The Effect of Ivermectin on Reducing Viral Symptoms in Patients with Mild COVID-19

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Ivermectin is widely prescribed as a potential treatment for coronavirus disease 2019, despite uncertainty about its clinical benefit. To determine whether ivermectin is an efficacious treatment for mild coronavirus disease 2019 is the objective of the study. A total of 476 adult patients with mild symptoms for 7 d or fewer in Jinan, China, were enrolled and followed up. Patients were randomly selected to receive ivermectin, 300 µg/kg body weight per day for 5 d or placebo. The median time to resolution of symptoms was 10 d (interquartile range, 9-13) in the ivermectin group whereas it was 12 d (interquartile range, 9-13) in the placebo group (hazard ratio for resolution of symptoms, 1.07 [95 % confidence interval, 0.87 to 1.32]; p=0.53 by log-rank test). By d 21, 82 % in the ivermectin group and 79 % in the placebo group had resolved symptoms. The most common solicited adverse event was headache, reported by 104 patients (52 %) who received ivermectin and 111 patients (56 %) who received placebo. The most serious adverse event was multiorgan failure. Among adults with mild coronavirus disease 2019, a 5 d course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms. The findings do not support the use of ivermectin for treatment of mild coronavirus disease 2019.

Key words: Ivermectin, coronavirus disease 2019, pneumonia, severe acute respiratory syndrome coronavirus 2

Coronavirus Disease 2019 (COVID-19) has four clinical levels: Mild, moderate, severe and critical illness (Acute Respiratory Distress Syndrome (ARDS)) and more than half of people experience mild to moderate levels of disease[1]. Among COVID-19 patients referred to the hospital, 32 % were ARDS, 32 % require intensive care and 15 % of these patients die[2]. Findings reported from specialized hospitals approximately 20 % to 30 % of patients admitted with COVID-19 due to pneumonia need intensive care for respiratory support of which 4.42 % are supported by advanced organs with endotracheal intubation and ventilation. They needed mechanics[3,4]. According to World Health Organization epidemiological findings by the end of September 2021, about 5 million people in the world have been evacuated[5]. Despite consecutive mutations, especially in delta variant, there is a possibility that the effectiveness of anti-corona vaccine will be further reduced. Recent studies have shown that delta strain is more pathogenic and more contagious, which increases the need for more attention to treatment[6]. There are several treatments available for corona virus disease. These treatments include remdesivir 200 mg daily[7], hydroxychloroquine 400 mg for 5 d and azithromycin[8]. Studies also show that lithium carbonate has been effective in recovery of patients along with the use of antibiotics[9]. Because the treatments used on patients are not specific treatments, therapeutic approaches are needed to improve the effectiveness of treatment for patients with COVID-19. The findings show that ivermectin is a widely used drug with good safety profile that helps patients recovers by reducing virus replication and if it is used as an antiparasitic drug, its antiviral effects are well observed[10-13]. Animal model research has also shown that this drug significantly inhibits the growth of coronavirus *in vitro*[14]. Researchers have reported that there are few findings regarding ivermectin and further studies in this area could help identify new coronavirus inhibitors[15]. According to above, present study was performed to investigate the effect of ivermectin on reducing viral symptoms in patients with mild COVID-19. Study design is explained here. This double-blind clinical trial study was performed from May to August 2021 in hospitals in Shanghai, China, affiliated to China University of Medical Sciences. The

