Efficacy and safety of ivermectin in the treatment of mild-to-moderate COVID-19 infection: A randomized, double blind, placebo, controlled trial

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Abstract

The emergent outbreak of coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emphasized the requirement for therapeutic opportunities to overcome this pandemic. Ivermectin is an antiparasitic drug that has shown to be effective against various agents, including SARS-CoV-2, and is under extensive research in clinical trials. In this randomized, double-blind, placebo-controlled trial among adult hospitalized patients with mild-to-moderate COVID-19, 72 patients (mean age 48.57 ± 14.80 years) were randomly assigned to either the ivermectin (n=36) or placebo (n=36) group, along with receiving standard care. The primary outcomes were a negative reverse transcription polymerase chain reaction (RT-PCR) result at day 7 and 14 of enrolment. The secondary outcomes were duration of hospitalization, frequency of clinical worsening, survival on day 28, and adverse events. At day 7 and 14, a negative RT-PCR result was not significantly different between the two groups. The other secondary outcomes were reported to be comparable. However, the time to resolution of many symptoms were shorter in the ivermectin group, albeit not significantly. No adverse events were reported. In conclusion, early symptomatic recovery was observed with no side effects after treatment with ivermectin and standard care in mild-to-moderate COVID-19 patients.

Introduction

The newly emerged coronavirus disease (COVID-19) has spread all around the globe, with recent estimates of more than 236 million cases and 4.8 million deaths reported, as of November 2021 [1]. Therapeutic approaches are required to improve outcomes in patients with COVID-19 since no antiviral agent has yet been proved to be conclusively beneficial in treating COVID-19 infection, especially in patients with mild-to-moderate severity. Despite the urgent need to find an effective antiviral treatment for COVID-19 through randomized controlled studies, certain agents are being used globally based on either *in vitro* or observational studies. The most frequently used agents in Thailand and globally include andrographolide, hydroxychloroquine, lopinavir/ritonavir, favipiravir, and remdesivir. Ultimately, none have proved to be efficacious or safe.

There has been a growing interest in the anti-parasitic drug, ivermectin, which was previously studied for its antiviral, antiinflammatory, and anticancer actions [2]. Ivermectin was also reported to have an *in vitro* activity against severe acute respiratory syndrome 2 (SARS-CoV-2), the virus that causes COVID-19 [3]. Its antiviral properties include its action on importin 2/β1 mediated nuclear transport. Ivermectin prevents the binding of viral proteins to importin 2/β1, rendering the viral proteins unable to enter the nucleus and subsequently cause infection [4]. It acts at different viral protein binding sites, thereby reducing viral replication. The blockage of the transport of viral proteins from the cytosol to the nucleus may be one mechanism of action.

Several clinical studies have found a beneficial effect of ivermectin in treating COVID-19 [5–9]. However, some studies did not find a significant difference between the group receiving ivermectin and the control group [10]. To date, controlled trials evaluating ivermectin for treating COVID-19 are lacking. Since

ivermectin is reported to be safe, with side effects of less than 1%; therefore, it is essential to conduct a clinical trial with ivermectin for treating patients with COVID-19. The objective of this study was to establish the efficacy of ivermectin for COVID-19 patients with mild-to-moderate disease, compare to usual care alone.

Results

Baseline demographic and clinical characteristics

Between 1 September 2021 and 30 November 2021, 208 patients with mild-to-moderate COVID-19 infection within 3 days of symptoms onset were assessed for eligibility. Of the 208 assessed individuals, 134 were excluded due to severe co-morbid diseases, such as asthma and active malignancies, age-related ineligibility, and unwillingness to participate. One patient each from the ivermectin and placebo group withdrew their consent during the study due to drug addiction and psychiatric problems. The remaining 72 patients were equally randomized to either the ivermectin plus standard care (n=36) group or the placebo plus standard care (n=36) group (Figure 1). The mean age of all the enrolled cases was 48.57± 14.80 years, patients in both groups were balanced in demographic and disease characteristics at baseline (Table 1).The mean age of cases in the control and intervention arms were not significantly different (47.72± 15.45 years versus 49.42± 29 years, p=0.631). The majority of patients in both the control and intervention group were female (63.9% and 61.1%, respectively). The main concomitant diseases were hypertension (49%), dyslipidemia (34.7 %), and diabetes mellitus (23.6 %). The biochemical parameters were not significantly different between both the groups and were all within normal limits (Supplemental File)

