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Use of Ivermectin and Outcomes from Covid-19: A Meta-Analysis of Randomized Clinical Trials on Severity and Mortality

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Abstract

Use of antiviral drug ivermectin in Covid-19 pneumonia. The study aims to analyze the efficacy of Ivermectin in improving the COVID-19 outcomes. We systematically searched the PubMed, Google Scholar, and Research Gate and Clinical Trials-based databases using keywords related to our aim until December 2021 from the start of the COID-19 Pandemic. All published randomized clinical studies both double-blind and open-labeled studies on COVID -19 and the use of ivermectin were retrieved. A total no of 10 Articles 6 double-blind and 4 were open-label randomized clinical trials found eligible for analysis. Among the 10 articles total no of 1878 patients were recruited for the study, in which intervention of ivermectin was given to 850 (45.26%) patients and 788 (41.95%) patients were given either placebo or standard treatment protocol as per the WHO norms served as a control in these studies. 1638 patients in eight studies reported on the severe COVID -19 outcome. Our meta-analysis showed that Ivermectin administration was associated with a

reduction in severe COVID-19 outcome which was statistically significant (Relative Risk 0.37, 95% CI 0.273 to 0.515, the z value of 6.05 with p<0.001 in fixed-effects modeling). Test for heterogeneity showed I Square value of 65.27%, 95% CI for I2-26.07 to 83.68 with P = 0.005. Egger's test was applied to find out the publication bias showed the P = 0.64. 1726 patients in eight studies reported on the mortality outcome. Our meta-analysis showed that ivermectin administration was associated with a reduction in mortality (n=894, Mortality 2.23% in ivermectin used group and 7.69% in Control group n=832) outcome was statistically significant (Relative Risk 0.27, 95% CI 0.174 to 0.447, the z value of 5.3, with p<0.0001 in fixed-effect modeling). Test for heterogeneity showed I Square value of 39.60%, 95% CI for I Square - 0.00 to 73.33 with P = 0.11. Egger's test was applied to find out the publication bias showed the P = 0.25. We conclude that the use of Ivermectin to COVID-19 diseased patients may decrease the severity and mortality.

Keywords

COVID-19, Ivermectin, Mortality, Relative Risk, Severity

Introduction

Newly emerged Coronavirus (COVID-19) disease emerged as pandemic since 2019 infecting 29,77,63,274 with mortality of 54,65,315million till date [1]. COVID-19 has various clinical manifestations ranging from mild respiratory distress, fever, cough, anosmia to shock [2]. To reduce the severity and mortality rate of COIVD-19 many therapeutic agents were evaluated in clinical trials and suggested for therapy such as remdesivir, dexamethasone, tocilizumab [3,4]. Ivermectin is a drug that is used to manage parasitic infection with broad-spectrum effectively and has been approved by The United States Food and Drug Administration (FDA). It has been known for the treatment of lymphatic filariasis, onchocerciasis, and scabies beside its anti-parasitic effects it showed potential effects on viral diseases. Ivermectin has also been suggested to offer benefits in improving the outcomes from COVID-19 because of its anti-viral effect. The current metanalysis aims to understand the effectiveness of ivermectin on COVID-19 patient's outcomes on severity and mortality.

Materials and methods

Eligibility Criteria

The protocol was approved by the institutional ethical committee. Research on randomized, both double-blind and open-labeled randomized trials was considered for metanalysis, where ivermectin was used as an intervention for COVID-19 Patients. Included articles were following PICO framework (P- population – COVID 19 patients, I-intervention- Ivermectin medication, C-Comparison -control group, O- outcome-severe COVID-19). In the articles where ivermectin is not used as a therapeutic agent, non-randomized clinical trials were excluded from the studies.

Search Strategy and Study Selection

Data were searched systematically by using keywords COVID-19, Ivermectin intervention in COVID-19, RT PCR test positive, and randomized clinical trials using Ivermectin on research portals of PubMed, Research Gate, Google Scholar, and Clinical Trial Govt Registry Database. Randomized clinical trials, double-blind and open-labeled randomized trials with the full-text paper published studies were considered for final inclusion of article into meta-analysis. Case series and case reports were not considered for the study (Figure 1).

Data Extraction and Quality Assessment

Authors extracted the data with extraction from developed to list the essential information about the study and its population characteristics, ivermectin dose and its time-to-time administration, control group medications and no of patients receiving the medication, and each outcome of COVID-19 patient's proportion (Table 1). This study's outcome of interest was the severity of illness and mortality on intervention with ivermectin.

Figure 1: PRISMA chart of selection studies.

