Effectiveness of Ivermectin/Doxycycline combination in COVID-19: a systematic review and meta-analysis

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Abstract

Background

This systematic review and meta-analysis aimed to assess the efficacy of the Ivermectin/Doxycycline combination for the treatment of coronavirus disease 2019 (COVID-19).

Methods

We searched PubMed, Web of Science, Scopus, ClinicalTrials.gov, and Google Scholar from database inception to August 26, 2021 for relevant studies. We included studies reporting at least one of the outcomes of interest: all-cause mortality; time to clinical recovery; hospital stay and viral clearance. The logarithm of risk ratios or mean differences and their corresponding standard errors for each outcome were pooled using a random-effects model. The risk of bias was assessed using the Cochrane Collaboration's tool for randomized clinical trials and the Newcastle-Ottawa Scale for cohort studies.

Results

Four randomized clinical trials and one prospective study involving 789 patients, including 399 in the Ivermectin/Doxycycline group and 390 in the control group, were enrolled. The all-cause mortality rate of patients with COVID-19 in the Ivermectin/Doxycycline group was 0.79% (2/253), which was lower than in the control group (3.6%; 9/250). However, the difference was not statistically significant (Log risk ratio=-1.288; 95% CI:-2.671, 0.096; $P = 0.068$; $I^2 = 0\%$). The effect of Ivermectin/Doxycycline on time to clinical recovery was found to be significant (Difference in means =-2.427 days; 95% CI:-4.033, -0.820; $P = 0.003$, $I^2 = 91.475\%$). There is no significant effect of Ivermectin/Doxycycline on hospital stay (Difference in means =-0.379 days; 95% CI:-1.965, 1.208; $P = 0.640$, $I^2 = 91.95\%$) and time to negative PCR or viral clearance (Difference in means =-0.768 days; 95% CI:-1.550, 0.013; $P = 0.054$, $I^2 = 91.48\%$).

Discussion

Based on low-quality evidence, this meta-analysis showed that Ivermectin/Doxycycline combination is accompanied with shorter time of clinical recovery in COVID-19 patients. However, it did not reduce all-cause mortality, viral clearance, and hospital stay significantly. Not only the number of the studies are limited but also they ranked methodologically medium to low with limited participants. To assess the exact effective dose and efficacy of this combination therapy, high-quality and large-scale randomized clinical trials are needed.

Other

This study was registered in Prospero (registration number: CRD42021272400). The authors declare they have no competing financial interests.

Introduction

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing Coronavirus disease 2019 (COVID-19) has become a global health issue (1). About 19% of involved patients undergo progressive worsening lead to pneumonia and its complications; however, most of the involved cases recover after a period of illness (2, 3).

Previous studies demonstrated that the disease course has 2 main phases: the first virus replication; and the following host inflammatory response phase. However, in some cases, a third late phase called the hyperinflammatory phase is

also possible (4). Since the beginning of the pandemic, therapeutic options like Azithromycin (5), Doxycycline(6, 7), Ivermectin(8, 9), Chloroquine and Hydroxychloroquine (10–12), Remdesivir (13–15), Lopinavir-Ritonavir (16, 17), Corticosteroids (18, 19), etc. targeted these two clinical phases. Despite using various drug protocols in different countries, no single therapeutic regimen has been approved yet.

Ivermectin is an antiparasitic drug that has been proposed as a COVID-19 therapeutic agent due to its antiviral effects (20, 21). In-vitro studies have demonstrated that Ivermectin can dramatically decrease viral replication (9, 22). However, clinical trials studying the clinical outcome of Ivermectin showed controversial findings (23–26). Recent efforts have revealed that a combination of Ivermectin, with broad-spectrum antiviral effects, and Doxycycline, a Tetracycline antibiotic with anti-inflammatory properties, may be beneficial and promising. Some clinical trial studies assessed the efficacy of the combination of Ivermectin/Doxycycline (IVE/DOXY) in COVID-19 treatment (27–29). Because of the scarcity of randomized controlled trials (RCTs) and inconclusive observational studies, reliable data to further shed light on the benefits and harms is needed. To the best of our knowledge, no meta-analysis has been conducted to summarize the findings of these studies and prepare a better insight. Therefore, we aim to review systematically the previous studies and perform a meta-analysis to measure the effectiveness of the combination of IVE/DOXY in COVID-19 treatment.