Clinical Outcomes

The most common symptoms were fever (43.1%), cough (77.8%), runny nose (50%), followed by loss of smell and taste (30.6 and 23.6%, respectively), sore throat (37.5%), and diarrhea (11%) (Table 2). The proportion of patients in the ivermectin group recovered from various symptoms sooner than those in the control group, such as cough (OR: 0.54; 95% CI: 0.15–1.94; p=0.346), smell disturbance (OR: 0.34; 95% CI: 0.04–3.11; p=0.342), runny nose (OR: 0.37, 95% CI: 0.08–1.67; p=0.196), fatique (OR: 0.13; 95% CI: 0.00–8.94; p=0.345), and headache (OR: 0.24; 95% CI: 0.03–1.71; p=0.153), although the difference was not statistically significant. Table 3 shows the baseline and follow-up hemodynamics and vital signs from day 1 to day 14. Both the control and treatment arms demonstrated stable blood pressure control, oxygen saturation, and respiratory rate throughout the disease course. None of the patients required intensive care (ICU) admission or invasive ventilation. Nearly all of the patients were discharged by day 14, except two patients that requested to get discharged on day 10, and returned to repeat their laboratory tests on day 14 on an outpatient basis. The hemodynamic characteristics were not significantly different between the two groups from baseline until day 14. Time till resolution of symptoms in patients assigned to the ivermectin versus placebo group was not significantly different between both the groups (HR: 1.18; 95% CI: 0.67–2.08; p=0.572) (Figure 2).

Primary Outcome

The proportion of patients in the treatment and control arm whose reverse transcription polymerase chain reaction (RT-PCR) result was negative on day 7 (7 [17.3%] vs 6 [14.3%], respectively; p=0.743) and day 14 (17 [47.2%] vs 16 [44.4%], respectively; p=0.813) of enrollment was not significant different (Table 4). Furthermore, the Ct ratio on day 14 was also not significantly different between the treatment and control groups (17.43 ± 16.82 vs 18.51 ± 17.34, respectively; p=0.788). One-third of the patients in each group still had residual abnormal chest radiograph at day 14 (12 [33%] vs 11 [30.6%] in the treatment and control group; p= 0.800).

Secondary Outcome

All patients survived at day 28 and almost all of them (,92.1%) were admitted in the hospital until day 14. The proportion of patients who felt healthy on day 14 were not significantly different between the two treatment groups. The remaining symptoms upon discharge in the treatment and control arms were cough (19.4% and 19.4%), dyspnea (5.6% and 0%), smell disturbance (0% and 8.3%), runny nose (0.28% and 0%), sore throat (5.6% and 0%), headache (0% and 5.6%), muscle pain (8.3% and 2.8%), and malaise (0% and 5.6%). None of the patients required escalation of care. There were no major differences in the evolution of vital signs (Table 3), inflammatory markers (C-reactive protein, procalcitonin, ferritin, and interleukin-6), and other laboratory parameters in patients belonging to each group (Supplemental File). However, the time to resolution of many symptoms, such as cough (HR: 1.19 [95% CI: 0.71–1.99]; p=0.513), runny nose (HR: 1.36 [95%CI: 0.84–2.21]; p=0.206), smell disturbances (HR: 1.23 [95% CI: 0.76–199]; p=0.391), and fatique (HR: 1.19 [95%CI: 0.73–1.92], p=0.488) were reported to be shorter, eventhough the difference was not statistically significant.

Effect of vaccination

The proportion of patients who received vaccination was not differed between the two groups, regardless of receiving one or two doses of a vaccine. Most patients were vaccinated with the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine. Of the vaccinated patients, 47.2% received their first dose while only 18% received both doses of the vaccine (p=0.636). Time from last dose of vaccination to COVID-19 infection was comparable in both the ivermectin and control group.

Adverse events

All patients completed the follow-up period of 28 days. No adverse events were recorded in any patients during the trial period (14 days) and up to 28 days of follow up. There were no major differences in the evolution of vital signs, inflammatory markers (C-reactive protein, procalcitonin, and interleukin-6), and other laboratory parameters of patients in both the groups (Supplemental File).

Discussion

Effective vaccines and drugs for COVID-19 infection are still being researched extensively. Potential therapies, such as hydroxychloroquine [11] and tocilizumab [12] have been proved ineffective. Recently, the United States Food and Drug Administration (FDA) has issued an emergency use authorization for Merck & Co.'s molnupiravir for the treatment of mild-to-moderate COVID-19 in adults [13]. However, molnupiravir is not authorised for use in patients younger than 18 years of age, for the pre- or post-exposure prevention of COVID-19, and also for the treatment of hospitalized patients, due to its effect on bone and cartilage growth and the uncertainty of its efficacy when the treatment is initiated after hospitalisation.

Ivermectin possesses antiparasitic and antiviral activities. Its efficacy has been previously shown *in vitro* against various viruses including dengue, zika virus, west nile virus, Venezuelan equine encephalitis virus, influenza virus, and SARS-CoV-2 [14].

In the present study, a 5 day course of ivermectin did not improve clinical and microbiological outcomes of patients with mild or moderate COVID-19 infection. However, the patients receiving ivermectin generally recovered from certain symptoms earlier than the placebo group. Some of the previous studies have reported more rapid viral clearance with the use of ivermectin [5, 8, 15, 16]. However, other studies have not reported such a benefical outcome [17, 18]. There was, however, some variation in the regimes used by these studies. Although the effect on viral clearance is not confirmed, there were many studies that reported a significant reduction in the time to recovery in the ivermectin group as compared to the control group [19–21]. Even when used to treat severe COVID-19 patients, ivermectin can provide an increase in clinical recovery, improvement in prognostic laboratory parameters, and a decrease in mortality rates [22]. Moreover, vaccination did not affect viral clearance with the use of ivermectin in our study. This could be due to the incomplete vaccination status of the patients, i.e., a single dose received instead of the two-dose regime; therefore, the patients might not have had enough neutralizing capacity.