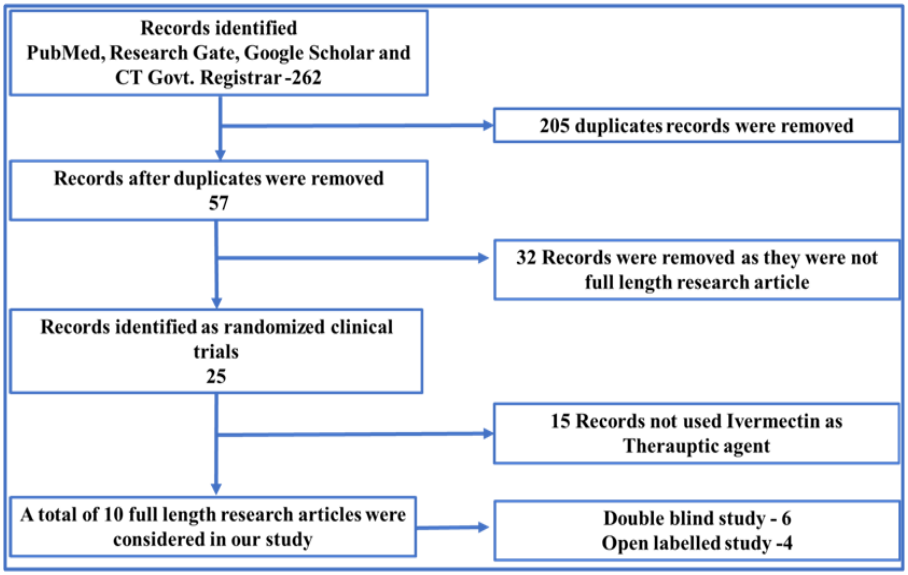


Table 1: Characteristic of included studies

Study Name	Sample Size	Study Design (Randomized clinical trails	Intervention	Control
Mohan A et al, 2021	125	Double-blind	Ivermectin	Placebo tablets
Lopez-Medina et al, 2021	398	Double-blind	Ivermectin	Dextrose 5%
Ravikriti et al, 2021	112	Double-blind	Ivermectin	Placebo tablets
Shahabaznejad et al, 2021	69	Double-blind	Ivermectin	Other drugs of COIVD -19 protocol
Niaee MS et al, 2020	180	Double-blind	Ivermectin	Standard symptomatic treatment
Mahumad R et al, 2020	363	Double-blind	Ivermectin	Placebo tablets
Pott-Junior et al, 2021	31	Open-label	Ivermectin	Drugs of COIVD -19 protocol
Elgazzar A et al, 2020	400	Open-label	Ivermectin	Hydroxychloroquine
Hashim HA et al, 2020	140	Open-label	Ivermectin	Standard symptomatic treatment
Okumus N et al, 2021	60	Open-label	Ivermectin	Standard symptomatic treatment

Statistical Analysis

Meta-analysis was performed by using MedCalc Version (20.2). Mantel-Haenzel's formula was done to obtain risk ratio (RR) and its 95% confidence interval (CI), heterogeneity was assessed by using the I^2 statistics. The results were considered significant when the $p<0.05$.Egger's test was done to rule out the publication bias.

Results

262 studies were found in the electronic database a total no of 10 Articles 6 double-blind and 4 were open-label randomized clinical trials found eligible for analysis. Among the 10 articles total no of 1878 patients were recruited for the study, in which intervention of ivermectin was given to 850 (45.26%) patients and 788 (41.95%) patients were given either placebo or standard treatment protocol as per the WHO norms served as a control in the studies.

Ivermectin and Its Outcome on the Severity

1638 patients in eight studies reported on the severe COVID-19 outcome. Our meta-analysis showed that Ivermectin administration was associated with a reduction in severe COVID-19 outcome which was statistically significant (Relative Risk 0.37, 95%CI 0.273 to 0.515, the z value of 6.05 with $p<0.001$ in fixed-effects modeling). Test for heterogeneity showed I^2 value of 65.27%, 95% CI for I^2-26.07 to 83.68 with P = 0.005. Egger's test was applied to find out the publication bias showed the P = 0.64. (Figure 2)

Ivermectin and Its Outcome on Mortality

1726 patients in eight studies reported on the mortality outcome. Our meta-analysis showed that ivermectin administration was associated with a reduction in mortality (n=894, Mortality 2.23% in ivermectin used group and 7.69% in control group n=832) outcome was statistically significant (Relative Risk 0.27, 95% CI 0.174 to 0.447, the z value of 5.3, with $p<0.0001$ in fixed-effect modeling). Test for heterogeneity showed I^2 value of 39.60%, 95% CI for I^2-0.00 to 73.33with P = 0.11. Egger's test was applied to find out the publication bias showed the P = 0.25. (Figure 3)