Material And Method

3.1. Search strategy

A systematic search of the published or unpublished studies earlier than August 26, 2021 was conducted using keywords (“COVID-19” OR “SARS-CoV-2” OR “Coronavirus” “2019 nCoV” OR “SARS CoV 2 “ OR “Severe Acute Respiratory Syndrome Coronavirus 2”)AND (“Ivermectin” OR “Doxycycline” OR “Stromectol” OR “Mectizan” OR “Eqvalan” OR “Ivomec” OR “Vibramycin” OR “Atridox” OR “Doryx” OR “Hydramycin” OR “Oracea” OR “Periostat” OR “Vibravenos”) in PubMed, Web of Science, Scopus, ClinicalTrials.gov, and Google Scholar databases by 2 independent investigators (M.O. and A.A.) to identify related articles. All keywords were selected from the Medical Subject Headings (MeSH) database. No language and time restrictions were imposed. After removing duplicates, a manual search was also performed to identify probable lost articles in electronic searches.

This study was registered on www.crd.york.ac.uk/Prospero (registration number: CRD42021272400) (30) and was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (31).

3.2. Inclusion criteria:

Studies comparing the clinical efficacy of the IVE/DOXY combination and its comparators for the treatment of COVID-19 and explicitly reporting at least one of the outcomes of interest, namely all-cause mortality, time to clinical recovery, hospital stay, and viral clearance (time to negative PCR), were included in our study. Considering a specific control arm by the articles was not a necessity to include.

3.3. Exclusion criteria

The exclusion criteria were as follows: I) case reports; II) single-arm studies; III) studies that did not report outcomes for IVE/DOXY in COVID-19; IV) in-vitro studies; V) review articles.

3.4. Data extraction

Studies were screened by 2 independent reviewers (M.O. and A.A.), examining titles and abstracts against predefined eligibility criteria. After selecting the group of potentially inclusive studies for analysis, their full texts were examined to apply the eligibility criteria. Any discrepancies were resolved by discussion between the two reviewers, or with a third

person (A.S.-A.) if consensus could not be reached. Studies that have eligibility criteria were taken for data extraction. The following information was extracted by 2 independent reviewers (M.O. and A.A.): author, year of publication, study design, country, patients' characteristics, the regimen of IVE/DOXY and comparative agent, the primary outcome (all-cause mortality), secondary outcome (time to clinical recovery, hospital stay, and viral clearance or time to negative PCR). If studies did not report the standard deviation (SD) changes from baseline, we calculated standard error (SE) and then converted them into SDs according to the formula provided in the Cochrane Handbook of Systematic Reviews (32).

The assessment of the risk of bias in individual studies

The risk of bias of all included studies was assessed by 2 reviewers (M.O. and A.A.) using the Cochrane Collaboration's tool for randomized clinical trials and the Newcastle-Ottawa Scale (NOS) for cohort studies (32–34). The Cochrane Collaboration's tool was assessed based on the following sources of bias: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants or personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective outcome reporting, and 6) other biases. Studies were categorized as low, high, or unclear risk for each source of biases. Studies that had a low risk of bias for all domains were regarded as good quality; studies had fair quality if one criterion was high risk or 2 criteria were unclear, and if 2 or more of the items were high risk or unclear risk of bias, the studies were listed as poor quality.

3.5. Statistical analysis

Comprehensive Meta-Analysis (CMA) software version 2 was used for the meta-analysis. The random-effects model, which considers the between-study variations, was used to derive the summary estimates. For continuous outcomes (time to clinical recovery, hospital stay, and time to negative PCR), we calculated mean differences and their corresponding SEs to be used as effect size for meta-analysis. For dichotomous outcomes (all-cause mortality), we calculated the logarithm of risk ratios and their corresponding SEs. Statistical heterogeneity among included studies was assessed using the I-squared (I^2) statistic. Heterogeneity was considered significant if the I^2 statistic was more than 25%. Sensitivity analysis was done to explore the extent to which inferences might depend on a particular study. P values of less than 0.05 were considered statistically significant.

Result

4.1. Search

The primary search was conducted up to August 26, 2021. Figure 1 shows the flow diagram of the included studies in detail. The search strategy initially yielded 1614 studies; after excluding 619 duplicate articles, 995 articles were screened. After examining titles and abstracts, 26 articles were identified for full-text review for eligibility. Twenty-one articles were excluded after full-text review according to the exclusion criteria. One study was excluded because of the outcome, not of interest; it reported the number of patients who got negative PCR on days 5, 6 in the IVE/DOXY group and on days 11, 12 in the control group (35). Finally, 4 randomized clinical trials (27, 29, 36, 37) and 1 prospective study (38) fulfilled our criteria for inclusion in the systematic review and meta-analysis. The studies included in this meta-analysis are summarized in Table 1. This meta-analysis involved a total of 789 patients, including 399 in the IVE/DOXY group and 390 in the control group. Three studies were conducted in Bangladesh (27, 29, 36). Two studies were performed in Iraq (37) and India (38).

