

## ORIGINAL ARTICLE

# Role of Ivermectin and Colchicine in Treatment of COVID-19: A Randomized Controlled Clinical Trial

Hemat Abd El-Salam Ahmed Salama<sup>1</sup>, Eman El-Sayed Ahmed<sup>2</sup>, Ghada Essam El-Din Amin<sup>1</sup>, Mohamed Farouk Allam<sup>1</sup>, Ahmed Nour El-Din Hassan<sup>3,4</sup>, Mohamed Abd El Rahman Hassan El Shayeb<sup>2</sup>

<sup>1</sup>Family Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

<sup>2</sup>Internal Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

<sup>3</sup>Clinical Pharmacology Department, Faculty of Medicine, Galala University, Suez, Egypt.

<sup>4</sup>Clinical Pharmacology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

**Abstract.** *Objective:* To assess the effectiveness of ivermectin and colchicine as treatment options for COVID-19. *Patients and methods:* A three-arm randomized controlled clinical trial was conducted in triage clinic of family medicine department at Ain Shams University Hospitals on participants who had been diagnosed as COVID-19 patients with moderate severity. Patients aged <18 years or >65 years with any co-morbidities, pregnant or lactating female and with mild or severe COVID-19 confirmed cases were excluded. Randomization was done by using sealed envelopes for intervention or control. Patients are followed up to improvement of patient's symptoms with no development of new symptoms over one month. *Results:* A total of 120 patients with COVID-19 were enrolled in the study, 40 patients in each arm. Their mean age was 40.16(SD 10.74) years. Out of them, 44 (36.6%) were male, 76(63.4%) were female. Mean duration of symptoms was 9.58 (SD 2.206), 9.9 (SD 2.07), and 9.53 (SD 2.37) in the ivermectin, colchicine and control groups, respectively. Most patients (67.5%, 70% and 72.5%) cured with residual symptoms with no difference in between the ivermectin, colchicine and control groups, respectively ( $P>0.05$ ). *Conclusion:* Ivermectin and colchicine have no beneficial effect over the standard care in treatment of COVID-19.

**Keywords:** Ivermectin, Colchicine, COVID-19, Clinical Trial, Ain Shams University.

## Introduction

COVID-19 is caused by SARS-CoV-2, a new corona virus that quickly spreads throughout the entire world (1).

By 24th May 2021, there were more than 167 million individuals that have been diagnosed and more than 3 million have died as a result of the worldwide illnesses (2).

To effectively minimize the spread of COVID-19 and especially the associated deaths, a highly effective treatment option is needed (3).

Many attempts have been made to repurpose existing and approved drugs for the treatment of COVID-19 infection as development of a new drug will need to a long time (4).

This involves anti-malarial drugs such as hydroxychloroquine and chloroquine, which have recently been shown to be less successful than initially believed, with a substantial risk of often fatal complications and interactions (5).

Another anti-parasitic drug which was proposed as a therapeutic option for COVID-19 is ivermectin (6). An in vitro study indicated that Ivermectin was dynamic against COVID-19 infected cell (7). Ivermectin has antimicrobial, antiviral, anticancer and immunomodulatory properties (8). This drug could reduce the viral load in COVID-19 infected patients, with potential effect on disease progression and spread (7). Recently, colchicine has shown to have anti-inflammatory and cardioprotective effects in COVID-19 patients (9).

It interferes with several inflammatory pathways. Colchicine reduces the expression of adhesion molecules on neutrophil membranes leading to a significant inhibition in migration and interaction with endothelial cells and modulates the production of proinflammatory cytokines (10). Colchicine may decrease the rate of death and hospitalization by preventing cytokine storm and subsequently decreasing complications caused by COVID-19 (9).

Till date, for patients who are not yet hospitalized, there is no currently accepted treatment. Treating patients before they need to be admitted or even prophylactically could greatly decrease the load on hospitals, protect healthcare workers and reduce the spread of COVID-19 (11).

Therefore, ivermectin and colchicine may be therapeutic options for home treatment of COVID-19. Several observational studies were conducted to evaluate their effect in COVID-19 (9,12,13). However, there is still a lack of evidence-based studies, especially clinical trials, to support their wide use.

## 2. Materials and Methods

### Study design and setting:

The study was a three-arm randomized controlled clinical trial conducted in Triage Clinic of Family Medicine Department at Ain Shams University Hospitals over a period of one year.

Inclusion criteria: COVID-19 Patients aged (18-64) with Moderate Severity.

Exclusion criteria: COVID-19 Patients with any co-morbidities (hypertension, DM, etc.), COVID-19 patients with mild or severe symptoms, lactating and pregnant women.

Sampling and study participants: The data was collected from 120 participants who met the inclusion criteria from the start of July 2021 till the end of November 2022.

