



## RESEARCH ARTICLE

# Clinical study evaluating the efficacy of ivermectin in COVID-19 treatment: A randomized controlled study

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## Abstract

Researchers around the world are working at record speed to find the best ways to treat and prevent coronavirus disease 2019 (COVID-19). This study aimed to evaluate the efficacy of ivermectin for the treatment of hospitalized mild to moderate COVID-19 infected patients. This was a randomized open-label controlled study that included 164 patients with COVID-19. Patients were randomized into two groups where Group 1 (Ivermectin group) included patients who received ivermectin 12 mg once daily for 3 days with standard care and Group 2 (control group) included patients who received standard protocol of treatment alone for 14 days. The main outcomes were mortality, the length of hospital stay, and the need for mechanical ventilation. All patients were followed up for 1 month. Overall, 82 individuals were randomized to receive ivermectin plus standard of care and 82 to receive standard of care alone. Patients in the ivermectin group had a shorter length of hospital stay ( $8.82 \pm 4.94$  days) than the control group ( $10.97 \pm 5.28$  days), but this was not statistically significant ( $p = 0.085$ ). Three patients (3.7%) in each group required mechanical ventilation ( $p = 1.00$ ). The death rate was three patients in the ivermectin group (3.7%) versus four patients (4.9%) in the control group without any significant difference between the two groups ( $p = 1.00$ ). Although there was no statistically significant difference in any endpoints by ivermectin doses (12 mg/day for 3 days); there was an observed trend to reducing hospital stay in the ivermectin-treated group.

## KEYWORDS

COVID-19, chloroquine, ivermectin, mortality, treatment

## 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first recognized amid an epidemic of respiratory illness cases

in Wuhan City, Hubei Province, China. It was originally reported to the World Health Organization (WHO) on December 31, 2019. The WHO declared COVID-19 a global pandemic on March 11, 2020.<sup>1,2</sup>

COVID-19 management depends on the severity of the disease. Mild cases usually recover at home, whereas moderate and

severe cases should be monitored closely and sometimes need hospitalization.<sup>3–5</sup>

Developing an effective therapy for COVID-19 infection is a complex process. Several immunotherapies, antiviral agents, and vaccines continue to be studied and developed as potential therapies for COVID-19.<sup>4,5</sup>

In March 2020, the WHO declared COVID-19 a global pandemic and an increasing number of cases of COVID-19 have been reported worldwide including in Egypt. The repurposing of commercially available COVID-19 pharmaceutical drugs has contributed to the production of hundreds of trials around the world.<sup>1–11</sup> Egyptian protocols to treat COVID-19 infection have mainly relied on many potential drugs, including, hydroxychloroquine, remdesivir, nitazoxanide, oseltamivir, favipiravir, lopinavir/ritonavir, and ivermectin.<sup>11</sup>

Ivermectin, *in vitro*, is an inhibitor of SARS-CoV-2 which is able to lead to approximately 5000-fold reduction in viral RNA at 48 h.<sup>10</sup> This beneficial mechanism of ivermectin on the COVID-19 virus was not known until recently and it was thought that it behaved in the same manner as other viruses. The nuclear importation of virus and host proteins has been known to be inhibited. Virus integrase protein and importin (IMP)  $\alpha/\beta 1$  heterodimer is responsible for nuclear import, further increasing infection are also, inhibited.<sup>10–26</sup>

Ivermectin may be a safe, affordable, and readily available therapy of COVID-19. Therefore, the use of ivermectin warrants the rapid implementation of controlled clinical trials to assess the efficacy against SARS-CoV-2.<sup>5</sup> There were observational studies suggesting a beneficial effect of ivermectin in the treatment of COVID-19. So, we aimed in this study to evaluate the efficacy and safety of ivermectin in the treatment of COVID-19.