4.2. Risk of bias

The assessed risk of bias using NOS for one prospective study was 4, indicated a high risk of bias (38). According to the Cochrane Collaboration's tool for randomized clinical trials, 2 trials were classified as fair (27, 36) and 2 had poor

quality (29, 37)(Fig. 2).

Common biases were related to the randomization process and allocation concealment; in fact, two trials randomized patients based on odd/even date of enrollment (37) or registration number (29). The details of random sequence generation and allocation concealment were not reported in one study (27). In addition, two studies did not report any information on the process of blinding (29, 37). Attrition bias was also present in one article (36) because about 10% of randomized patients were not included in the analysis. All the studies reported outcomes and none of them had selective reporting bias. Other biases were not observed in any of the included studies.

4.3. Clinical outcome

4.3.1. All-cause mortality

Among all studies, mortality was observed in only two trials (36, 37). In the rest of the studies, all-cause mortality was reported to be zero in both the IVE/DOXY and control groups. A total of 503 participants were included. The all-cause mortality rate of patients with COVID-19 in the IVE/DOXY group was 0.79% (2/253), which was lower than in the control group (3.6%; 9/250). However, the difference was not statistically significant (Log risk ratio=-1.288; 95% CI:-2.671, 0.096; $P=0.068$; $I^2=0\%$) (Fig. 3).

4.3.2. Time to clinical recovery

The meta-analysis of four studies (29, 36–38) which reported the mean number of days to clinical recovery ($n=741$ participants) showed a significant reduction in time to clinical recovery after IVE/DOXY (Difference in means =-2.427 days; 95% CI:-4.033, -0.820; $P=0.003$, $I^2=91.475\%$) (Fig. 4). Sensitivity analysis after deleting every individual study successively revealed the same findings. The heterogeneity was tangibly reduced after removing a study done by Hashim et al. (37) (Difference in means =-1.151 days; 95% CI:-1.581, -0.721; $P=0.000$, $I^2=0\%$).

4.3.3. Viral clearance

Two studies assessed the mean number of days to negative PCR or viral clearance outcome (164 participants) (27, 38). The IVE/DOXY group had a shorter period of time to negative PCR than the control group. The difference, however, was not statistically significant (Difference in means =-0.768 days; 95% CI:-1.550, 0.013; $P=0.054$, $I^2=91.48\%$) (Fig. 4). The findings of individual studies are all the same.

4.3.4. Hospital stay

Two studies (27, 38) including 170 participants reported the mean number of days of hospital stay. The overall meta-analysis showed there was no significant effect of IVE/DOXY on hospital stay (Difference in means =-0.379 days; 95% CI:-1.965, 1.208; $P=0.640$, $I^2=91.95\%$) (Fig. 5). Although no significant difference was found in the Ahmed et al. (27) study, a significant difference was reported in the Spoorthi et al. (38) study.

Discussion

Due to the pandemic of COVID-19 and the lack of effective treatment, many efforts are being made to find a regimen to improve patients' clinical outcomes. Recently, IVE/DOXY combination has been proposed by a couple of studies in treatment of COVID-19. To the best of our knowledge, this is the first meta-analysis investigating the effect of the IVE/DOXY combination on clinical outcomes of patients with COVID-19.

Doxycycline is an antibiotic which can be used to treat atypical bacterial pneumonia and community-acquired pneumonia (39). In mammalian cells, doxycycline has an anti-inflammatory action that is mediated by chelating zinc compounds on matrix metalloproteinases (MMPs) (40). Murine coronaviruses rely on MMPs for cell fusion and viral

multiplication, according to prior in vitro research (41). COVID-19's pathologic characteristics are similar to those of previous SARS-CoV infections, in which MMPs play a key role in disease development (42). Doxycycline's pharmacokinetics indicate that it is dispersed in pulmonary tissue following oral administration, with the drug's concentration in the lungs being 18–23% of the serum concentration in humans (43). As a result, doxycycline might be useful in the treatment of COVID-19 infection.