Based on the results of the current study, we found that shorter time to significant improvement in clinical symptoms was the main advantage of ivermectin.These significant effects of ivermectin were on symptoms such as runny nose, anosmia, fatique, and cough, which may indicate less progressive disease and rapid recovery. Ivermectin may help quicken the recovery by promoting faster viral clearance during disease onset, which might have prevented significant immune system involvement. In addition, early intervention rapidly reduced the viral load, thus preventing disease transmission in the general population. A larger randomized controlled clinical trial of ivermectin treatment is warranted to further validate these significant findings.

In the present study, we could not compare the length of hospital stay since the health policy in our country at the time of the study specified that every patient should be isolated for 14 days either in the hospital or at home. The effect of ivermectin on the length of hospital stay was therefore inconclusive. Bukhari et al. [23] randomized 86 patients with confirmed COVID-19 into standard of care (SOC) treatment and ivermectin (single dose of 12 mg) plus SOC treatment groups. They reported early viral

clearance in the ivermectin group as compared to the SOC group (p=0.001). No adverse reactions were noted in the intervention arm. Ravikerti et al. reported that patients who were administered 12 mg ivermectin for two days had no difference in the primary outcome, i.e., negative RT-PCR report on day 6 of admission. However, a significantly higher proportion of patients were alive and discharged from the hospital when they received ivermectin [24]. Viral clearance was earlier in the 5-day ivermectin treatment arm when compared to the placebo group (9.7 days vs 12.7 days, respectively, p=0.02) in the study by Ahmed [25]; however, the clearance of symptoms was not significantly different between the two groups. Chaccour et al. [20] also found a marked reduction of self-reported anosmia/hyposmia, a reduction of cough and a tendency to lower viral loads and lower IgG titers in a pilot, double-blind, placebo-controlled, single-center, parallel-arm, superiority, randomized clinical trial that compared a single dose of ivermectin with placebo in patients with non-severe COVID-19 without any risk factors. These results provide evidence of the potential benefits of early intervention with ivermectin for the treatment of mild-to-moderate COVID-19.

This study also has some limitations. First, the sample size was too small. This is due to the fact that the incidence of COVID-19 at the time of the study was rapidly decreasing in our country. We contained the pandemic quite well with low rates of new cases. Second, the duration of follow-up was short, i.e., up to 28 days only. A longer follow-up time might reveal long-term benefits of ivermectin. Third, we included patients mild-to-moderate COVID-19, wherein the disease might subside spontaneaously without any proven benefit of any medications. Finally, the ivermectin dosage has varied from study-to-study, and we still do not know the exact appropriate dose of ivermectin. Although in *in vitro* studies, the dose of ivermectin needed for inducing antiviral effects was higher than the approved usual dose in humans [20], high-dose antiviral therapy could lead to severe adverse effects [26]. Further investigations are needed to adjust the proper dose of the medication to be approved as a COVID-19-specific treatment.

In conclusion, ivermectin seems to control the course of the disease in patients with COVID-19. Adding ivermectin to those who are mild-to-moderately symptomatic may be beneficial to prevent disease progression and community spread. Therefore, given the urgent need to manage COVID-19 patients with a safe, financially feasible, and widely available drug, the present findings suggest that ivermectin can be considered as a first-line treatment for containing SARS-CoV-2 to prevent severe irreversible respiratory complications and community transmission. A multicenter, double-blind, drug-controlled study will strengthen our findings.

Methods

Study population

The study population included 72 COVID-19 patients, confirmed using a positive RT-PCR, with mild-to-moderate symptoms, within 72 hours of a positive result or onset of symptoms. This study was approved by the Vajira Institutional Review Board no. 171/64 and was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained

from all patients. More details of the trial can be found in the protocol (Supplement 1). The inclusion criteria were adult men and women aged 18–80 years, non-pregnant or breast-feeding women, and mild-to-moderate symptoms as defined by the World Health Organization (WHO) severity score for COVID-19 [27]. Mild disease was defined as cough, runny nose, anosmia, fever, and diarrhea without dyspnea or tachypnea. Moderate disease was defined as pneumonia with oxygen saturation >90%.

The patients were excluded if they were allergic to ivermectin; had the potential for a drug-drug interaction with ivermectin, such as tamoxifen or warfarin; were previously treated with ivermectin in the last 7 days; had received any herbal medicine; had severe chronic illness (severe congestive heart failure, chronic kidney disease stage 4–5, chronic liver disease, terminal cancer); had concurrent bacterial infection; or were unwilling to participate in the trial. Patients with severe symptoms, likely due to cytokine release syndrome, uncontrolled co-morbidities, and immunocompromised status were also excluded.

Study design

This study was a randomized, double-blind, placebo controlled trial, conducted at the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, from September 2021 to November 2021.