## 2 | METHODS

### 2.1 | Study design and participants

This was a 1:1 randomized, open-label, parallel-group clinical trial of ivermectin versus standard of care for the treatment of hospitalized patients with COVID-19. The study took place between March 2020 and October 2020 at Tanta and Assiut University Hospitals, two tertiary hospitals in Egypt. The study was conducted in isolation units in both hospitals.

All adult patients from ages 20 to 65 with mildly to moderately affected COVID-19 infection confirmed by pharyngeal swab polymerase chain reaction (PCR) were included in the study. Patients who had an allergy or contraindication to the drugs used in the study, pregnant and lactating mothers, and patients with cardiac problems were excluded from the study.

### 2.2 | Randomization

The included patients were randomized using a computer random number generator to select random permuted blocks with a block

size of eight and an equal allocation ratio. Sequentially numbered, opaque, sealed envelopes were used to ensure concealment. Three members of the study team (Soliman S, Mai Khalaf, and Eslam Saber Esmail) recruited, enrolled, and assigned participants to a computer-generated randomization sequence, held by an independent observer. During randomization, the proportional allocation of each clinical stratum was equalized in both groups. The included patients were first stratified according to their age (18–25, 26–40, 40–55, and >55), then by their gender (inside each stratum into males and females) and then their associated morbidities (absent and present). We tried to keep the randomization equalized inside each stratum as much as we could.

### 2.3 | Procedures

Patients and physicians were aware of the assigned treatments. The patients were divided into two groups:

Group 1: (Ivermectin group) 82 patients who received a single dose of oral ivermectin tablets (12 mg) every day for 3 days added to the standard protocol of treatment according to the Egyptian Ministry of Health (MOH) protocol of COVID-19 treatment.<sup>11</sup> Ivermectin tablets (Iverzine tablets, Unipharma) were used in the study.

Group 2: (Control group) 82 patients received standard protocol of treatment alone for 14 days. All patients were followed up for 1 month. All participants were submitted to the following demography: age, sex, weight, and height measurements and calculation of body mass index (BMI), history-associated symptoms and co-morbidities, clinical examination, and medication history. The following blood tests were done for all the patients in the trial including CBC analysis (WBCs-lymphocytes-PLTs-hemoglobin), liver function tests, Chest X-ray, PCR for pharyngeal swab and ECG, computed tomography according to CO-RADS score.<sup>26</sup>

The Egyptian MOH adopted a standard of care treatment protocol for patients with COVID-19. It included paracetamol, oxygen, fluids (according to the condition of the patient), empiric antibiotic, oseltamivir if needed (75 mg/12 h for 5 days), and invasive mechanical ventilation with hydrocortisone for severe cases if PaO<sub>2</sub> less than 60 mm Hg, O<sub>2</sub> saturation less than 90% despite oxygen or noninvasive ventilation, progressive hypercapnia, respiratory acidosis (pH < 7.3), and progressive or refractory septic shock.<sup>11</sup> Any side effects of the studied medication were assessed using by questionnaire done by the patients or their guardians.

### 2.4 | Outcomes

The primary outcome was the assessment of clinical efficacy of ivermectin in the form of the analysis of all-cause mortality within 1 month after randomization and the secondary outcomes were the length of hospital stay, the need for mechanical ventilation, and the assessment of the safety of ivermectin.

## 2.5 | Ethical considerations

The study was approved by the Tanta University faculty of medicine ethical committee and was registered on [clinicaltrials.gov](https://clinicaltrials.gov) with registration number (NCT04403555). Informed consent was obtained from all participants in this study. Privacy of participants and confidentiality of the data were assured. Risks and benefits were declared and any unexpected risks which appeared during the course of the research were cleared to participants and the ethical committee on time.