Ivermectin is a well-known antiparasitic medication that is used to treat a variety of parasites all over the world. A meta-analysis demonstrated that ivermectin can not only reduce the number of COVID-19 deaths, but also lead to significant reduction in the number of progressive disease cases if started in early clinical course (8). In preclinical models of numerous additional diseases, ivermectin has exhibited immunomodulatory and anti-inflammatory functions. Ivermectin has been shown to inhibit the synthesis of inflammatory mediators such as nitric oxide and prostaglandin E2 in vitro studies (44). In mice given a fatal dosage of lipopolysaccharide, Ivermectin decreased TNF- α , IL-1, and IL-6, and increased survival (45). Subcutaneous ivermectin reduced the IL-6/IL-10 ratio in the lung tissues of Syrian golden hamsters infected with SARS-CoV-2 and prevented clinical deterioration (46). Ivermectin's antiviral activity against SARS-CoV-2 in Vero/hSLAM cells has been proven. However, after oral administration of the medication to patients, the concentrations necessary to suppress viral multiplication in vitro ($EC_{50} = 2.8\mu M$; $EC_{90} = 4.4\mu M$) are not attained systemically (22, 47). Although the standard dose of a single 200 μg /kg oral of ivermectin for treating strongyloidiasis is thought to accumulate in lung tissues (2.67 times that in plasma), there is no evidence that this dosage regimen would result in ivermectin reaching an antiviral concentration in the lungs (48, 49). As a result, alternative administration methods for ivermectin in COVID-19 should be considered, such as utilizing in combination with medicines that increase ivermectin activity through mechanisms such as increasing ivermectin pulmonary penetration (50). Therefore, we aim to perform a systematic review and meta-analysis to determine the efficacy of the IVE/DOXY combination in COVID-19 therapy.

Based on a meta-analysis of five related studies, the combination of IVE/DOXY significantly reduced the time to clinical recovery. Although the mortality rate was lower in the IVE/DOXY group than in the control group, there was no significant difference. The IVE/DOXY group had a shorter period of time to a negative PCR than the control group. The difference, however, was not statistically significant. Co-administration of ivermectin and doxycycline did not differ in the length of hospital stay.

These findings, however, should be taken with caution. It must be considered that the low mortality rate which was reported in just two studies is due to that majority of enrolled patients were inclined to mild to moderate. On the other hand, in the Hashim et al. (37) study, no critical patients were included in the control group. In the Mahmud et al. (36) study, the number of patients with at least one comorbidity and the tendency of mild patients to be in the IVE/DOXY group was lower. The three patients who died in the control group had a higher mean age than the others (63 years vs. 39 years). Furthermore, both studies assessing hospital stay (27, 38) were of poor quality.

Three studies in this meta-analysis reported adverse events in patients administered IVE/DOXY. Serious adverse drug reactions with the use of IVE/DOXY, though uncommon, have been reported. In the study by Mahmud et al. (36) adverse drug reactions occurred in 9 patients (2.5%); Two of them showed signs of erosive esophagitis and 7 developed non-ulcer dyspepsia. In the study by Spoorthi et al. (38) 11% (7/62) in the IVE/DOXY group and 6.6% (4/60) in the control group experienced gastrointestinal disturbances. One patient in the treatment group experienced pruritus. In the report by Chowdhury et al. (29) the most common adverse events included lethargy in 14 (23.3%), nausea in 11 (18.3%), and occasional vertigo in 7 (11.66%) patients in the IVE/DOXY group.

Although the methodological quality of all studies was medium to low, study's limitations must be taken into account. There were few trials and limited patients, and adverse events were not reported in the majority of the studies. Thus,

further large-scale randomized controlled studies are required to clarify the findings.

Conclusion

Based on low-quality evidence, this meta-analysis revealed that IVE/DOXY combination is accompanied with shorter period of time of clinical recovery in COVID-19 patients. However, it did not reduce all-cause mortality, time to negative PCR, and hospital stay significantly. Due to the undetermined appropriate IVE/DOXY regimen dosage and its efficacy in COVID-19 patients, the need for larger and high quality randomized controlled trials is felt yet.

Declarations

Funding

None

Competing interests

The authors declare that they have no conflicts of interest.

Abbreviations

SARS-CoV-2

Severe Acute Respiratory Syndrome Coronavirus 2

COVID-19

Coronavirus disease 2019

IVE/DOXY

Ivermectin/Doxycycline

RCTs

Randomized Controlled Trials

MeSH

Medical Subject Headings

SD

Standard Deviation

SE

Standard Error

NOS

Newcastle-Ottawa Scale

CMA

Comprehensive Meta-Analysis

I^2

I-squared

MMPs

Matrix Metalloproteinases

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Table

Table 1 is available in the Supplementary Files section.

Figures

Figure 1

The flowchart of search strategy and study selection.

Figure 2

Study quality and risk of bias assessment using Cochrane collaboration tool.

Figure 3

Forest plot of studies reported all-cause mortality.

Figure 4

Forest plot of studies that assessed the mean number of days to clinical recovery (time to clinical recovery).

Figure 5

Forest plot of studies that assessed the mean number of days to negative PCR (viral clearance).

Figure 6

Forest plot of studies that assessed hospital stay.

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