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CLINICAL OUTCOMES OF IVERMECTIN IN COVID-19 TREATMENT: AN EVIDENCE-BASED CASE REPORT FROM SYSTEMATIC REVIEWS AND META-ANALYSES

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ABSTRACT

Background: *Ivermectin has demonstrated beneficial results on clinical outcomes in COVID-19 patients. Several countries have included ivermectin in their guidelines, though WHO recommended against its usage. Therefore, this study was aimed to establish the clinical outcomes of ivermectin in COVID-19 patients by an evidence-based method.*
Case Illustration: *A 23-year-old man was diagnosed COVID-19 with a positive RT-PCR result three days after the first day of his symptoms. He was prescribed 500 mg paracetamol tablets, vitamin C 2 x 500 mg, vitamin D 1000 mg, and zinc sulfate monohydrate 2 x 20 mg as supportive outpatient treatment. He then bought ivermectin tablets online and consumed regularly one tablet per day. He came back to take the RT-PCR test after ten days he was diagnosed because he felt that his symptoms improved. The result of this RT-PCR test was negative.*
Method: *Article searching was completed in PubMed, Cochrane, and Scopus from July 9 - 10 2021. The results were limited to only systematic reviews and meta-analyses. Hand searching was conducted to obtain relevant studies from external resources. The results were evaluated using inclusion and exclusion criteria. The full texts were obtained and critically reviewed using Oxford Centre for Evidence-Based Medicine critical appraisal tools.*
Result: *Three systematic reviews and meta-analyses were selected and critically reviewed. All three studies were considered valid, important, and applicable. However, the quality of these studies varied from low to high.*
Conclusion*: Overall studies showed that ivermectin has the potency to improve clinical outcomes in COVID-19 patients.*

Keywords: *COVID-19, Ivermectin, Outcomes*

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HASIL UJI KLINIS IVERMECTIN DALAM PENGOBATAN COVID-19: LAPORAN KASUS BERDASARKAN TINJAUAN SISTEMATIS DAN META ANALISIS

ABSTRAK

Latar Belakang: Ivermectin telah menunjukkan luaran klinis yang baik pada pasien COVID-19. Beberapa negara telah memasukkan ivermectin ke dalam panduan tata laksana mereka walaupun WHO merekomendasikan untuk tidak menggunakan obat tersebut. Studi ini bertujuan untuk menelaah luaran klinis ivermectin pada pasien COVID-19 dengan metode berbasis bukti.
Ilustrasi Kasus: Seorang pria 23 tahun terdiagnosis COVID-19 dengan RT-PCR positif tiga hari sejak timbul gejala. Pasien diresepkan paracetamol tablet 500 mg, vitamin C 2 x 500 mg, vitamin D 1000 mg, dan zinc sulfate monohydrate 2 x 20 mg sebagai terapi suportif rawat jalan. Pasien kemudian membeli ivermectin secara online dan mengonsumsi teratur satu tablet per hari. Pasien datang kembali sepuluh hari untuk uji RT-PCR setelah terdiagnosis karena merasa gejala telah membaik. Hasil RT-PCR negatif.
Metode: Penelusuran artikel dilakukan di *PubMed*, *Cochrane*, dan *Scopus* pada 9 – 10 Juli 2021. Hasil penelusuran terbatas pada tinjauan sistematis dan meta-analisis. Telusur tangan dilakukan untuk memperoleh studi relevan dari sumber eksternal. Hasil yang diperoleh dievaluasi berdasarkan kriteria inklusi dan eksklusi. *Full-text* diperoleh dan ditelaah kritis menggunakan *Oxford Centre for Evidence-Based Medicine critical appraisal tools.*
Result: Tiga tinjauan sistematis dan meta-analisis dipilih dan ditelaah kritis. Ketiga studi absah, penting, dan mampu diterapkan. Akan tetapi, kualitas studi bervariasi dari rendah ke tinggi.
Kesimpulan: Keseluruhan studi menunjukkan ivermectin mempunyai potensi untuk meningkatkan luaran klinis pasien COVID-19.