## 2.6 | Statistical analysis

The primary analysis was done based on an intention-to-treat basis including all randomly assigned individuals. By the time of planning this study, there were very few pre-print pilot studies of ivermectin on humans (e.g., The study by Gorial et al.<sup>16</sup>) The study included all the eligible patients who agreed to participate. The calculated post hoc sample power was 0.80 based the following inputs: two-tailed sample power, 0.44 effect size, 0.05  $\alpha$  error probability, and 82 as the sample size in each group (the outputs were: 3.02 as noncentrality parameter  $\delta$ , 1.97 as critical  $t$ , 162 as  $df$ ).<sup>21</sup>

The normality of the variables was tested by the Shapiro–Wilks test. Data were analyzed by Statistical Package for Social Sciences (SPSS) V. 23 and were expressed in number (No), percentage (%) mean ( $\bar{x}$ ), and standard deviation (SD). Student's  $t$ -test was used for normally distributed continuous variables and Mann–Whitney's test for not normally distributed variables. A  $\chi^2$  test (with Z test to compare column proportions) was used to study the association between categorical variables, and whenever any of the expected cells were less than five, Fisher's Exact test was used. Binary logistic regression was used to ascertain the effect of the potential risk factors on the patients' mortality. The regression model was a simple one including one variable at each time. The included risk factors were age, gender, smoking, alanine aminotransferase (ALT), albumin, creatinine, ferritin, C-reactive protein (CRP), need for mechanical ventilation, diabetes mellitus, and ivermectin treatment. All the variables were continuous except for gender, smoking, need for mechanical ventilation, presence of diabetes, and treatment with ivermectin (each was of two categories only). Two-sided  $p$  value of less than 0.05 was considered statistically significant.

## 3 | RESULTS

A total number of 170 patients with mildly to moderately affected COVID-19 infection confirmed by pharyngeal swab PCR were invited to the study. Eight patients refused to complete the study, 164 patients were enrolled and they were randomized to receive ivermectin plus standard of care (82 patients) and 82 to receive standard of care alone. All the patients continued the study medications to the end of the duration of treatment and follow-up.

**TABLE 1** Patients' characteristics and clinical presentation at baseline

Variable	Ivermectin (n = 82) No. (%)	Control (n = 82) No. (%)	p value (of $\chi^2$ )
Age (mean $\pm$ SD)	42.38 $\pm$ 16.02	39.38 $\pm$ 16.92	0.23 <sup>a</sup>
Gender			
Male	37 (45.1)	45 (54.9)	0.21
Female	45 (54.9)	37 (45.1)	
Diabetes	17 (20.7)	10 (12.2)	0.14
Hypertension	18 (21.9)	14 (17.1)	0.52
Comorbidities	36 (43.9)	45 (54.9)	0.16
Fever	52 (63.4)	43 (52.4)	0.16
Headache	34 (41.5)	21 (25.6)	0.42
Sore throat	22 (26.8)	26 (31.7)	0.49
Anorexia	19 (23.2)	23 (28.0)	0.47
Anosmia	12 (14.6)	9 (1.2)	0.48
Pallor	2 (2.4)	1 (1.2)	0.56 <sup>b</sup>
Cyanosis	2 (2.4)	2 (2.4)	1.00 <sup>b</sup>
Fatigue	55 (67.1)	46 (56.1)	0.14
Abdominal pain	22 (26.8)	16 (19.5)	0.27
Diarrhea	30 (36.6)	35 (42.7)	0.43
Vomiting	4 (4.9)	11 (13.4)	0.06
Cough	56 (68.3)	56 (68.3)	1.00
Dyspnea	20 (24.4)	26 (31.7)	0.29
CT according to CO-RADS score <sup>26</sup> (level of suspicion for pulmonary involvement of COVID-19)			0.67
0 (Not interpretable)	28 (34.1)	23 (28.0)	
1 (Very low)	12 (14.6)	18 (22.0)	
2 (Low)	31 (37.8)	27 (32.9)	
3 (Equivocal)	9 (11.0)	10 (12.2)	
4 (High)	2 (2.4)	3 (3.7)	
5 (Very high)	0 (0.0)	1 (1.2)	

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; SD, standard deviation;  $\chi^2$ , chi squared test.

<sup>a</sup>Mann–Whitney test.

