White blood cells	2.9 (0.5-5.8)	3.8 (0.1-6.5)	-0.096	0.923
Neutrophil	9.9 (-2.8-16.9)	4.85 (-0.25-15.90)	-0.835	0.404
Lymphocytes	-6.5 (-15.1-0.3)	-3.6 (-14.4-1.3)	-0.385	0.700
Platelets	58.0 (18.0-97.2)	38.0 (-7.0-92.5)	-1.479	0.139
Biochemical				
Urea, mg/dL	9.0 (3.3-13.0)	5.0 (2.0-11.0)	-2.106	0.035
Lactate dehydrogenas, units/L	3.0 (-149.0-105.0)	-14.0 (-114.0-150.0)	-0.251	0.802
Ferritin, ng/mL	37.0 (-319.5-204.0)	37.4 (-57.5-246.7)	-0.709	0.478
C-reactive protein, mg/dL	-22.4 (-45.8-1.2)	-16.6 (-28.8--6.2)	-0.369	0.712
Potassium	-0.10 (-0.50-0.55)	0.10 (-0.40-0.44)	-0.563	0.574
Sodium	0.0 (-2.5-2.0)	1.0 (-1.0-3.0)	-1.261	0.207

Comparison between groups was performed using Mann-Whitney U test. All of the variables were presented as median (IQR).

Table 4. Clinical outcomes of the participants.

Variable	Ivermectin group (n=33)	Control group (n=32)	Critical values	P-value
ICU admission, n (%)	8 (24.2)	6 (18.8)	0.097	0.764
Length of stay in ICU, days	3.0 (1.8-8.5)	6.5 (2.5-7.0)	-0.494	0.622*
Intermittent mandatory ventilation, n (%)	3 (37.5)	1 (16.7)	0.350	0.580
Length of stay in hospital, days	6.0 (5.0-9.0)	6.0 (4.0-7.0)	-1.379	0.168*
In-hospital mortality, n (%)	5 (15.2)	2 (6.3)	1.449	0.427

*Mann-Whitney U test was carried out when data were presented as median (IQR), and others were performed by Pearson Chi-square or Fisher's exact test when values were presented as n (%). The data reported for "length of stay in ICU" and "intermittent mandatory ventilation" are only for patients admitted to the ICU. Data were collected after five days of randomization. IQR: interquartile range.

ivermectin group or in the control group) experienced adverse drug reactions (Supplementary Table 8).

4. Discussion

In this randomized controlled trial, we found that ivermectin treatment added to standard supportive care was not associated with clinical improvement or mortality in mild and moderate patients with COVID-19 or any significant difference from that associated with standard care alone (control group). No significant differences were found between the ivermectin group and the control group in terms of ICU admission, length of stay in ICU, length of stay in the hospital, in-hospital mortality, and even in laboratory findings of the participants except urea.

A similar study by López-Medina *et al*. found that among adults with mild COVID-19, a 5-day course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms[19].

A randomized trial of ivermectin for 180 mild hospitalized patients with COVID-19 showed a reduction in mortality and shortening of hospital stay[20]. In another study, a 5-day course of ivermectin was shown to result in an earlier clearance of the virus compared to placebo. However, in this study, it was noted that no significant difference was observed between the ivermectin group and the control group in the improvement of clinical symptoms such as the mean duration of hospitalization after treatment, fever, cough, and sore throat[21]. Although ivermectin may cause viral clearance to occur earlier in patients, it does not appear to have a significant

effect on improving clinical symptoms and reducing mortality[22].

In another study, the administration and use of ivermectin were shown to have a significant effect on patients with severe COVID-19 and reduced their mortality. However, their study also showed that the effectiveness of ivermectin in patients with non-severe (mild to moderate) COVID-19 and their length of stay in hospital were not significantly different from the control group[23].

Our study has some limitations. The small sample size is one of the limitations and therefore, future studies with larger sample sizes are warranted to reduce the statistical errors. Also, grading patients' status according to the WHO guidelines could increase the quality and validity of our study results. Multi-center clinical trials with longer follow-up of patients and stronger blinding can give stronger results compared to our study.

In conclusion, among adult hospitalized patients with mild to moderate COVID-19 patients, there was no significant relation between ivermectin single dose administration in five-day course and reduction of ICU admission, length of stay in ICU, length of stay in the hospital, and in-hospital mortality. This means that we could not find any significance to confirm our hypothesis regarding "whether administration of ivermectin can improve symptoms and reduce mortality in patients with COVID-19". Still, more trials and studies are needed to investigate the effectiveness of ivermectin for patients with COVID-19.

Conflict of interest statement

The authors declare that they have no competing interests.

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Authors' contributions

EB, MH, and MF designed the study; AM and SG recruited the subjects and followed them up; SH analyzed the data; MHE wrote the manuscript; MHE, AM and SG edited and revised the manuscript according to the journal's instructions. All authors read and approved the final manuscript.

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