The patients were randomized in a permuted block of four in a randomized sequence prepared by a pharmacist, who was unblinded, in Microsoft excel [28]. Allocation assignment was concealed from the investigators and patients. The patients were allocated in one of the two groups: group A (Ivermectin arm) or group B (control arm), as shown in Figure 1. The patients were randomized in a 1:1 ratio. Group A received 12 mg per day of ivermectin for 5 days, as recommended by previous studies [23, 25], along with standard care. Group B received standard care alone, which included favipiravir or andrographolide, corticosteroids, cetrizine and paracetamol.

Intervention

The study coordinatior reviewed the patient's history to screen for eligibility.The potential study participants were contact by telephone to obtain informed consent. Eligible patients unerwent physical examination by the doctor in the ward. Baseline characteristics, such as age, sex, comorbidities, duration of symptoms, and disease severity on admission were recorded at the time of enrollment. All patients were confirmed as having COVID-19 using a baseline nasopharyngeal swab for RT-PCR. A follow up RT-PCR was performed on days 7 and 14 following drug intervention to estimate the change in viral load. Complete blood count, renal and liver function tests, C-reactive protein, D dimer, and chest radiography were performed at the day of enrollment and on day 14. Patients were contacted via telephone by the research team every day through day 14. On day 28, a telephonic interview was performed for the final questions pertaining general health, well-being, and the possible development of side effect after treatment with ivermectin.

Processing and analysis of respiratory samples

Nasopharyngeal swabs were collected from suspected COVID-19 cases by trained medical technologists. The swabs were stored in 2 mL of viral transport media (VTM) (Dewei Medical equipment Co., Ltd., China), transported at 4°C, and processed within 4 hours at the Biomolecular Unit, central laboratory of Vajira Hospital. Viral RNA extraction was performed on each VTM sample using the commercial kit (Zybio Nucleic acid extraction kit) on automated nucleic acid extraction system (Magnetic bead method) (Zybio Inc., China), according to the manufacturer's instructions. RT-PCR tests were run on a Slan 96P Real Time PCR System using a 2019-nCoV Nucleic Acid Diagnostic Kit (Sansure Biotech Inc.). The kit is designed to detect N and ORF1 ab genes of SARS-CoV-2, along with one housekeeping gene as the internal amplification control. A 40 µL reaction contained 26 µl of reaction buffer, 4 µl of 2019-nCoV-PCR-Enzyme Mix, and 10 µl of RNA. Thermal cycling was performed at 50°C for 30 min for reverse transcription and one cycle at 95°C for 1 min. Then 45 cycles at 95°C for 15 s and at 60°C for 31 s were performed and analyzed using ABI 7500 software. A positive RT-PCR result was defined when both target genes reach a cycle threshold (Ct) of <40.

Outcome Measurement

The primary outcome was to evaluate the efficacy of ivermectin in viral clearance of SARS-CoV-2 on day 7 and 14 after intervention, and compare that to placebo. The secondary outcomes were duration of hospitalization, frequency of clinical worsening, need for mechanical ventilation, all-cause mortality in both groups, survival on day 28, and adverse events in the study group.

Statistical analysis

All descriptive data were expressed as mean (standard deviation) and frequency (percentage). Comparisons between the treatment group were determined by the Student t-test for parametric continuous variables or the Mann–Whitney U for nonparametric continuous variables, as appropriate, and by the Pearson X^2 test for categorial variables. Comparisons between the mean duration of viral clearance and duration of hospitalization were evaluated by the independent t-test or Mann–Whitney U test, as appropriate. Univariate analysis of the primary mortality outcome and comparisons between the treatment groups were determined using Chi-squared test. The primary end point of time from randomization to day 28 with ivermectin versus placebo was assessed by a Kaplan–Meier plot and compared with a long rank test. The hazard ratio and 95% confidence interval for the cumulative incidence of clinical worsening in both the treatment groups were estimated using the Cox proportional hazards model. Statistical significance was set as $P<0.05$, and all testes were 2 tailed. Statistical analysis were performed using STATA version 18.1 (stata group).

References

1. COVID-19 dashboard. https//coronavirus.jhu.edu/map:html, (2021).

2. Omura, S. & Crump, A. Ivermectin: Panacea for resource-poor communities? *Trends Parasitol.* **30**, 445–455 (2014). 10.1016/j.pt.2014.07.005, Pubmed:25130507.

3. US Senate Committee on Homeland Security & Governmental Affairs. Early outpatient treatment: an essential part of a COVID-19 solution, part II. Accessed December 19, 2020. https://www.hsgac.senate.gov/early-outpatient-treatment-anessential-part-of-a-covid-19-solution-part-ii

4. Chen, I. S. & Kubo, Y. Ivermectin and its target molecules: Shared and unique modulation mechanisms of ion channels and receptors by ivermectin. *J. Physiol.* **596**, 1833–1845 (2018). 10.1113/JP275236, Pubmed:29063617.

5. Alam, M. T. *et al.* A case series of 100 COVID-19 positive patients treated with combination of ivermectin and doxycycline. *J. Bangladesh Coll. Phys..* **38**, 10–15 (2020). 10.3329/jbcps.v38i0.47512.