<sup>b</sup>Fisher's Exact test.

The studied groups were matched for age and gender. The mean was 42.38  $\pm$  16.02 year for Group 1 and 39.38  $\pm$  16.92 for Group 2 ( $p = 0.231$ ). Males represented 45.1% of Group 1 and 54.9% of Group 2 ( $p = 0.212$ ) (Table 1). They had no significant difference regarding the presence of comorbidities ( $p = 0.160$ ). Among Group 1, 20.7% had diabetes and 21.9% had hypertension or other cardiovascular diseases, while among Group 2, 12.2% had diabetes and 17.1% had

Clinical course	Ivermectin (n = 82) No. (%)	Control (n = 82) No. (%)	p value
Length of hospital stay (in days) mean (SD)	8.82 ± 4.94	10.97 ± 5.28	0.08 <sup>a</sup>
Need for mechanical ventilation	3 (3.7)	3 (3.7)	1.00 <sup>b</sup>
Fate within 1 month			
Survived	79 (96.3)	78 (95.1)	1.00 <sup>b</sup>
Died	3 (3.7)	4 (4.9)	

<sup>a</sup>Mann-Whitney test.

<sup>b</sup>Fisher's Exact test.

hypertension or other cardiovascular diseases. The clinical signs and symptoms of the disease did not show any significant difference between the two groups. Moreover, the laboratory tests did not show any significant difference between the two groups.

The ivermectin group had a shorter hospital stay (8.82 ± 4.94 days) than the control group (10.97 ± 5.28) but this was not statistically significant ( $p = 0.085$ ). Three patients (3.7%) needed mechanical ventilation in each group ( $p = 1.00$ ). Death among patients of the two groups did not show any significant difference either, as three patients (3.7%) died in the ivermectin group and four patients (4.9%) died in the control group ( $p = 1.00$ ) (Table 2).

The univariable regression analysis showed that the patients' age, ALT, creatinine, ferritin, and CRP were independently related to the patients' mortality ( $p = 0.004$ ,  $0.001$ ,  $< 0.001$ ,  $0.008$ , and  $< 0.001$ , respectively) (Table 3). Mild side effects were recorded; they were minimal in the ivermectin group with nausea in one patient and diarrhea in two patients. Ivermectin was not significantly related to the patients' mortality ( $p = 0.700$ ).

## 4 | DISCUSSION

The purpose of this randomized controlled trial was to determine the effectiveness and safety of ivermectin in COVID-19 therapy. Our study involved 164 patients who met the enrollment criteria and were enrolled and randomized to the ivermectin group ( $n = 82$ ) or the control group ( $n = 82$ ). The baseline demographic and clinical presentations in the two studied groups were similar without any significant difference. The laboratory parameters and the radiological findings were not significantly different either. In this study, the two groups did not show any statistically significant difference in clinical outcomes. Although there was no statistically significant difference, a trend to reducing the length of hospitalization was observed in the ivermectin. This favorable outcome of ivermectin was in accordance with Ahmed et al.<sup>12</sup> and Elgazzar et al.,<sup>13</sup> who observed that early incorporation of ivermectin to the standard of care was very successful for the treatment of COVID-19 patients with shortened hospital stay duration; and was even associated with higher viral clearance.<sup>12</sup> Also, a pilot study by Chaccoura et al.<sup>22</sup> showed a tendency to lower viral loads in the ivermectin group as well as a

**TABLE 2** Clinical course of the disease

**TABLE 3** Univariable binary logistic regression analysis of predictors of mortality (each row represents a separate model with one predictor)

Variable	Univariate			
	p value	OR	95% CI Lower	Upper
Age	0.004	1.100	1.032	1.174
Gender	0.583	0.652	0.141	3.008
Smoking	0.998	–	–	–
ALT	0.001	1.031	1.013	1.049
Albumin	0.217	0.332	0.053	1.944
Creatinine	<0.001	226.346	11.483	4457.78
Ferritin	0.008	1.004	1.001	1.006
CRP	<0.001	1.022	1.010	1.034
Need for mechanical ventilation	0.99	–	–	–
DM	0.07	4.156	0.874	19.75
Ivermectin	0.70	0.741	0.160	3.417