Patients were recruited from Triage COVID-19 Outpatient Clinic and every patient was subjected to the following: Clinical history was obtained about socio-demographic data such as age, gender, residence, marital status, and smoking history. Medical history included weight, current medication, symptoms (onset, course, duration) and presence of co-morbidities.

Full general examination included temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation.

Suspected patients according to CDC criteria were subjected to laboratory and radiological confirmation with (PCR-COVID-19, complete blood count (CBC), CRP, Ferritin and D-Dimer, and high-resolution CT chest.

After confirmation of the diagnosis, patients were classified as moderate based on laboratory and radiological findings.

Grouping: All 120 patients enrolled in the study according to the calculated sample size were equally divided randomly into 3 groups using sealed envelope containing code for each group.

Group A (Ivermectin group): COVID-19 patients with moderate severity received standard treatment according to the protocol of the Egyptian Supreme Council of University Hospitals plus ivermectin in the form of oral tablets e.g., Iverzine 6mg (200 mcg/kg/day); 4 tablets in the first day and then 2 tablets in the second and third day on an empty stomach (6).

Group B (Colchicine group): COVID-19 patients with moderate severity received standard treatment according to the protocol of the Egyptian Supreme Council of University Hospitals plus Colchicine 0.5mg tablets; 3 times/day after meal for 3 days then twice daily for 4 days (9).

Group C (Control group): COVID-19 patients with moderate severity received standard treatment according to the protocol of the Egyptian Supreme Council of University Hospitals; Vitamin C 500mg tablet twice daily, Vitamin D3 2000–4000 IU/day, Zinc 75mg tablet once daily for two weeks and needed protocol of management according to case assessment and severity.

Thereafter patients in all groups received instructions of home isolation.

Randomization: The researcher used sealed envelopes containing code for intervention or control.

Follow up: Participants were followed up twice weekly by telephone evaluating their symptoms (increase or decrease, duration of symptoms and development of new symptoms) compliance on treatment, daily measurement of temperature, oxygen saturation, need for oxygen inhalation, need for hospital admission, ICU admission, mechanical ventilation, mortality, and improvement of inflammatory markers (CBC, CRP, Ferritin and D-dimer).

Final evaluation: Discharge from isolation after 10 days after symptom onset or 10 days after their first positive swab (14). Participants were asked about improvement of symptoms or residual symptoms. Inflammatory markers (CBC, CRP, Ferritin and D-dimer) will be re-tested on day 14 then after 1 month from onset of symptoms.

End point: The study was continued up to complete the sample size, improvement of patient's symptoms, no development of new symptoms, need for hospitalization or ICU admission and occurrence of adverse events (AES) or serious adverse events (SAEs) throughout the study duration.

#### Ethical considerations

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Ain Shams University. Written informed consent was obtained from all participants after explaining the objectives of the study. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical analysis: The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test/ANOVA F test was used for comparison between groups. P value  $\leq 0.05$  was statistically significant.

### 3.Results

A total of 120 patients with COVID-19 were enrolled in the study, 40 patients in each arm. Their mean age was 40.16(SD 10.74) years. Out of them, 44 (36.6%) were males and 76(63.4%) were females, and 99(82.5%) were married. Most of them (n. 100, 83.3%) lived in urban areas and there was no statistically significant difference between the three groups in terms of demographic data (Table 1). Table 2 shows different clinical data including duration of symptoms, number of symptoms, severity of symptoms, residual symptoms, CT findings and the fate. Severity of symptoms increased over one week then decreased in most of patients in the three groups (P-value  $>0.05$ ). Most of patients in the ivermectin, colchicine and control groups were cured with residual symptoms after 2 weeks (P-value  $>0.05$ ). No statistically significant difference was found between the mean durations of symptoms in the ivermectin, colchicine and control groups. Similarly, no statistically significant difference was observed between the mean numbers of symptoms in the ivermectin, colchicine and control groups (P-value  $>0.05$ ). In general, the mean difference regarding clinical data wasn't statistically significant in between the three groups. Regarding laboratory data, a statistically significant difference was found in all the parameters, except the lymphocytes, over the three points of time (5 days, 2weeks, and 4weeks). Improvement of inflammatory markers over time occurred in each of the three groups, with no statistically significant difference in between them (Table 3).

**Table 1.** Comparison between the three treatment groups regarding the socio-demographic data

		Ivermectin group	Colchicine group	Control group	Test value	P-value
		No. = 40	No. = 40	No. = 40		
Age (years)	Mean $\pm$ SD	41.05 $\pm$ 10.97	39.78 $\pm$ 10.88	39.65 $\pm$ 10.37	0.208•	0.812
Sex	Male	14 (35%)	18 (45%)	12 (30%)	2.010**	0.366
	Female	26 (65%)	22 (55%)	28 (70%)		
Marital status	Single	8 (20%)	7 (17.5%)	6 (15%)	0.393*	0.954
	Married	32 (80%)	33 (82.5%)	34 (85%)		
Residence	Rural	8 (20%)	6 (15%)	6 (15%)	0.480**	0.787
	Urban	32 (80%)	34 (85%)	34 (85%)		

\*Fisher exact test. \*\*F test.