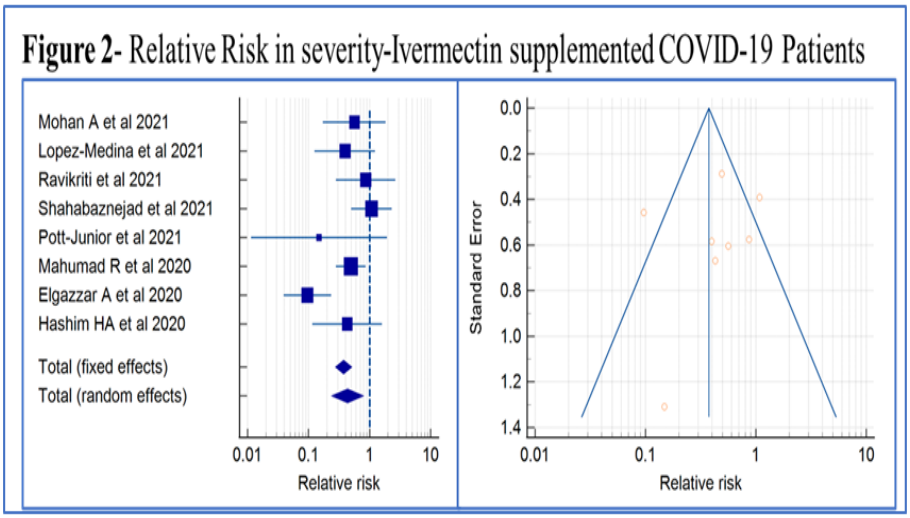
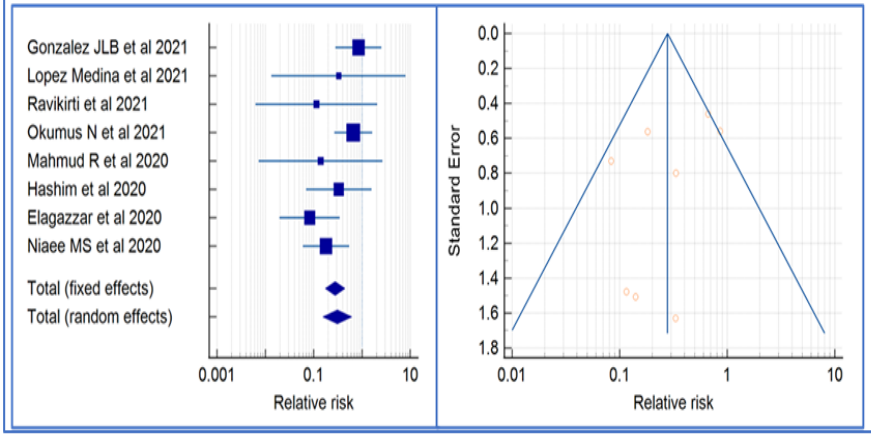


Figure 2- Relative Risk in severity-Ivermectin supplemented COVID-19 Patients

Figure 3- Relative Risk in mortality - Ivermectin supplemented COVID-19 Patients



Discussion

According to our meta-analysis ivermectin showed an association with a higher benefit in reducing the severity and mortality outcomes from COVID-19. Few researchers might have explained these findings. The sequestration of the COVID-19 viral nucleocapsid protein (NCP) into the host nucleus through the nuclear pore complex is avital step in viral pathogenesis and defence against host immune response. Ivermectin can selectively inhibit the host importin α/β transporter protein which can decrease translocation of SARS-COV-2 NCP from the cytoplasm to the nucleus, alteration of NCP distribution will lead to viral propagation disruption and survival [5]. The in-vitro study by Caly et al, [6] has proved that giving ivermectin in one dose was able to reduce the viral RNA load by 99.9% at 48H and replication of an Australian isolate of SARS COV-2 in Vero/hSLAM cells by 500 folds. Therefore it has a potent effect in altering disease progression and spread. These in-vitro findings were further supported with the results from a randomised double-blind, placebo-control trial study, showing that patients who received ivermectin 400μg/kg as a single dose have a lower median viral load on 4th day and 7th day of the treatment [8]. The differences were found, rising from a threefold decrease on the fourth day to about an 18-fold decrease on the 7th day when compared to placebo 49 [9]. Second, the pathology which underlies severe COVID-19 involves hyper inflammatory response as an accumulation of cytokines, called cytokine strome [10]. Meta-analysis studies have demonstrated that severe COVID-19 patients tend to produce higher levels of interleukin-6 (IL-6) and tumor necrosis factor (TNFα) in comparison to non-severe cases 60 [11-17]. On the other hand, both in-vivo and in-vitro studies demonstrated the anti-inflammatory effect of ivermectin [18]. Authors demonstrated that ivermectin can reduce the IL-6 and TNF α production and suppress lipopolysaccharide-induced nuclear factor-kappa B translocation [19]. The suppression of mucus dueto hyper secretion in the respiratory tract, the reduction on immune cell recruitment, and a decrease in the production of cytokines and immunoglobin E and G_1 in broncho alveolar lavage of experimental mice, were found as a consequence of 2 mg/kg of ivermectin administration [20]. These studies suggest that ivermectin has a

potential anti-inflammatory effect on the lung tissue and anti-viral effect, which might help to reduce the severity and mortality in COVID -19 patients and which were on par with our findings of meta analysis.

Conclusion

Our meta-analysis of randomized clinical studies indicates that ivermectin administration has an association with favorable outcomes of COVID -19, compromising a higher rate of severity and mortality. This study suggests that ivermectin may be a potential therapeutic agent for the management of COVID -19 to give better outcomes on severity and mortality. However, more randomized clinical trial studies are still necessary and encouraged to be done for confirming the results. Finally, ivermectin may be considered an essential drug for future CVOID -19 therapy models.

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