6. Bhattacharya, R., *et al.* Observational Study on Clinical Features, Treatment and Outcome of COVID 19 in a tertiary care Centre in India- a retrospective case series. *medRxiv* (2020.08.14). 10.1101/2020.08.12.20170282.

7. Hector, C., *et al.* Safety and Efficacy of the Combined Use of Ivermectin, Dexamethasone, Enoxaparin and Aspirin against COVID-19. *medRxiv* (2020.09.15). 10.1101/2020.09.10.20191619.

8. Khan, M. S. I., *et al.* Ivermectin treatment may improve the prognosis of patients with COVID-19. *Arch. Bronconeumol.* **56**, 828–830 (2020). 10.1016/j.arbres.2020.08.007

9. Rajter, J. C., *et al.* Use of ivermectin is associated With lower mortality in hospitalized patients With coronavirus disease 2019 - The ICON study. *Chest* (2020).

10. Chachar, A. Z. K. *et al.* Effectiveness of ivermectin in SARS-CoV-2/COVID-19 patients. *Int. J. Sci.* **9**, 31–35 (2020).

11. Galan, L. E. B. *et al.* Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection. *Pathog. Glob. Health* **115**, 235–242 (2021). 10.1080/20477724.2021.1890887, Pubmed:33682640.

12. Cortegiani, A. *et al.* Rationale and evidence on the use of tocilizumab in COVID-19: A systematic review. *Pulmonology* **27**, 52–66 (2021). 10.1016/j.pulmoe.2020.07.003, Pubmed:32713784.

13. US Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain.

14. Caly, L., Druce, J. D., Catton, M. G., Jans, D. A. & Wagstaff, K. M. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res.* 178, 104787 (2020). 10.1016/j.antiviral.2020.104787, Pubmed:32251768.

15. Espitia-Hernandez, M. L. *et al.* Effects of ivermectin-azithromycin-cholecalciferol combined therapy on COVID-19 infected patients: A proof of concept study. *Biomed. Res.* **31**, 129–133 (2020).

16. Mahmud, R. *et al.* Ivermectin in combination with doxycycline for treating COVID-19 symptoms: A randomized trial. *J. Int. Med. Res.* **49**, 3000605211013550 (2021). 10.1177/03000605211013550, PMID: 33983065, PMCID: PMC8127799.

17. Camprubí, D. *et al.* Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients. *PLOS ONE* **15**, e0242184 (2020). 10.1371/journal.pone.0242184. Pubmed:33175880.

18. Chowdhury, A. T. M. M., *et al.* A Randomized Trial of Ivermectin-Doxycycline and HydroxychloroquineAzithromycin Therapy on COVID19 Patients. 10.21203/rs.3 (DOI, Research Square).

19. Hashim, H. A. *et al.* Controlled randomized clinical trial on using ivermectin with doxycycline for treating COVID-19 patients in Baghdad, Iraq. *medRxiv* **2020**. 10.1101/2020.10.26.20219345 [Preprint 27 October 2020].

20. Chaccour, C. *et al.* The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial. *EClinicalmedicine* **32**, 100720 (2021). 10.1016/j.eclinm.2020.100720.

21. Shahbaznejad, L. *et al.* Effects of ivermectin in patients With COVID-19: A multicenter, double-blind, randomized, controlled clinical trial. *Clin. Ther.* **43**, 1007–1019 (2021). 10.1016/j.clinthera.2021.04.007, PMID: 34052007, PMCID: PMC8101859.

22. Okumuş, N. *et al.* Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients. *BMC Infect. Dis.* **21**, 411 (2021). 10.1186/s12879-021-06104-9, PMID: 33947344, PMCID: PMC8093585.

23. Bukhari, S. K. H. S., *et al.* Efficacy of ivermectin in COVID-19 patients with mild to moderate disease. *medRxiv* **2021**. 10.1101/2021.02.02.21250840 [Preprint 5 February 2021].

24. Ravikirti, R. R., *et al.* Ivermectin as a potential treatment for mild to moderate COVID-19–A double blind randomized placebo-controlled trial. *medRxiv* **2021**. 10.1101/2021.01.05.21249310 [Preprint 9 January 2021].

25. Ahmed, S. *et al.* A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int. J. Infect. Dis.* **103**, 214–216 (2021). 10.1016/j.ijid.2020.11.191, Pubmed:33278625.

26. Heidary, F. & Gharebaghi, R. Ivermectin: A systematic review from antiviral effects to COVID-19 complementary regimen. *J. Antibiot. (Tokyo)* **73**, 593–602 (2020). 10.1038/s41429-020-0336-z, Pubmed:32533071. 9. Caly, L., Druce, J. D., Catton, M. G., Jans, D. A. & Wagstaff, K. M. The FDA-approved

drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res.* **178**, 104787 (2020). 10.1016/j.antiviral.2020.104787, Pubmed:32251768.

