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Coronavirus Pandemic

Role of ivermectin and colchicine in the treatment of COVID-19: a randomized controlled clinical trial

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Abstract

Introduction: The objective of this study was to assess the effectiveness of ivermectin and colchicine as treatment options for coronavirus disease 2019 (COVID-19).

Methodology: A three-arm randomized controlled clinical trial was conducted in the Triage Clinic of the family medicine department at Ain Shams University Hospitals on participants who had been diagnosed with moderate COVID-19. Patients aged < 18 years or > 65 years, with any co-morbidities, pregnant or lactating females, and those with mild or severe COVID-19 confirmed cases were excluded. Sealed envelopes were used for randomization of intervention or control. Patients are followed until there was improvement of symptoms and no development of new symptoms for over one month.

Results: A total of 120 patients (40.16 ± 10.74 years) with COVID-19 were enrolled; 40 patients in each arm. Out of them, 44 (36.6%) were male and 76 (63.4%) were female. Fever and cough were the predominant symptoms in each group. There was no statistically significant difference in the mean duration of fever between the ivermectin, colchicine, and control groups (7.3 ± 1.68, 6.6 ± 1.58, and 7.075 ± 1.58 days, respectively). The majority of patients (67.5%, 70%, and 72.5%) were completely cured within 10 days of infection, with no differences between the three groups ($p > 0.05$). A statistically significant improvement of inflammatory markers occurred in each of the three groups over time with no statistically significant difference between them.

Conclusions: Ivermectin and colchicine have no beneficial effect over standard care in the treatment of COVID-19.

Key words: ivermectin, colchicine, COVID-19, clinical trial, Ain Shams University.

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new corona virus that quickly spread throughout the world [1]. More than 167 million individuals had been diagnosed and more than 3 million had died as a result of COVID-19 by 24 May 2021 [2]. A highly effective treatment option was needed to effectively minimize the spread of COVID-19 and especially the associated deaths [3].

Many attempts were made to repurpose existing and approved drugs for the treatment of COVID-19 infection because development of a new drug would need a long time [4]. This included anti-malarial drugs such as hydroxychloroquine and chloroquine, which had recently been shown to be less successful than initially believed, with a substantial risk of fatal complications and interactions [5]. Another anti-parasitic drug which was proposed as a therapeutic option for COVID-19 was ivermectin [6]. An in vitro study indicated that ivermectin was effective against the COVID-19 infected cells [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 been 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].

To date, there is no accepted treatment for patients who are not hospitalized. 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 patients [9,12,13]. However, there is still a lack of evidence-based studies, especially clinical trials, to assess the effectiveness of ivermectin and colchicine as treatment options for COVID-19.

Methodology

Study design and setting

The study was a three-arm randomized controlled clinical trial conducted in the Triage Clinic of the Family Medicine Department at Ain Shams University Hospitals over a period of one year. The inclusion criteria were COVID-19 patients aged 18–64 years with moderate severity. The exclusion criteria were COVID-19 patients with any co-morbidities (hypertension, diabetes mellitus, etc.), COVID-19 patients with mild or severe symptoms, and 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 until the end of November 2022. The patients were recruited from Triage COVID-19 Outpatient Clinic and the following data were recorded for every patient: clinical history; 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. The full general examination included temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation.

Patients who were suspected to have COVID 19, according to the Centers for Disease Control and Prevention (CDC) criteria, were subjected to laboratory and radiological confirmation with the COVID-19 polymerase chain reaction (PCR) test; complete blood count (CBC); C-reactive protein (CRP), ferritin and D-dimer tests; and high-resolution computed tomography (CT) of the chest.

After confirmation of the diagnosis, patients were classified as mild, moderate, and severe based on laboratory and radiological findings. Only moderate COVID-19 patients were included in this study.

Grouping

The patients enrolled in the study, according to the calculated sample size, were equally and randomly divided into the three groups using a sealed envelope containing the code for intervention or control (block randomization).

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

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

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 500 mg tablet twice daily, vitamin D3 2000–4000 IU/day, zinc 75 mg tablet once daily for two weeks, and symptomatic treatment.

Thereafter patients in all groups received instructions for home isolation.

Participants were followed up, twice weekly by telephone, to evaluate their symptoms (increase or decrease, duration of symptoms, and development of new symptoms); compliance with treatment; daily measurement of temperature, oxygen saturation; and assessment of the need for oxygen inhalation; need for hospital admission; intensive care unit (ICU) admission; mechanical ventilation; mortality; and improvement of inflammatory markers (CBC, CRP, Ferritin and D-dimer).