Kata kunci: COVID-19, ivermectin, luaran

1. INTRODUCTION

On July 12, 2021, Indonesia faced the highest peak of 40,427 new daily coronavirus disease 2019 (COVID-19) cases for the first time in one and a half years of the pandemic.[1] Medical resource, hospital beds, personal protective equipment (PPE), oxygen, and medical staff were facing a shortage.[2]

COVID-19 clinical symptoms varied from mild conditions such as cough, fever, and anosmia to severe and critical conditions such as respiratory distress, arrhythmia, sepsis, and shock.[3-5] Although many drugs, such as azithromycin, levofloxacin, oseltamivir, favipiravir, and remdesivir, have been used for treatment, their results have variable success.[6-10] These drugs are beneficial in treating COVID-19 because of their effect on cytokine storm, which is a major factor in clinical progression.[11]

Despite the extensive use and studies regarding antivirals, antimalarials, antibiotics, and corticosteroids in COVID-19, the utility of anti-parasitic drugs have mostly been overlooked.[12-15] Several countries have included ivermectin in their treatment guidelines, though WHO recommended against its usage except for clinical trials.[16-18] Therefore, this study was aimed to establish the clinical outcome of ivermectin, either as single or adjuvant therapy, in COVID-19 patients by an evidence-based method.

2. CASE ILLUSTRATION

2.1 Anamnesis

A 23-year-old man was diagnosed COVID-19 with a positive RT-PCR result three days after the first day of his symptoms. On the first day, he experienced a 38.1^{o}C fever and dry cough. Muscle pain occurred on the second day of his disease and was relieved. On the third day, his muscle pain was relieved and anosmia occurred.

2.2 Physical Examination

His body weight was 62 kilograms. Respiratory rate was 18 per minute, pulsation was 94 per minute, oxygen saturation was 98%, and blood pressure was 126/82 mmHg.

2.3 Treatment

He was prescribed 500 mg paracetamol tablets, vitamin C 2 x 500 mg, vitamin D 1000 mg, and zinc sulfate monohydrate 2 x 20 mg as supportive outpatient treatment. He asked the doctor to prescribe him ivermectin because of the information about the good outcomes of ivermectin in improving clinical symptoms. The doctor refused to prescribe him ivermectin because of lacking evidence of this drug. He then bought 12 mg ivermectin tablets online and consumed regularly one tablet per day.

2.4 Follow Up

He came back to take the RT-PCR test after ten days he was diagnosed because he felt that his symptoms improved. The result of this RT-PCR test was negative.

3. METHODS

Clinical questions were determined based on the population, intervention, comparison, and outcome (PICO) of this study. The population (P) is symptomatic adult COVID-19 patient; the intervention (I) is ivermectin; the comparison (C) is standard therapy or placebo; the outcome (O) is clinical improvement and viral clearance. The PICO and clinical question are provided in **Table 1**.

Table 1. Clinical Question

Population	Intervention	Comparison	Outcome
Symptomatic adult COVID-19 patients	Ivermectin	Standard therapy or placebo	Clinical improvement and viral clearance
Clinical aspect	Intervention		
Study design	systematic review and meta-analysis		
Clinical question	Is ivermectin capable of providing clinical improvement and viral clearance in COVID-19 patients?		

The literature search was conducted on July 9th – 10th 2021 with keywords that were appropriate to the authors' clinical questions. A literature search was done using the booleans OR and AND in PubMed, Cochrane, and Scopus. In addition, hand searching was also conducted to obtain relevant studies from external sources. The

search strategy and keywords used are provided in **Table 2**.

Title screening was performed based on a study design that was appropriate to the authors' clinical questions. Article selection was limited to systematic reviews and meta-analyses. Articles not written in English and not PICO compliant were excluded. Full-text selection is based on the availability of full-text articles. Double screening was carried out to exclude duplicate articles.

These studies were critically reviewed using the Oxford Center of Evidence-based Medicine (CEBM) critical appraisal tools by two authors. The results were extracted and noted in a spreadsheet. If there is a difference of perception between the two authors, the determination of the results is carried out based on a third party who is also one of the authors. The search and selection process is presented in **Figure 1**.