27 Zu, Z. Y. *et al.* Coronavirus Disease 2019 (COVID- 19): A perspective from China. *Radiology* **296**, 15–25 (2020). 10.1148/radiol.2020200490.

28 Kim, J. & Shin, W. How to do random allocation (Randomization). *Clin. Orthop. Surg.* **6**, 103–109 (2014). 10.4055/cios.2014.6.1.103.

Declarations

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Author contributions: AM: Supervised the project, had full access to the data in the study, and contributed to the study design. KP: Contributed to data collection and conceived and designed the study. SS: Collected and interpreted the data. JM: Contributed in reviewing the design of the study and acquiring the data. WR: Coordinated sample collection and oversaw data collection. UP: Conducted and analysed the laboratory results. TT: designed the study, analyzed and interpreted the data, and contributed towards the writing of the manuscript. All authors approve the final version of the manuscript for submission.

Data availability: Upon publication, all data supporting the results will be archived in a public repository accessible at Mendeley Data, V1, doi: 10.17632/ppg255h3bj.1

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Conflict of Interest

The authors declare no conflict of interest.

Tables

Table 1. General characteristics of the patients

Variables	Total (n = 72)	Treatment (n = 36)	Control (n = 36)	p-value
Sex				
Male	27 (37.5)	14 (38.9)	13 (36.1)	0.808
Female	45 (62.5)	22 (61.1)	23 (63.9)	
Age (years), Mean ± SD	48.57 ± 14.80	49.42 ± 14.29	47.72 ± 15.45	0.631
<40 years	18 (25.0)	10 (27.8)	8 (22.2)	0.937
40-65 years	46 (63.9)	22 (61.1)	24 (66.7)	
>65 years	8 (11.1)	4 (11.1)	4 (11.1)	
Underlying diseases				
Diabetes	17 (23.6)	11 (30.6)	6 (16.7)	0.165
Hypertension	29 (40.3)	16 (44.4)	13 (36.1)	0.471
Dyslipidemia	25 (34.7)	16 (44.4)	9 (25.0)	0.083
Ischemic heart disease	2 (2.8)	1 (2.8)	1 (2.8)	1.000
Peripheral arterial disease	0 (0.0)	0 (0.0)	0 (0.0)	NA
Malignancy	0 (0.0)	0 (0.0)	0 (0.0)	NA
HIV	0 (0.0)	0 (0.0)	0 (0.0)	NA
Cerebrovascular disease	2 (2.8)	0 (0.0)	2 (5.6)	0.493
Alcoholism	0 (0.0)	0 (0.0)	0 (0.0)	NA
Chronic liver disease	0 (0.0)	0 (0.0)	0 (0.0)	NA
Chronic kidney diseasestage	5 (6.9)	2 (5.6)	3 (8.3)	1.000
Others	29 (40.3)	13 (36.1)	16 (44.4)	0.471
Known mode of transmission	26 (36.1)	15 (41.7)	11 (30.6)	0.326
COVID-19 Vaccine	48 (66.7)	23 (63.9)	25 (69.4)	0.617
1 dose	34 (47.2)	18 (50.0)	16 (44.4)	0.636
2 dose	13 (18.1)	5 (13.9)	8 (22.2)	
Booster dose	1 (1.4)	0 (0.0)	1 (2.8)	
AstraZeneca	41 (56.9)	20 (55.6)	21 (58.3)	0.812
Sinovac	3 (4.2)	2 (5.6)	1 (2.8)	1.000
Sinopharm	5 (6.9)	1 (2.8)	4 (11.1)	0.537
Time from last vaccine	57 (34 - 66)	59 (38 - 70)	44 (11 - 64)	0.104

Data are presented as number (%), mean ± standard deviation or median (interquartile range).

P-value corresponds to Independent samples t-test, Mann–Whitney U test, Chi-square test or Fisher’s exact test.