Patients were discharged from isolation 10 days after symptom onset or 10 days after their first positive swab [14]. Upon discharge, participants were asked about improvement of symptoms or residual symptoms. Inflammatory markers (CBC, CRP, Ferritin and D-dimer) were re-tested on day 14, and then after 1 month from the onset of symptoms.

The study on each patient was continued up to the time of improvement of patient's symptoms; and no development of new symptoms, need for

Table 1. Comparison of socio-demographic data of the three treatment groups.

Socio-demographic data		Ivermectin group No. = 40	Colchicine group No. = 40	Control group No. = 40	Test value	*p* value
Age (years)	Mean ± SD	41.05 ± 10.97	39.78 ± 10.88	39.65 ± 10.37	0.208•	0.812
Gender	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.

hospitalization or ICU admission, or occurrence of adverse events (AES) or serious adverse events (SAEs).

Ethical considerations

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Ain Shams University (No. FWA0001785). 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 data were analyzed with the Statistical Package for Social Sciences (SPSS) version 20 for Windows (IBM Corp, Armonk, NY, USA). Qualitative data were defined as numbers and percentages. The 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 ≤ 0.05 was considered statistically significant. Intention to treat analysis was used.

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 ± 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 indicating matched groups (Figure 1 and Table 1).

Table 2 shows the clinical data, including presenting symptoms, duration of symptoms, duration of fever, different levels of COVID-19 Reporting and Data System (CO-RADS), and outcome. Fever and cough were the main presenting symptoms in our participants. The majority of CT findings corresponded to CO-RADS3 and 4. Most patients, in all three groups, were completely cured within 10 days of infection. No statistically significant difference was found between the mean duration of fever and symptoms in the ivermectin, colchicine, and control groups. Similarly, no statistically significant difference was observed between the outcome in the ivermectin, colchicine, and control groups ($p > 0.05$). In general, there was no statistically significant difference in the mean clinical data of the three groups.

In the case of laboratory data, a statistically significant difference was found over the three time points (5 days, 2 weeks, and 4 weeks) in all the parameters, except the lymphocytes. Improvement of inflammatory markers over time occurred in each of the three groups, with no statistically significant difference between them (Table 3).

Figure 1. CONSORT flow diagram.

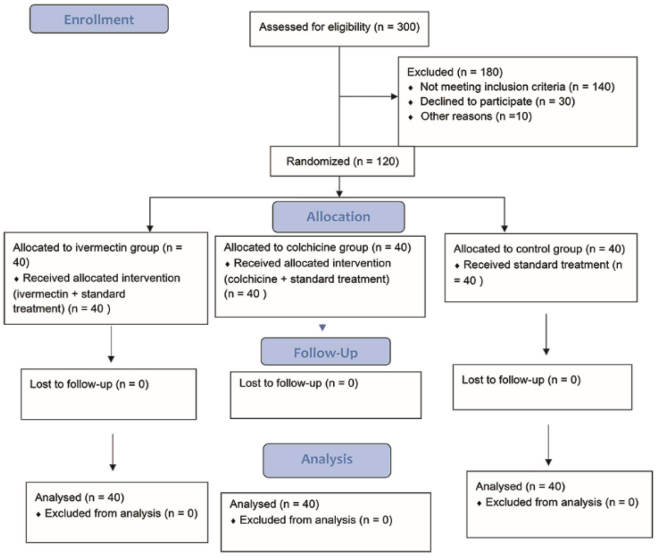

Table 2. Comparison of clinical data of the three treatment groups.