Table 2. Search Results

Database	Keywords in Search	Result
PubMed	("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]) OR "SARS-CoV2"[All Fields]) AND ("ivermectin"[MeSH Terms] OR "ivermectin"[All Fields] OR "ivermectine"[All Fields] OR "ivermectin s"[All Fields] OR "ivermectins"[All Fields])	243
Cochrane	#1 COVID-19 therapy #2 ivermectin #3 treatment outcome #1 AND #2 AND #3	27
SCOPUS	covid-19 AND therapy AND ivermectin AND treatment AND outcome	530
Hand searching	COVID-19 AND ivermectin AND outcome	

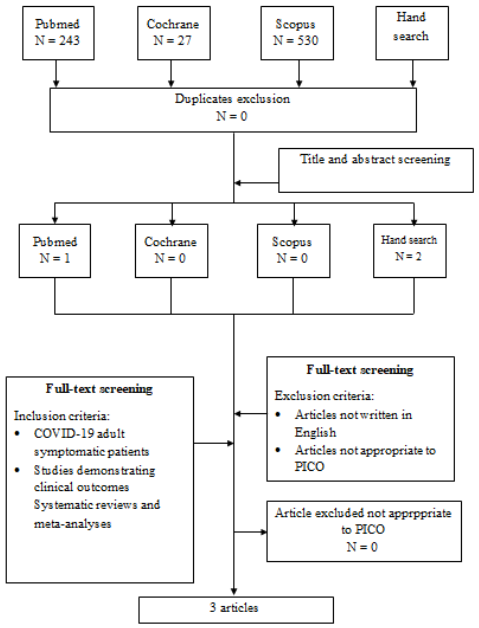

Figure 1. Search and Selection Process

4. RESULT

A total of 800 articles were obtained from searches on the PubMed, Cochrane, and SCOPUS databases. Three relevant studies were obtained for the preparation of this study. The summary of the studies can be seen in **Table 3**. All studies showed that ivermectin has a statistically significant effect on better clinical outcomes in COVID-19 patients.

Three systematic reviews and meta-analyses were reviewed with the Oxford CEBM critical appraisal tools specifically for systematic reviews and meta-analyses. The critical appraisal results of the systematic reviews and meta-analyses can be seen in **Table 4**. All three studies were considered valid. However, Padhy BM et al included low-quality studies with a high risk of bias.[19]

All these meta-analyses were also considered important due to their significant variables correlation and their precisions showed by the narrow range of confidence intervals. However, it also should be noted that the studies of Hariyanto TI et al and Hill A et al have significant heterogeneity showed by high I^2 values.[20,21]

All these studies were also considered applicable because the characteristics of the participants included in these studies were similar to the authors' patients. However,

education to the patients about this drug was required because ivermectin still needed more trials to prove its efficacy in treating viral diseases such as COVID-19, therefore this drug can't be administered freely.

Table 3. Study Summary

Author	Subject	Results
Padhy BM et al[19] (2020)	Four observational studies with a total of 629 patients	Clinical improvement was better in the ivermectin group than in the control group (3 studies, n = 483, OR = 1.98, 95% CI: 1.11, 3.53, p = 0.02, I^2 = 0%)
Hariyanto TI et al[20] (2021)	Nineteen randomized controlled trials with a total of 2768 patients	Viral clearance rate by negative RT-PCR in ivermectin vs control/placebo (9 studies, n = 1205) RR 1.23 [95% CI: 1.02, 1.51; p = 0.04, I^2 = 91%], viral clearance time RT-PCR in ivermectin vs control/placebo (6 studies, n = 782) MD -3.29 days [95% CI: -5.69, -0.89; p = 0.007, I^2 = 96%], rate of clinical improvement of ivermectin vs control/placebo (8 studies, n = 1535) RR 1.23 [95% CI: 1.03, 1.46; p = 0.02, I^2 = 85%], time to clinical improvement of ivermectin vs control/placebo (6 studies, n = 950) MD -0.68 days [95% CI: -1.07, -0.29; p = 0.0007, I^2 = 68%].
Hill A et al[21] (2021)	Twenty four randomized controlled trials with a total of 3328 patients	Duration of viral clearance of study group vs control MD -3 days, 95% CI -4.96, -1.03; p = 0.003. RT PCR results were negative on days 6 - 7 in the study group vs. control RR 1.35 95% CI: 1.05, 1.75; p = 0.02, I^2 = 56%. Duration of clinical improvement in study group vs control MD -1.58 days, 95% CI -2.8, -0.35, p = 0.01. Clinical improvement at 7-10 days in the study group vs. control RR 1.29 95% CI: 1.12, 1.47; p = 0.003, I^2 = 80%.