Table 2. Resolution of COVID-19 symptoms

Symptoms	Total (n = 72)		Treatment (n = 36)		Control (n = 36)		p-value[a]	Resolution of symptoms[b]		
								HR[c]	95%CI	p-value
All Symptoms	66	(91.7)	33	(91.7)	33	(91.7)	1.000	1.18	(0.67 to 2.08)	0.572
Duration (days), median (IQR)	8	(4.5 – 14)	8	(3.5 – 14)	8	(5 – 14)	0.525			
Cough	58	(80.6)	28	(77.8)	30	(83.3)	0.551	1.19	(0.71 to 1.99)	0.513
Duration (days), median (IQR)	6.5	(3 – 10)	5	(2.5 – 10)	8	(4 – 10)	0.269			
Runny nose	40	(55.6)	18	(50.0)	22	(61.1)	0.343	1.36	(0.84 to 2.21)	0.206
Duration (days), median (IQR)	2	(0 – 6)	0.5	(0 – 5)	2.5	(0 – 6.5)	0.270			
Sore throat	30	(41.7)	16	(44.4)	14	(38.9)	0.811	0.95	(0.59 to 1.51)	0.814
Duration (days), median (IQR)	0	(0 – 5)	0	(0 – 4.5)	0	(0 – 5.5)	0.801			
Smell disturbance	23	(31.9)	11	(30.6)	12	(33.3)	0.800	1.23	(0.76 to 1.99)	0.391
Duration (days), median (IQR)	0	(0 – 3)	0	(0 – 2.5)	0	(0 – 3)	0.609			
Taste disturbance	19	(26.4)	13	(36.1)	6	(16.7)	0.061	0.93	(0.58 to 1.49)	0.769
Duration (days), median (IQR)	0	(0 – 1)	0	(0 – 2)	0	(0 – 0)	0.125			
Muscle pain	21	(29.2)	13	(36.1)	8	(22.2)	0.195	0.82	(0.51 to 1.33)	0.415
Duration (days), median (IQR)	0	(0 – 1)	0	(0 – 2)	0	(0 – 0)	0.212			
Headache	20	(27.8)	8	(22.2)	12	(33.3)	0.293	1.25	(0.78 to 2.02)	0.354
Duration (days), median (IQR)	0	(0 – 2)	0	(0 – 0)	0	(0 – 2)	0.263			
Fever	34	(47.2)	18	(50.0)	16	(44.4)	0.637	0.90	(0.57 to 1.43)	0.650
Duration (days), median (IQR)	0	(0 – 1)	0.5	(0 – 2)	0	(0 – 1)	0.511			
Dyspnea	17	(23.6)	8	(22.2)	9	(25.0)	0.781	0.93	(0.58 to	0.747

									1.48)	
Duration (days), median (IQR)	0	(0 – 0)	0	(0 – 0)	0	(0 – 0.5)	0.886			
Runny nose	10	(13.9)	4	(11.1)	6	(16.7)	0.735	1.11	(0.69 to 1.78)	0.660
Duration (days), median (IQR)	0	(0 – 0)	0	(0 – 0)	0	(0 – 0)	0.494			
□□□□□□	13	(18.1)	7	(19.4)	6	(16.7)	0.759	1.03	(0.65 to 1.65)	0.888
Duration (days), median (IQR)	0	(0 – 0)	0	(0 – 0)	0	(0 – 0)	0.834			
Chest pain	2	(2.8)	0	(0.0)	2	(5.6)	0.493	1.06	(0.66 to 1.69)	0.811
Duration (days), median (IQR)	0	(0 – 0)	0	(0 – 0)	0	(0 – 0)	0.154			
Fatique	6	(8.3)	1	(2.8)	5	(13.9)	0.199	1.19	(0.73 to 1.92)	0.488
Duration (days), median (IQR)	0	(0 – 0)	0	(0 – 0)	0	(0 – 0)	0.080			
Sneezing	3	(4.2)	1	(2.8)	2	(5.6)	1.000	1.05	(0.66 to 1.67)	0.843
Duration (days), median (IQR)	0	(0 – 0)	0	(0 – 0)	0	(0 – 0)	0.547			
Vomitting	1	(1.4)	0	(0.0)	1	(2.8)	1.000	1.03	(0.65 to 1.63)	0.906
Duration (days), median (IQR)	0	(0 – 0)	0	(0 – 0)	0	(0 – 0)	0.317			

Data are presented as number (%) or median (interquartile range).

[a]P-value corresponds to Mann–Whitney U test, Chi-square test or Fisher’s exact test.

[b] Resolution of symptoms was defined as the first day free of symptoms.

[c] Hazard ratio for resolution of symptoms was estimated by the Cox proportional-hazard model.

Abbreviation: IQR, interquartile range.

Table 3. Evolution of symptoms from day 1 to day 14

Outcomes	Group	Day 1	Day 7	Day 14	p-value within groups[a]	p-value between groups[b]
Temperature (°C)	Treatment	36.54 ± 0.66	36.40 ± 0.35	36.54 ± 0.24	0.395	0.467
	Control	36.65 ± 0.49	36.50 ± 0.30	36.48 ± 0.21	0.139	
	p-value[c]	0.441	0.176	0.584		
Heart rate (bpm)	Treatment	90.86 ± 19.27	76.46 ± 14.82	76.43 ± 16.93	0.003	0.962
	Control	90.63 ± 15.53	75.36 ± 11.66	74.83 ± 10.84	<0.001	
	p-value[c]	0.956	0.730	0.804		
Systolic blood pressure (mmHg)	Treatment	135.97 ± 25.54	118.11 ± 15.58	123.86 ± 10.57	0.041	0.548
	Control	129.69 ± 15.12	122.19 ± 16.30	121.67 ± 10.04	0.017	
	p-value[c]	0.221	0.285	0.658		
Diastolic blood pressure (mmHg)	Treatment	79.49 ± 14.31	72.69 ± 10.32	76.29 ± 11.34	0.074	0.461
	Control	75.88 ± 12.77	70.50 ± 11.38	69.00 ± 8.29	0.095	
	p-value[c]	0.282	0.400	0.124		
Mean arterial pressure (mmHg)	Treatment	98.31 ± 16.83	87.83 ± 9.97	92.14 ± 9.64	0.025	0.459
	Control	93.81 ± 11.39	87.73 ± 11.77	86.56 ± 7.67	0.031	
	p-value[c]	0.201	0.970	0.181		
Respiratory rate (bpm)	Treatment	20.06 ± 0.58	19.94 ± 0.34	20.00 ± 0.00	0.376	0.291
	Control	19.94 ± 0.59	19.89 ± 0.67	19.67 ± 0.78	0.475	
	p-value[c]	0.421	0.670	0.166		
Oxygen saturation (%)	Treatment	97.72 ± 1.23	97.67 ± 1.45	97.75 ± 1.59	0.165	0.629
	Control	97.58 ± 1.46	97.75 ± 1.52	97.81 ± 1.21	0.394	
	p-value[c]	0.664	0.813	0.393		