Clinical data		Ivermectin group No. = 40	Colchicine group No. = 40	Control group No. = 40	Test value	*p* value
Presenting symptoms	Fever	30 (75%)	28 (70%)	31 (77.5%)	0.609*	0.737
	GIT symptoms	9 (22.5%)	11 (27.5%)	7 (17.5%)	1.147*	0.564
	Respiratory symptoms	35 (87.5%)	34 (85%)	36 (90%)	0.457*	0.796
Duration of fever	Mean ± SD	7.3 ± 1.68	6.6 ± 1.58	7.075 ± 1.58	1.961•	0.145
Duration of symptoms	Mean ± SD	9.58 ± 2.206	9.9 ± 2.07	9.53 ± 2.37	0.336•	0.715
CT findings	CO-RADS1	2 (5.0%)	0 (0.0%)	2 (5.0%)		
(CO-RADS)	CO-RADS2	7 (17.5%)	5 (12.5%)	4 (10.0%)		
	CO-RADS3	10 (25.0%)	16 (40.0%)	15 (37.5%)	4.933*	0.765
	CO-RADS4	16 (40.0%)	13 (32.5%)	13 (32.5%)		
	CO-RADS5	5 (12.5%)	6 (15.0%)	6 (15.0%)		
Outcome	Completely cured within 10 days	27 (67.5%)	28 (70%)	29 (72.5%)	0.238*	0.888
	Symptoms progression after 10 days	13 (32.5%)	12 (30%)	11 (27.5%)	0.238*	0.888
	Symptoms progression after one month	3 (10%)	2 (5%)	3 (7.5%)	0.268*	0.875

*Fisher exact test. **F test. CO-RADS: COVID-19 Reporting and Data System; CT: computed tomography; GIT: gastrointestinal tract; SD: standard deviation.

Table 3. Comparison of laboratory data during the follow up period in the three treatment groups.

Variable	Ivermectin group (Mean ± SD)	Colchicine group (Mean ± SD)	Control group (Mean ± SD)	*p* value
Hb initial day	12.65 ± 1.76	13.44 ± 1.48	13.45 ± 1.50	0.086
Hb 2 weeks	12.61 ± 1.74	13.39 ± 1.39	13.43 ± 1.51	0.076
Hb 4 weeks	12.83 ± 1.60	13.54 ± 1.35	13.52 ± 1.45	0.106
p value	0.031	0.025	0.465	---
	Median/Range	**Median/Range**	**Median/Range**	
TLC initial day	5.1 (3.8–6.3)	4.85 (3.1–6.3)	4.85 (4.1–7.2)	0.588
TLC 2 weeks	6.35 (5.8–8)	6 (5–7)	6.7 (5.01–8.5)	0.186
TLC 4 weeks	7 (6.1–8.2)	7.15 (6.4–8.4)	7.35 (6.5–8)	0.592
p value	< 0.001	< 0.001	< 0.001	---
Lymphocytes initial day	1.85 (1.2–2.52)	1.65 (0.95–2.32)	1.55 (1.3–2.5)	0.658
Lymphocytes 2 weeks	1.9 (1.5–2.52)	1.6 (1.3–2)	1.8 (1.5–2.6)	0.029
Lymphocytes 4 weeks	1.65 (1.5–2.3)	1.85 (1.5–2.1)	1.85 (1.5–2)	0.893
p value	0.893	0.076	0.371	---
Monocytes initial day	0.5 (0.3–0.7)	0.42 (0.2–0.67)	0.5 (0.24–0.9)	0.525
Monocytes 2 weeks	0.3 (0.2–0.4)	0.3 (0.2–0.4)	0.32 (0.25–0.5)	0.211
Monocytes 4 weeks	0.29 (0.2–0.4)	0.22 (0.2–0.32)	0.27 (0.2–0.4)	0.887
p value	0.001	0.008	0.009	---
Neutrophils Initial day	2.44 (1.8–3.1)	2.55 (1.3–3.6)	2.89 (1.9–4.14)	0.411
Neutrophils 2 weeks	4 (3–5.39)	3.95 (2.9–5)	4 (2.75–5.1)	0.588
Neutrophils 4 weeks	4.75 (3.9–5.5)	4.85 (4.3–6)	5.2 (3.7–6)	0.527
p value	< 0.001	< 0.001	< 0.001	---
CRP initial day	16 (6–28)	21.4 (15–42)	12.45 (8.4–30.3)	0.190
CRP 2 weeks	4.75 (3–6)	4 (2.4–6)	5 (2–7)	0.798
CRP 4 weeks	1.35 (0.06–3)	1.85 (1–3)	3 (1.1–5)	0.092
p value	< 0.001	< 0.001	< 0.001	---
S ferritin initial day	75 (54.6–177)	154.5 (60–186)	139 (54–278.2)	0.341
S ferritin 2 weeks	50 (39–78)	60 (45–75)	71.5 (45–110)	0.452
S ferritin 4 weeks	50.5 (39–70)	60.5 (49–70)	57.5 (45–98)	0.436
p value	0.021	< 0.001	0.051	---
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 2 weeks	0.34 (0.2–0.43)	0.36 (0.27–0.45)	0.36 (0.23–0.5)	0.773
D-dimer 4 weeks	0.25 (0.12–0.3)	0.25 (0.18–0.34)	0.27 (0.2–0.32)	0.586
p value	< 0.001	< 0.001	< 0.001	---

Hb: hemoglobin; TLC: total leucocytic count; CRP: C reactive protein; S ferritin: serum ferritin.