*CI: confidence intervals; MD: mean difference; RR: relative risk; $p < 0.05$ is statistically significant

Table 4. Critical Appraisal of Systematic Reviews and Meta-analyses

	Padhy BM et al[19] (2020)	Hariyanto TI et al[20] (2021)	Hill A et al[21] (2021)
Validity			
Is PICO appropriate?	Yes: P: symptomatic adult COVID-19 patients; I: ivermectin added to standard therapy; C: standard therapy; O: mortality, hospitalization, duration of virological clearance, clinical improvement	Yes: P: COVID-19 patients; I: ivermectin; C: standard therapy or placebo; O: severity, mortality, negative RT-PCR result, duration of illness until negative RT-PCR, symptom improvement, duration until symptom improvement, duration of hospitalization	Yes: P: COVID-19 patients; I: ivermectin; C: standard therapy or placebo; O: mortality, duration of virological clearance, negative PCR result on day 7, clinical improvement, duration to clinical improvement, mechanical ventilation, duration of hospital stay, number of hospitalizations
PICO compatibility with traceability?	Yes: “Ivermectin” OR “Anthelminthic” AND “COVID-19” OR “Severe acute respiratory syndrome coronavirus 2”	Yes: 'ivermectin' OR 'stromectol' OR 'stromectal' OR 'sklice' OR 'ivomec' OR 'mectizan' AND 'SARS-CoV-2', OR 'coronavirus disease 2019' OR 'Covid-19'	Yes: COVID, SARS-CoV-2, and ivermectin
Is the evidence appropriate?	Yes	Yes	Yes
Has the study been critically reviewed?	Yes, risk of bias was assessed by ROBINS-I, publication bias was assessed by funnel plot, quality of evidence was assessed by GRADE profiler software	Yes, study quality is assessed by Jadad scale assessment	Yes, the risk of bias is assessed with the Cochrane Collaboration risk of bias standardized assessment tool
High-quality studies?	No	Moderate to high quality	Low to good quality
Tables and plots match?	Yes	Yes	Yes
Heterogeneity clear?	Yes	Yes	Yes
Valid?	Yes	Yes	Yes
Importance			
Study results	Clinical improvement was better in the study group than in the control (3 studies, n = 483, OR = 1.98, 95% CI: 1.11, 3.53; p = 0.02, I^2 = 0%)	Virological clearance rate by negative RT-PCR in ivermectin vs control/placebo (9 studies, n = 1205) RR 1.23 [95% CI: 1.02, 1.51; p = 0.04, I^2 = 91%], virological clearance time RT-PCR in ivermectin vs control/placebo (6 studies, n = 782) MD -3.29 days [95% CI: -5.69, -0.89; p = 0.007, I^2 = 96%], rate of clinical improvement of ivermectin vs control/placebo (8 studies, n = 1535) RR 1.23 [95% CI: 1.03, 1.46; p = 0.02, I^2 = 85%], time to clinical improvement of ivermectin vs control/placebo (6 studies, n = 950) MD -0.68 days [95% CI: -1.07, -0.29; p = 0.0007, I^2 = 68%].	Duration of virological clearance of study group vs control MD -3 days, 95% CI: -4.96, -1.03, p = 0.003. RT-PCR results were negative on days 6 - 7 in the study group vs. control RR 1.35 95% CI: 1.05, 1.75; p = 0.02, I^2= 56%. Duration of clinical improvement in study group vs control MD -1.58 days, 95% CI: -2.8, -0.35; p = 0.01. Clinical improvement at 7-10 days in the study group vs. control RR 1.29 95% CI: 1.12, 1.47; p = 0.003, I^2 = 80%.
Important?	Yes	Yes	Yes
Applicability	Yes, all three studies were applicable because the characteristics of the participants included in these studies were similar to the authors' patient		

*CI: confidence intervals; MD: mean difference; RR: relative risk; $p < 0.05$ is statistically significant

5. DISCUSSION

Ivermectin, a widely-used anti-parasitic drug with a favorable safety profile, has demonstrated beneficial results on clinical outcomes in COVID-19 patients due to its ability to inhibit importin (IMP) α/β integrase which allows nuclear import of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) in vitro.[22-24] Other observational studies have also evaluated the effectiveness of ivermectin in COVID-19 patients and reported favorable results.[25-28]