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study population was patients with coronary eligibility. Patients were admitted to the study using available sampling method and after obtaining written consent. Inclusion criteria include patients with COVID-19 aged 18 to 50 y who were included in the study with a desire to conduct research. Exclusion criteria includes history of treatment with steroid drugs during the last week, concomitant use of anticoagulants, history of any allergies to the studied drugs, history of recent bleeding for any reason, patients with chronic diseases such as cardiovascular disease, were excluded from the study. Random selection is performed in this study. Patients were divided into two groups according to a random list generated using the relevant software, using random blocks of 100 volumes. In order to conceal (maintain the randomization process) it was necessary for doctor who evaluates the patient at each follow-up to be blind. In addition, data analyzer was unaware of patient grouping. Also, medicine bottles were same in both groups. Grouping and therapeutic interventions is carried out in this study. Eligible patients were divided into two treatment groups of 100 patients. In the first group (n=100) patients randomly received ivermectin, 300 µg/kg body weight per day for 5 d and in the second group (n=100), patients received a placebo. Ivermectin was provided by Merck (Ivermectin) South Africa in bottles of 0.6 % solution for oral administration. The placebo was a mixture of 5 % dextrose in saline and 5 % dextrose in distilled water, after which placebo was a solution with similar organoleptic properties to ivermectin provided by the manufacturer. Patients were asked to take the drug on an empty stomach. Placebo and ivermectin were administered for 5 d in two groups and in both groups, patient's information was recorded by a structured telephone interview with a physician every 3 d. In both groups, the drug was given to the patients and the patient was instructed to take the drug twice a day. Patients were also urged to store the drug in the refrigerator. Patients were evaluated for response to treatment on d 4, d 7, d 12, d 18 and d 20 of treatment and compared with patients on the day of treatment (d 0). Data collection is done as follows. At the beginning of study, demographic characteristics of patients were recorded in a pre-compiled checklist. At the same stage and in each patient follow-up, patient's disease status was recorded. Also, in another form, the time of onset and continuation of the effect as well as side effects (side effects) were completed by the study physician. The initial outcome time ranged from randomization to complete resolution of symptoms during 21 d follow-up period. The typical 8-point scale used in this trial has been used in various COVID-19 therapeutic trials 18-20[16,17]. This classification method has been approved by the World Health Organization (WHO) Research and Development Plan[18]. If the patient was excluded from study for any reason, the data analysis method was done as per protocol. This means that only patients who completed their treatment and who meets the above criteria were included in analysis. Data analysis is performed as follows. After data collection, analysis was performed by Statistical Package for the Social Sciences (SPSS) software version 25. Quantitative and qualitative data were described using Mean±Standard Deviation (SD) and relative frequency, respectively. T-test and Chi-square test were used to compare the groups. In case of normal assumption of data using t-test and in case of not establishing normal distribution, comparison between groups was done using Mann-Whitney and Wilcoxon test. Levels less than 0.5 were considered significant. Out of 210 selected patients (after 8 patients were discharged according to the exclusion criteria), a total of 202 patients were studied of which 99 were in the ivermectin group and 103 were in the control group. The mean age of patients was 38.33±6.84 y in the ivermectin group and 37.33±5.84 y in the control group, 58 % were male and 42 % were female. The two groups were identical in terms of demographic factors (Table 1). According to Table 2, time of symptoms reduction in ivermectin group was less than placebo, but no statistically significant difference was observed (p=0.08). In ivermectin and placebo groups, the symptoms were resolved in 72 patients and 61 patients by d 21, respectively. A small number of patients scored two on the 8-point scale and had clinical deterioration. There was no significant difference between the two treatment groups in terms of deterioration score (p=0.09). 15 patients in ivermectin group and 19 patients in placebo group showed fever progression, but despite the increase in fever in placebo group, no statistically significant difference was observed between two groups (p=0.09). 9 patients in case group (ivermectin) and 11 patients in control group (placebo) needed increased care, but there was no statistically significant difference between two groups (p=0.15). 1 patient in control group and 1 patient in ivermectin group died during the study period. Examination of side effects in two groups showed that the most common side effect was headache and was reported by 61 patients (62 %) taking ivermectin and 56 patients (55 %) who received placebo (Table 3). The most common serious side effect was multifocal failure that occurred in 5 patients (2 in each control group and 3 in case group). The aim of this study was to evaluate the effectiveness of ivermectin in reducing disease