**Table 2.** Comparison between the three treatment groups regarding the clinical data

Variable		Ivermectin group		Colchicine group		Control group		Chi-square	P-value
		No	%	No	%	No	%		
Severity of symptoms	Absent	0	(0.0%)	0	(0.0%)	0	(0.0%)	3.386**	0.495
	Mild	4	(13.3%)	1	(3.3%)	5	(16.7%)		
	Moderate	8	(26.7%)	10	(33.3%)	10	(33.3%)		
	Severe	18	(60%)	19	(63.3%)	15	(50%)		
Residual symptoms	No	13	32.5	12	30.0	11	27.5	0.238	0.888
	Yes	27	67.5	28	70.0	29	72.5		
CT findings (CO-RADS)	CO-RADS1	2	5.0	0	0.0	2	5.0	5.097 *	0.773
	CO-RADS2	16	40.0	13	32.5	13	32.5		
	CO-RADS3	10	25.0	16	40.0	15	37.5		
	CO-RADS4	7	17.5	5	12.5	4	10.0		
	CO-RADS5	5	12.5	6	15.0	6	15.0		
Outcome	Cured with residual symptoms after 2 weeks	27	67.5	28	70.0	29	72.5	0.238	0.888
	Completely cured within 2 weeks	13	32.5	12	30.0	11	27.5		
Number of symptoms Mean $\pm$ SD		6.6 $\pm$ 1.58		7.3 $\pm$ 1.68		7.075 $\pm$ 1.58		1.961 **	0.145
Duration of symptoms Mean $\pm$ SD		9.58 $\pm$ 2.206		9.9 $\pm$ 2.07		9.53 $\pm$ 2.37		0.336 **	0.715

\*Fisher exact test. \*\*F test

**Table 3.** Comparison between the three treatment groups according to laboratory data

Variable	Ivermectin Group (Mean $\pm$ SD)	Colchicine Group (Mean $\pm$ SD)	Control Group (Mean $\pm$ SD)	P-value
Hb Initial day	12.65 $\pm$ 1.76	13.44 $\pm$ 1.48	13.45 $\pm$ 1.50	0.086
Hb2weeks	12.61 $\pm$ 1.74	13.39 $\pm$ 1.39	13.43 $\pm$ 1.51	0.076
Hb4weeks	12.83 $\pm$ 1.60	13.54 $\pm$ 1.35	13.52 $\pm$ 1.45	0.106
<b>P-value</b>	<b>0.031</b>	<b>0.025</b>	0.465	---
TLC Initial day	5.1 (3.8 – 6.3)	4.85 (3.1 – 6.3)	4.85 (4.1 – 7.2)	0.588
TLC 2weeks	6.35 (5.8 – 8)	6 (5 – 7)	6.7 (5.01 – 8.5)	0.186
TLC 4weeks	7 (6.1 – 8.2)	7.15 (6.4 – 8.4)	7.35 (6.5 – 8)	0.592
<b>P-value</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	---
Lymp Initial day	1.85 (1.2 – 2.52)	1.65 (0.95 – 2.32)	1.55 (1.3 – 2.5)	0.658
Lymp2weeks	1.9 (1.5 – 2.52)	1.6 (1.3 – 2)	1.8 (1.5 – 2.6)	0.029
Lymp4weeks	1.65 (1.5 – 2.3)	1.85 (1.5 – 2.1)	1.85 (1.5 – 2)	0.893
<b>P-value</b>	0.893	0.076	0.371	---
Mono Initial day	0.5 (0.3 – 0.7)	0.42 (0.2 – 0.67)	0.5 (0.24 – 0.9)	0.525
Mono 2weeks	0.3 (0.2 – 0.4)	0.3 (0.2 – 0.4)	0.32 (0.25 – 0.5)	0.211