Discussion

The COVID-19 pandemic has triggered a tremendous burden on healthcare services round the world, due to its rapid unfolding 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 which have already been shown to be effective in treating comparable viruses.

Hydroxychloroquine and chloroquine are examples of such drugs that were most widely used for 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 of such drugs.

In this randomized controlled clinical trial, the mean age of the study participants was around 40 years. Most of the COVID-19 infected patients in the study were females. There were no statistically significant differences in age, gender, and disease severity between the interventions and control groups in the present study, indicating matched groups.

Regarding clinical data in the present study, respiratory symptoms (cough, dyspnea, rhinorrhea, and nasal congestion) were the most presenting symptoms in our participants followed by fever; while gastrointestinal tract (GIT) symptoms were the least presenting symptoms. The mean duration of fever in the present study was 7 days while the mean duration of symptoms was 10 days. There was no statistically significant difference regarding clinical data between the interventions and control groups.

Regarding laboratory data, there was a statistically significant difference in all the parameters, except lymphocytes, over the three time points. The CBC changed significantly during the study period – the mean level of hemoglobin (Hb) decreased initially, and then increased; total leukocytic count (TLC) and neutrophils increased, while the mean monocyte level decreased. Inflammatory markers (CRP, serum ferritin, and D-dimer) showed statistically significant early elevation followed by reduction as the condition improved. There were no statistically significant differences in the laboratory data among the three groups.

Regarding the COVID-19 outcomes in the present study, most of symptoms recovered after 10 days of infection; while about 30% of research participants experienced symptoms that lasted for more than ten days in each of the three groups (interventions and control) with no statistically significant difference in between them.

Thus, based on the results of our three arms randomized controlled clinical trial, adding ivermectin or colchicine to usual COVID-19 care did not provide better clinical outcomes with regard to presenting symptoms and its duration of fever, outcome, and improvement of inflammatory markers. Although ivermectin had shown early promising results in treating COVID-19 [19–24], several studies have negated this effect [25–27]. A 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 the recognized dosing regimens [29]. Chaccour *et al.* reviewed the role of ivermectin in COVID-19 and concluded that ivermectin is incorrectly used to treat COVID-19 without scientific evidence of demonstrable efficacy and safety [30].

Colchicine also had no beneficial effect on clinical improvement or inflammatory markers in COVID-19 patients in our study. In a large multicenter randomized control trial (COLCORONA), the effect of colchicine on clinical improvement in community-treated patients – those who did not require hospitalization and were treated at home – was not statistically significant [31]. Although colchicine showed promising effects in small preliminary randomized controlled clinical trials [33,34], the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines has strong recommendation against the use of colchicine in COVID-19 [32]. In a recently published meta-analysis on the safety and efficacy of colchicine, patients receiving colchicine did not show significant reduction in mortality, length of hospital stay, or ventilatory support. In addition, they had a higher rate of adverse effects [35]. Therefore, treatment with colchicine must not be recommended for COVID-19 until greater proof is available to support advantageous outcomes [36].

Thus, the use of ivermectin and colchicine in COVID-19 should be limited to clinical trials until scientific evidence for their safe and effective usage is found.

Conclusions

Adding ivermectin or colchicine to the standard care did not result in any benefit. Future multi center randomized controlled trials with larger sample sizes may be conducted to confirm these results.

Limitations

Our study lacked data from COVID-19 real time reverse transcriptase PCR (RT-PCR) tests; so, the effect of colchicine and ivermectin on viral load could not be assessed. Not all the inflammatory markers were measured in this study. Therefore, complete data on the effect of ivermectin and colchicine on these

inflammatory markers cannot be determined. Our sample size was not large; and further studies with larger sample size can be conducted to allow generalization of data.

Trial registration

The clinical trial was registered at the Protocol Registration and Results System with number NCT05930002 on 20 June 2023.

Data availability

Data will be available when necessary.

Authors' contributions

All authors declare that they contributed to the study equally in data collection, data management and manuscript writing.

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