Clinical outcome in this study is shown by clinical improvement and negative RT-PCR results. Overall studies showed that there was clinical improvement in all symptomatic patients from mild to severe symptoms.[19-21] The duration of clinical recovery and negative RT-PCR were also demonstrated in Hariyanto TI et al[20] and Hill A et al[21], this also showed a statistically significant correlation. However, it should also be noted that the quality of studies included in Padhy BM et al[19] study was very low due to the risk of bias, indirectness, inconsistency, and publication bias.

The administration dose of ivermectin in treating COVID-19 is still unclear. In Padhy BM et al study, the ivermectin dose varied from 150 to 200 ug/kg body weight given as a single dose.[19] On the other hand, the ivermectin dose in Hill et al study varied from 0.2 mg/kg for one day to 0.6 mg/kg for five days.[21] In an animal study, subcutaneous ivermectin injection 400 µg/kg in hamsters did not affect viral loads. However, there was a decrease in olfactory deficit and interleukin-6 (IL-6): IL-10 ratio in the lung.[29] The wide range of ivermectin doses in Hill et al study explained that the dose of ivermectin in treating COVID-19 is still unclear, this also explains the significant heterogeneity in this study.[21]

In severe COVID-19 patients, cytokine levels such as interleukin-6 (IL-6), IL-8, IL-10, and tumor necrosis factor-alpha (TNF-α) were elevated compared to mild to moderate cases.[30] On the other hand, ivermectin also demonstrated anti-inflammatory effects both in vivo and in vitro studies by reducing IL-1, IL-6, and TNF-alpha production and suppressing the lipopolysaccharide-induced nuclear factor-kappa B translocation.[31] Ivermectin also prevents the “cytokine storm” typical of severe COVID-19. Cytokine storm involves STAT-3 mediated upregulation of TNFα and IL-6 in macrophages. STAT-3 is responsible for the transcription of IL-6 which leads to an increase in TGF-β causing lung fibrosis. This also explains the effect of ivermectin in treating severe COVID-19.[32]

These findings also supported the results of subgroup analysis in Hariyanto TI et al[20] study which also demonstrated that there was statistically significant difference in clinical outcomes of severe COVID-19 patients between ivermectin group and control group. Among the severe COVID-19 patients, there was improvement in clinical recovery rate ($n = 260$, RR 1.66; 95% CI: 1.37, 2.00; $p < 0.0001$, $I^2 = 10\%$) and clinical recovery duration (6 studies, $n = 950$, MD -1 days; 95% CI: -1.14, -0.86; $p = 0.0001$, $I^2 = 0\%$).[20]

A negative RT-PCR result is associated with SARS-CoV2 viral clearance. Several studies reported that ivermectin has the potential to inhibit viral replication and assembly.[33,34] Hariyanto TI et al[20] and Hill A et al[21] also demonstrated that ivermectin improved the duration and rate of negative RT-PCR results in COVID-19 patients. However, the mechanism of this process is still not clearly described.

Although all three studies were applicable according to the critical review, ivermectin was still not recommended by WHO in treating COVID-19 except for clinical trials.[16-18] This was due to the ongoing trials which weren’t completed. The existing studies also included very minimal RCTs, hence it was prone to bias due to observational studies. The mechanism of action of this drug in treating COVID-19 should be explored in further studies. The maximum dose should also be investigated to determine the safety of this drug. Further high-quality clinical trials were required to establish the efficacy of this anti-parasitic drug in treating viral diseases such as COVID-19.

More studies should also be conducted to evaluate the efficacy of this drug in treating each symptomatic degree of COVID-19 from mild to critical separately.

6. CONCLUSION

Overall studies showed that ivermectin has the potency to improve symptoms and virological clearance in COVID-19 patients. Ivermectin might also have the potential to reduce the duration of clinical recovery and virological clearance. However, the quality of these studies varied from low to high. More high-quality trials are required to evaluate the efficacy and safety of ivermectin in treating COVID-19. The mechanism of action of this drug in treating COVID-19 should be more investigated. Ivermectin dose administered to the COVID-19 patients should be also evaluated in further studies.

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