**Continued**

Mono4weeks	0.29 (0.2 – 0.4)	0.22 (0.2 – 0.32)	0.27 (0.2 – 0.4)	0.887
<b>P-value</b>	<b>0.001</b>	<b>0.008</b>	<b>0.009</b>	---
NEUT Initial day	2.44 (1.8 – 3.1)	2.55 (1.3 – 3.6)	2.89 (1.9 – 4.14)	0.411
NEUT 2weeks	4 (3 – 5.39)	3.95 (2.9 – 5)	4 (2.75 – 5.1)	0.588
NEUT 4weeks	4.75 (3.9 – 5.5)	4.85 (4.3 – 6)	5.2 (3.7 – 6)	0.527
<b>P-value</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	---
CRP Initial day	16 (6 – 28)	21.4 (15 – 42)	12.45 (8.4 – 30.3)	0.190
CRP 2weeks	4.75 (3 – 6)	4 (2.4 – 6)	5 (2 – 7)	0.798
CRP 4weeks	1.35 (0.06 – 3)	1.85 (1 – 3)	3 (1.1 – 5)	0.092
<b>P-value</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	---
S. Ferritin Initial day	75 (54.6 – 177)	154.5 (60 – 186)	139 (54 – 278.2)	0.341
S. Ferritin 2weeks	50 (39 – 78)	60 (45 – 75)	71.5 (45 – 110)	0.452
S. Ferritin 4weeks	50.5 (39 – 70)	60.5 (49 – 70)	57.5 (45 – 98)	0.436
<b>P-value</b>	<b>0.021</b>	<b>&lt;0.001</b>	<b>0.051</b>	---
D-dimer Initial day	0.53 (0.4 – 0.78)	0.67 (0.56 – 0.8)	0.54 (0.33 – 0.8)	0.171
D-dimer 2weeks	0.34 (0.2 – 0.43)	0.36 (0.27 – 0.45)	0.36 (0.23 – 0.5)	0.773
D-dimer 4weeks	0.25 (0.12 – 0.3)	0.25 (0.18 – 0.34)	0.27 (0.2 – 0.32)	0.586
<b>P-value</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	---

TLC: total leucocytic count, LYMP: lymphocytes, Mono: Monocytes, Neut: Neutrophils.

**4. Discussion**

The COVID-19 pandemic has triggered a tremendous burden on healthcare services round the world, due to its rapid unfold with devastating consequences. Currently, no medication is recommended for moderate COVID-19. The development of a new drug takes a long time, so researchers are attempting to discover the effectiveness of existing drugs in treating SARS-CoV-2, which have already been shown to be effective in treating comparable viruses. Hydroxychloroquine and chloroquine are examples for these drugs that most widely used in treating COVID-19. Early observational studies found considerable benefit of these drugs (15, 16). However, later in randomized controlled clinical trials, these presumed benefits had been negated (17,18). Ivermectin and Colchicine are other examples for these drugs. In these three arms randomized controlled clinical trial, adding ivermectin or colchicine to usual care doesn't provide better clinical outcomes as regard to duration of symptoms, number of symptoms, severity of symptoms, residual symptoms, CT findings, fate, and improvement of

inflammatory markers. There wasn't significant difference in age, sex, and disease severity between the interventions and control groups and thus eliminating the selection bias. Although ivermectin had been shown early promising results in treating COVID-19 (19,20,21,22,23,24), several studies had been negated this effect (25,26,27). Another randomized controlled trial conducted in Bangladesh reported that ivermectin had no beneficial effect in treating COVID-19 over the usual care (28). The ineffectiveness of ivermectin on the overall COVID-19 outcome is no longer unexpected. Available pharmacokinetic information from clinically relevant and excessive doses suggests that the concentration of ivermectin required to inhibit COVID-19 in humans is not likely to be attainable in serum and tissue with recognized dosing regimens (29). In a review about role of ivermectin in COVID-19, Chaccour et al. concluded that ivermectin is incorrectly used to treat COVID-19 without scientific evidence of demonstrable efficacy and safety (30). Regarding colchicine, in our study colchicine also had no beneficial effects on clinical improvement or inflammatory markers.

In a large multicenter randomized control trial (COLCORONA), the effect of colchicine in clinical improvement in community-treated patients wasn't statistically significant (31). European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines declared strong recommendation against use of colchicine in COVID-19 (32). Colchicine showed promising effects in small preliminary randomized controlled clinical trials (33,34). In a recent meta-analysis about safety and efficacy of colchicine, patients receiving colchicine didn't show significant reduction in mortality, length of hospital stay or ventilatory support. Also, they had a higher rate of adverse effects (35). Treatment with colchicine in COVID-19 must now not be recommended till greater proof is available to assist advantageous outcomes (36). Using ivermectin and colchicines in COVID-19 should be limited on clinical trials until scientific evidence for their usage would be found.

## 5. Conclusion

Adding ivermectin or colchicine to the standard care didn't show any benefit. Future multicentre randomized controlled trial with larger sample size could be conducted to confirm these results.

**Conflict of Interest Statement:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Correspondence:

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Hemat Abd El-Salam Ahmed, Department of Family Medicine, Faculty of Medicine, Ain Shams University, 11566 Abbasia, Cairo, Egypt Mobile: + (2) 01012884607

E-mail: [hemat\\_abdelsalam@med.asu.edu.eg](mailto:hemat_abdelsalam@med.asu.edu.eg)