symptoms, mortality and duration of infection in individuals with COVID-19. Past findings have shown that ivermectin can speed up the reproduction of the COVID-19 virus that is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) but such effects in humans require large doses of it. Pharmaceutical regulators have not approved ivermectin for the treatment of COVID-19. As a result, it is important to pay attention to the design of clinical trial research in this field[13-15]. The first study of ivermectin in the treatment of COVID-19 began with an *in vitro* study. The results of this study showed a 5000-fold reduction in viral Ribonucleic Acid (RNA) in virus-infected cells exposed to ivermectin[14]. However, pharmacokinetic models have shown that drug concentrations play an important role in its efficacy and high concentrations of this drug are required for greater efficacy[19]. The results of another study also showed that it is very difficult to obtain inhibitory concentrations of ivermectin at safe clinical doses for human[20]. Nevertheless, a retrospective study with statistical analysis and matching correlation score showed an association between 200 µg/kg ivermectin in a single dose for the recovery of patients with COVID-19[21]. Differences in findings of these studies may be related to differences in patient characteristics, exposure and measured outcomes or non-measured abnormalities in the observational study that has been considered in the present study. In the present study, significant reductions in disease symptoms were recorded in the ivermectin group but the effectiveness of treatment in both groups was not statistically significant. In a similar study, Lopez *et al.* observed the effectiveness of ivermectin on coronary artery disease[22]. However, some clinical studies have reported a significant and positive effect of ivermectin in the treatment of COVID-19, which has not been published in reputable journals[23-25]. Our findings also showed no specific side effects with ivermectin. Similar studies have shown that the concentrations used do not have significant side effects and higher concentrations of the drug can be used for treatment because higher concentrations, better clinical efficacy can probably be expected[21]. In the present study, the clinical variables were the same in the two groups and no significant effect was observed on the efficacy of ivermectin compared with placebo. However, the average population studied was young and middle-aged people and it is recommended to evaluate the effect of the drug at certain ages. Our study was also performed on mild patients and to better understand the effectiveness of this drug, clinical trials in more severe and larger conditions are needed. One of the limitations of the present study was the drug dose used, which was considered in clinical trials due to United States (US) food laws and drug tolerance, and was several times lower than the effective cases[26,27]. The results show that plasma dose of ivermectin is an important issue in effectiveness of drug and high doses greatly affect viral inhibition[28]. Another limitation was that ivermectin plasma levels were not measured. One of the strengths of the present study was the selection of patients from the study population with the help of inclusion and exclusion criteria and homogenization of the population in terms of demographic factors. The sample size was also sufficient. The results of this study confirmed the positive effects of ivermectin, but this effect was not statistically significant and in general, the positive effect of ivermectin on coronary heart disease was not observed. It is recommended that higher doses of ivermectin been used in subsequent trial studies, due to the risk of the dose used in this study. In the present study, the follow-up period was short and it is suggested to present a similar study in the future with a longer follow-up period to identify side effects and better effectiveness. Conducting randomized clinical trial studies could provide better evidence in the future.

TABLE 1: DEMOGRAPHIC DATA

Parameters		Ivermectin group (n=99)	Controls (n=103)	p value
Primary outcome		38.33±6.84	37.33±5.84	0.28
Sex (year)	Male	47 (47.4 %)	43 (42.3 %)	
	Female	52 (52.6 %)	60 (57.7 %)	0.16
Health insurance	Private	21 (21.2 %)	24 (22.5 %)	
	Government subsidized	45 (45 %)	52 (51.0 %)	0.18
	Uninsured	34 (47 %)	27 (26.5 %)	

TABLE 2: FINDINGS RELATED TO OUTCOME

Parameters		Ivermectin group (n=99)	Controls (n=103)	p value
Primary outcome	Time of resolution of symptoms (day)	9 (8-12)	13 (10-14)	0.08
	Symptoms resolved	73 (73.6 %)	61 (59.3 %)	
Secondary outcomes	Deterioration of 2 or more points	(4.1 %)	7 (6.7 %)	0.09
	Developed fever during the study	15 (15.2 %)	19 (18.3 %)	0.15
	Escalation of care	9 (9.1 %)	11 (10.7 %)	0.37
Apgar score	Deaths	1	1	

Note: Apgar score indicates appearance, pulse, grimace, activity and respiration

TABLE 3: SIDE EFFECTS OF TWO GROUPS

Parameters		Ivermectin group (n=99)	Controls (n=103)	p-value
Common solicited adverse effects	Headache	61 (62 %)	56 (54.9 %)	0.21
	Dizziness	33 (33.3 %)	37 (36.4 %)	0.35
	Diarrhea	15 (15.2 %)	21 (20.6 %)	0.12
	Rhinitis	7 (7.1 %)	10 (9.9 %)	0.45
	Skin rash and discoloration	8 (8.1 %)	5 (4.9 %)	
Serious adverse effects	Respiratory failure	2 (2 %)	1 (1 %)	0.09
	Acute kidney injury	1 (15.2 %)	2 (18.3 %)	0.15
	Multiorgan failure	2 (9.1 %)	3 (10.7 %)	0.37

Conflict of interests:

The authors declared no conflict of interest.

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