Abbreviations: ALT, alanine transaminase; DM, diabetes mellitus; CI, confidence interval; OR, odds ratio.

tendency to lower IgG titers. This result may be due to its effect on the suppression of a number of inflammatory cytokines contributing to the “storm of cytokines” and then all disease squalls.<sup>10</sup>

In a nonrandomized study by Gorial et al.,<sup>16</sup> the addition of ivermectin to hydroxychloroquine significantly shortened the length of hospital stay in comparison to hydroxychloroquine alone. Also, three recent clinical trials confirmed the beneficial impact of the addition of ivermectin to the standard of care for the outcome of decreasing hospital stay.<sup>17</sup> However, Podder et al.<sup>18</sup> and Chachar et al.<sup>19</sup> did not demonstrate any benefit of the addition of ivermectin to the treatment of COVID-19 in relation to our observations.

The ivermectin group did not show any significant difference either in the need for mechanical ventilation ( $p = 1.00$ ) or the patients' mortality ( $p = 1.00$ ) from the control group. In contrast, Elgazzar et al.,<sup>13</sup> showed that ivermectin treatment was associated

with lower mortality during treatment of COVID-19, especially in patients with severe pulmonary involvement.

The addition of ivermectin to the treatment protocol in our study did not show any significant association with the patients' mortality by univariate binary logistic regression analysis ( $p = 0.700$ , odds ratio 0.471; 95% confidence interval: 0.160–3.417). However, other risk factors like the patient's age, serum ALT, creatinine, ferritin, and CRP being significantly related to all-cause mortality may be attributable to the small dose of ivermectin. Accessible pharmacokinetic evidence from clinically significant and excessive dosage trials indicates that the concentration of ivermectin needed to suppress SARS-CoV-2 in humans with known dosing regimens is unlikely to be reached in serum and tissue.<sup>20–30</sup> Pott-Junior et al.<sup>24</sup> as well as Babalola et al.<sup>25</sup> supported our results that higher doses of ivermectin may have a greater antiviral effect, but also showed that supra-lethal toxic doses are unnecessary to inhibit viral replication.

Owing to the scarce resources of our developing country, the limitations of research outcomes may depend primarily on the patients' health conditions, the need for intensive care unit entry, and the consequences of mortality, and not the viraemic response. Another drawback is the small ivermectin dosage which we recommend to be increased in further trials. Small sample size, lack of blindness, and lack of placebo group were additional limitations to our study.

In conclusion; the usage of ivermectin did not achieve significance for any of the endpoints. However; there was an observed trend to reducing hospital stay in the ivermectin-treated group. These findings may suggest using ivermectin as an add-on therapy to protocols used for the treatment of COVID-19. However, these results are needed to be validated in a larger prospective follow-up study.

## CONFLICT OF INTERESTS

All the authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

Sherief Abd-Elsalam was responsible for the concept, design, definition of intellectual content, and manuscript preparation. Sherief Abd-Elsalam, Rasha Abdel Noor, and Rehab Badawi were responsible for literature search, manuscript review, and manuscript editing. Sherief Abd-Elsalam, Rasha Abdel Noor, Rehab Badawi, Mai Khalaf, Eslam Saber Esmail, Mohamed Samir Abd El Ghafar, Mohamed Elbarnasawy, Ehab F. Moustafa, Sahar M. Hassany, Mohamed Alboraie, Haidi Karam-Allah Ramadan, Mohamed Alboraie, Mohamed Alboraie, Ahmed Cordie, and Gamal Esmat were responsible for data acquisition, Clinical studies. Shaimaa Soliman and Sherief Abd-Elsalam were responsible for data analysis, statistical analysis. All authors have been read and approved the final version of the manuscript.

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