Ivermectin for the prevention of COVID-19: addressing potential bias and medical fraud

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Short Report

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Abstract

Background

Ivermectin is an antiparasitic drug being investigated in clinical trials for the prevention of COVID-19. However, there are concerns about the quality of some of these trials.

Objectives

To conduct a meta-analysis with randomised controlled trials of ivermectin for the prevention of COVID-19, while controlling for the quality of data.

Methods

We conducted a sub-group analysis based on the quality of randomised controlled trials evaluating ivermectin for the prevention of COVID-19. Quality was assessed using the Cochrane Risk of Bias measures (RoB 2) and additional checks on raw data, where possible.

Results

Four studies were included in the meta-analysis. One was rated as being potentially fraudulent, two as having a high risk of bias and one as having some concerns for bias. Ivermectin did not have a significant effect on preventing RT-PCR confirmed COVID-19 infection. Ivermectin had a significant effect on preventing symptomatic COVID-19 infection in one trial with some concerns of bias, but this result was based on post-hoc analysis of a multi-arm study.

Conclusions

This meta-analysis demonstrates that the currently available randomised trials evaluating ivermectin for the prevention of COVID-19 are insufficient and of poor quality.

Introduction

COVID-19 was declared a pandemic by the World Health Organisation (WHO) in March 2020¹. In the early stages of the pandemic, there were multiple uncertainties regarding the timeline of vaccine development and production². Therefore, investigational drugs were being assessed for the prevention of COVID-19. For example, the REGEN-COV monoclonal antibody therapy, which was granted Emergency Use Authorization as a post-exposure prophylaxis by the U.S Food and Drug Administration (FDA) in October 2021³.

Although vaccines have been approved for use since January 2021, several challenges face worldwide uptake⁴. Additionally, individuals who are immunocompromised are contraindicated for the COVID-19 vaccine⁵. Furthermore, transmission of SARS-CoV-2 can continue to occur despite an individual being vaccinated⁶. This suggests that a drug could play an additional role in the prevention of COVID-19.

Clinical trials are being conducted globally to evaluate the efficacy and safety of drugs to prevent COVID-19 infection. For example, Molnupiravir is currently being evaluated in the MOVe-AHEAD trial⁷. However, there are concerns regarding the quality of some of these trials evaluating drugs for COVID-19. For example, an observational study on hydroxychloroquine for COVID-19, published in the Lancet, was retracted due to concerns about the validity of the data⁸. The company providing the data for this study, Surgisphere, claimed to have access to patient data. However, on further investigation major inconsistencies were identified in the data, suggesting it was fabricated⁸.

Ivermectin is an FDA approved anti-parasitic drug which was shown to have anti-viral effects against SARS-CoV-2 in-vitro⁹. Following this, ivermectin has been evaluated for re-purposing against SARS-CoV-2 in clinical trials globally. An analysis suggested that the significant effect of ivermectin on the treatment of COVID-19 was based on high risk and potentially fraudulent studies¹⁰. Therefore, the purpose of this review is to analyse randomised controlled trials of ivermectin for the prevention of COVID-19, while controlling for the quality of data.

Methods

The systematic review and meta-analysis were conducted according to PRISMA guidelines. A systematic search was conducted on eight electronic databases to identify randomized control trials (RCTs) evaluating ivermectin for the prevention of SARS-CoV-2 infection. In addition to the standard Cochrane risk of bias tool (RoB 2), a detailed assessment of study quality was performed¹¹. Firstly, we evaluated trials based on the effectiveness of their randomisation process by comparing baseline characteristics across treatment arms using the chi-square test. Secondly, randomisation dates were checked to ensure patients were randomised into the treatment arms on similar dates. Thirdly, checks were conducted to evaluate if recruitment to treatment arms was balanced at each investigational centre. Furthermore, we analysed patient-level databases, where available, to check for any evidence of duplicate participants, unexpected homogeneity or heterogeneity. From this, a meta-analysis was conducted with sub-groups of clinical trials at different risk of bias levels. The primary outcome was RT-PCR confirmed COVID-19 infection. The secondary outcome was rate of symptomatic COVID-19 infection.

Quality assessment

Four studies met the criteria and were included in the meta-analysis (Table 1). Two studies were conducted in Egypt^{12,13}, one in Argentina¹⁴ and one in Singapore¹⁵. The studies included a range of participants, for example - high risk migrant workers living in dormitories, healthcare personnel and close

contacts. The duration of treatment with ivermectin ranged between one day to once per week for four weeks across the studies. The meta-analysis includes a total of 1974 participants.

The study by Elgazzar et al (Egypt), was identified to be potentially fraudulent¹². On 15th July 2021, their study was retracted from pre-print server Research Square due to “ethical concerns”. It has been reported that the data for approximately 79 participants were duplicates, some deaths were recorded on dates before the trial had started and instances of plagiarism were also identified in the text.

The trial conducted by Shoumann et al (Egypt) was rated as having a high risk of bias¹³. On detailed evaluation, several methodological flaws were identified in this study. Firstly, the control arm was terminated half-way through the trial but the treatment arm was continued. This may have caused non-concurrent randomisation of participants and led to a significant difference in the size of the intervention arms. This change in methodology was not reported in the trial registry. Secondly, RT-PCR tests were only performed for 12% of participants in the control arm and 2% of participants in the treatment arm, due to challenges with obtaining the required number of RT-PCR tests. For the other participants, COVID-19 was detected by checking for symptoms or using clinical tests, which are not as precise as RT-PCR tests. These variations may have resulted in significant differences between the intervention arms.