a) p-value from analysis of variance repeated on time;
b) p-value from repeated measure one way analysis of variance;
c) p-value from independent sample t-test;

Figures

Figure 1

Study Protocol and Randomization

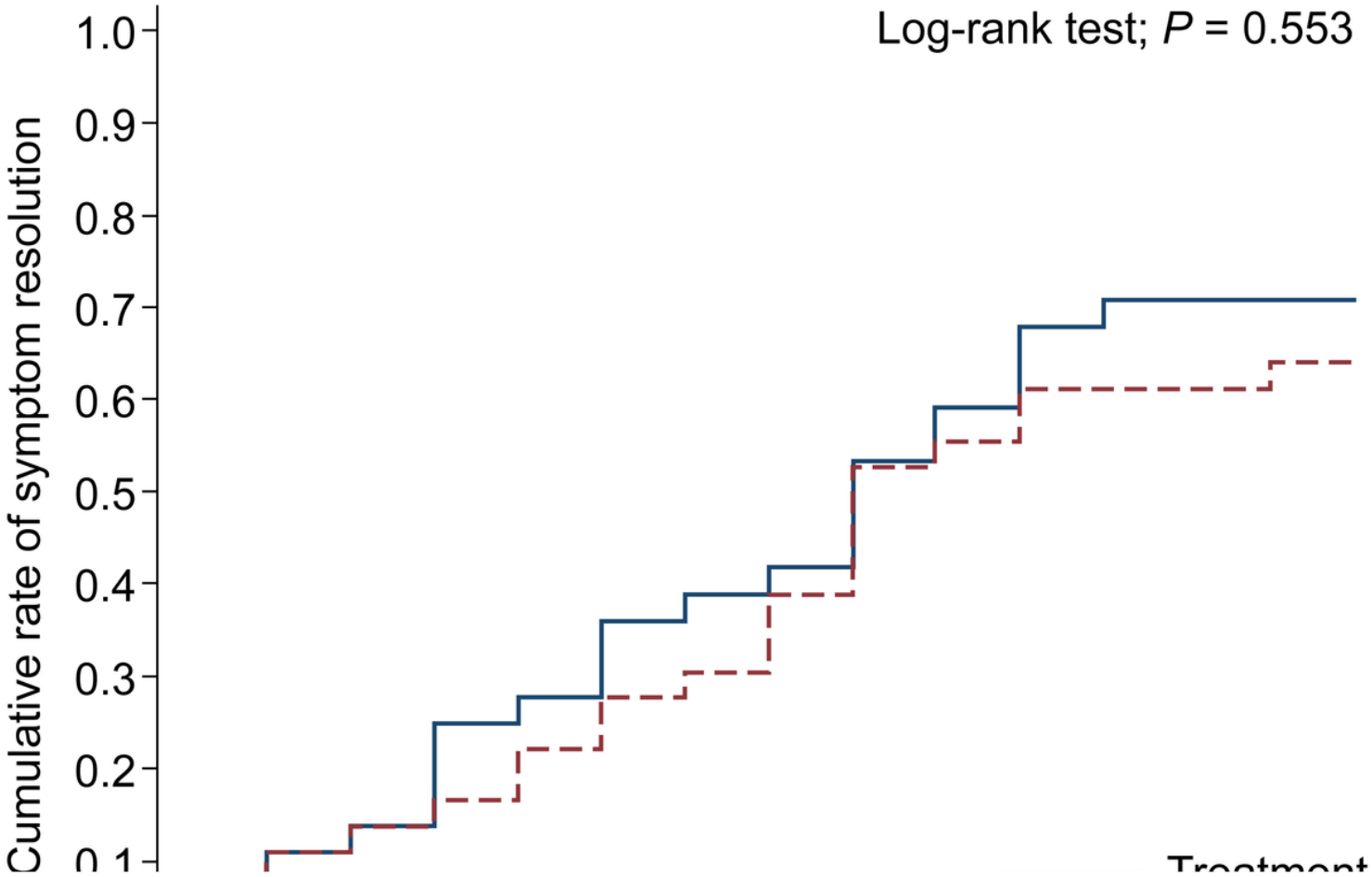

Figure 2

Kaplan Meier survival analysis curve for time to resolution of symptoms in Ivermectin group (n=32) versus controls (n= 32) (p =0.553)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalFileIvermectinFinal.docx