The trial conducted by Chahla et al (Argentina), was rated as having a high risk of bias¹⁴. Following a comprehensive assessment some discrepancies were identified in the reported results. Some values stated in the tables differed from what was in the text of the paper. Additionally, they evaluated both healthcare and non-healthcare workers and there was a significant difference in the allocation of these participants to the two intervention arms. These variations may have resulted in significant differences between both arms.

The trial conducted by Seet et al (Singapore), was rated as having some concerns of bias¹⁵. This was a complex study which involved five treatment arms. Participants in this trial were randomised using a cluster randomisation method. However, results were not reported based on these clusters. According to the results presented in Table 1, hydroxychloroquine, Zinc and Vitamin C, Povidone-iodine and Vitamin C were more effective than ivermectin at preventing RT-PCR confirmed COVID-19 infection. However, it was observed that ivermectin was more effective than hydroxychloroquine, Zinc and Vitamin C, Povidone-iodine and Vitamin C at preventing symptomatic COVID-19 infection. Therefore, their results for ivermectin in the prevention of COVID-19 were inconsistent.

Meta-analysis results

In the meta-analysis for prevention of RT-PCR confirmed COVID-19 infection, three studies were included (Figure 1, Table 1). On including all three studies, ivermectin did not have a significant effect on preventing confirmed infections ($p=0.17$). When the potentially fraudulent Elgazzar et al study was excluded, ivermectin did not have a significant effect on preventing confirmed infections ($p=0.39$). On

excluding the high-risk Chahla et al study, ivermectin failed to prevent confirmed infection in comparison to control ($p=0.67$).

In the meta-analysis for prevention of symptomatic COVID-19 infection, two studies were included (Table 1). On including both studies, ivermectin did not have a significant effect on preventing symptomatic infections ($p=0.07$). On excluding the high-risk Shoumann et al study, there was one study remaining. This study, by Seet et al, had multiple arms and varying endpoints. Based on this study, ivermectin had a significant effect on preventing symptomatic infections ($p=0.003$).

Discussion

This analysis demonstrates there is no evidence from high quality trials on the prevention of PCR-confirmed COVID-19 infection. Ivermectin only had a significant effect on the prevention of symptomatic COVID-19 infection, which was based on a single study with multiple arms and inconsistent results across endpoints. Overall, three out of the four randomised trials evaluating ivermectin for the prevention of COVID-19 are at a high risk of bias or potentially fraudulent.

Non-randomised trials have also been conducted to assess the effect of ivermectin on the prevention of COVID-19. However, there are concerns about the quality of some of these studies as well. For example, an observational study by Carvalho et al which suggested a 100% benefit for ivermectin in the prevention of COVID-19, has been suggested to be unreliable¹⁶. Firstly, several discrepancies were identified between the registry, graphs and text in the paper for this trial. Additionally, a hospital described as being a site for this study has denied any participation. Furthermore, the raw data for this study was revealed to have duplicates for several participants and was inconsistent with results provided in the paper.

Lastly, there are real-life epidemiological surveys, where infection rates were analysed in countries including Peru and Brazil which recommended ivermectin for use as a prophylaxis¹⁷. However, there are several confounding factors which make it challenging to assign cause and effect from such epidemiological surveys. For example, any reduction in COVID-19 infection rate following the recommendation of ivermectin could also be due to herd immunity, lockdown or vaccinations. We cannot use these examples as definite evidence for the efficacy of ivermectin as a preventive measure.

This suggests that the available evidence is insufficient to make a recommendation about ivermectin for the prevention of COVID-19. In order for COVID-19 vaccines to receive regulatory approval, there had to be evidence from large high-quality randomised trials which were independently audited by regulatory authorities. At this moment, we do not have such evidence for ivermectin in the prevention of COVID-19. Currently, there are multiple trials in progress, but we are not aware of any encouraging results so far.

Declarations

Funding: The Rainwater Charitable Foundation

Potential Conflicts of Interest: None of the authors has declared a conflict of interest

Patient Consent Statement: All the clinical trials included in the meta-analysis were approved by local ethics committees and all patients gave informed consent.

Transparency declarations: None to declare

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Table

Table 1: Studies included in the meta-analysis

Study	Risk of bias	Treatment arm	RT-PCR confirmed infection	Symptomatic infection
Elgazzar ¹² (Egypt)	Potential fraud	Ivermectin	2/100 (2%)	-
		Control	10/100 (10%)	-
Shoumann ¹³ (Egypt)	High risk	Ivermectin	-	15/203 (7.4%)
		Control	-	59/101 (58.4%)
Chahla ¹⁴ (Argentina)	High risk	Ivermectin	4/117 (3.4%)	-
		Control	25/117 (21.4%)	-
Seet ¹⁵ (Singapore)	Some concerns	Ivermectin	90/617 (14.6%)	32/398 (8%)
		Hydroxychloroquine	32/432 (7.4%)	29/212 (13.7%)
		Povidone-iodine	50/735 (6.8%)	42/338 (12.4%)
		Zinc & Vitamin C	50/634 (7.9%)	33/300 (11%)
		Vitamin C	85/619 (13.7%)	64/433 (14.8%)

Figures

Figure 1