Clinical efficacy and safety of ivermectin (400 ug/kg, single dose) in patients with severe COVID-19: a randomized clinical trial

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Clinical efficacy and safety of ivermectin (400 µg/kg, single dose) in patients with severe COVID-19: a randomized clinical trial

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Abstract

Purpose: To evaluate the clinical efficacy of including Ivermectin (single dose on day 1 of 400 µg/kg PO) in the standard of care in hospitalized adults with severe COVID-19.

Methods: Double-blinded, parallel, placebo-controlled, single-center, randomized clinical trial. Seventy-five patients were randomly assigned (1:1) to receive standard of care plus ivermectin or placebo and were followed up for 21 days. Primary outcome measure was admission to ICU and secondary outcomes were the requirement of intensive mechanical ventilation (IMV) and in-hospital death. Intention-to-treat analyses, estimated risk differences (RD), and Hazard ratios (HR) with Cox regression were performed.

Results: Enrollment stopped due to the lack of eligible patients. Thirty-seven patients were assigned to intervention and 38 to placebo. Patients in the ivermectin group were 54.5 years on average, 62.2% were male. Comorbidities were more prevalent in the control group (78.9% vs. 56.8%). There was no difference in the 21-day risk of admission to the ICU between ivermectin (21.6%) and placebo (15.8%) (RD= 5.8%; 95%CI: -11.8%-23.5%); neither in the risk of requirement of IMV (18.9% vs 13.2%), mortality (5.4% vs 10.5%) or in adverse events (32.4% vs. 28.9%).

Discussion: Ivermectin showed no significant benefit in reducing the requirement of ICU, IMV, or mortality for severe COVID-19 patients.

Keywords: Ivermectin, COVID-19, ICU admission, mechanical ventilation, mortality, randomized, placebo

Eficacia clínica y seguridad de ivermectina (400 µg/kg, única dosis) en pacientes COVID-19 severo: un ensayo clínico aleatorizado

Resumen

Propósito: Evaluar la eficacia clínica de incluir Ivermectina (dosis única el día 1 de 400 µg/kg via oral) en el estándar de atención en adultos hospitalizados con COVID-19.

Métodos: ensayo clínico aleatorizado, doble ciego, paralelo, controlado con placebo, de un solo centro. Setenta y cinco pacientes fueron asignados al azar (1:1) para recibir tratamiento estándar de atención más ivermectina o placebo y fueron seguidos durante 21 días. La medida de resultado primaria fue la admisión a la UCI y los resultados secundarios fueron el requerimiento de ventilación mécanica intensiva (IMV) y muerte intrahospitalaria. Se realizaron análisis por intención de tratar, diferencias de riesgo estimadas (DR) y cocientes de riesgos instantáneos (HR) con regresión de Cox.

Resultados: La inscripción se detuvo debido a la falta de pacientes elegibles. Treinta y siete pacientes fueron asignados a la intervención y 38 al placebo. Pacientes en la ivermectina grupo tenían 54,5 años en promedio, el 62,2% eran del sexo masculino. Las comorbilidades fueron más prevalentes en el grupo control (78,9% vs. 56,8%). No hubo diferencia en el riesgo a 21 días de ingreso en UCI entre ivermectina (21,6%) y placebo (15,8%) (DR= 5,8%; IC95%: -11,8%-23,5%); ni en el riesgo de requerimiento de IMV (18,9% vs 13,2%), mortalidad (5,4% vs 10,5%) o en eventos adversos (32,4% vs 28,9%).

Discusión: La ivermectina no mostró un beneficio significativo en la reducción del requisito de UCI, IMV o mortalidad para pacientes graves con COVID-19.

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Introduction

Since COVID-19 started at the end of 2019 and until January 26, 2022, around 360 million infections and 5.5 million deaths were reported[1]. Therefore, researchers worldwide have sought treatments and vaccines to address this situation and contribute to the lack of knowledge about the disease, treatment, and prevention[2]. Specifically, drug repurposing, identifying novel clinical uses for approved drugs, is one of the approaches considered in COVID-19 treatment research[3]. Moreover, the advantage of repurposing drugs is the prior knowledge of their safety, pharmacokinetics, dosage, and side effects that could help to manage the current SARS-CoV-2 pandemic situation, in addition to the significant reduction of costs and time compared to developing new drugs[4].

Notably, ivermectin is considered an essential medicine by the World Health Organization; it has been used for over 30 years to treat various infectious diseases [scabies, blind river disease, helminthiasis, among others], and its low profile of adverse effects is well known[5,6]. Additionally, in *in vitro* studies, ivermectin has demonstrated the capability to inhibit the replication of SARS-CoV-2 in Vero/hSLAM cells[7]. However, the concentrations required to inhibit viral replication *in vitro* (EC50 = 2.8mM; EC90 = 4.4mM) are not achieved after oral administration to humans[7,8]. Furthermore, ivermectin accumulates in lung tissues, but its concentration is insufficient to reach an antiviral effect[8,9].

Ivermectin is usually a mixture of two enantiomers and two major metabolites[10]. However, there is insufficient information to determine whether an enantiomer or circulating metabolite of ivermectin has antiviral action against SARS-CoV-2, requiring further investigation. Currently, hypotheses postulate that ivermectin acts as an immunomodulatory and anti-inflammatory compound. Moreover, *in vitro* studies showed that ivermectin suppressed inflammatory mediators like nitric oxide and prostaglandin E2[11], and Avermectin [from which ivermectin is derived] decreased pro-inflammatory cytokine secretion (IL-1β and TNF-α) and increased secretion of the immunoregulatory cytokine IL-10[12], two of the mechanisms that explain the exacerbated immunological response in moderate and severe COVID-19.

Furthermore, studies using animal models showed that ivermectin reduced TNF-α, IL-1, and IL-6 and improved survival in mice given a lethal dose of lipopolysaccharide[13]. For instance, murine models of atopic dermatitis and allergic asthma showed ivermectin's immunomodulatory and anti-inflammatory mechanisms of action[14,15]. In addition, Syrian Golden Hamsters infected with SARS-CoV-2 were injected with subcutaneous ivermectin, showing a reduction in the IL-6/IL-10 ratio in lung tissues and preventing pathological deterioration[16]. Also, ivermectin appeared to be more active in females than in males, showing a lower impact on viral titers in the lungs or nasal turbinates, and favoring a mechanism of action related to anti-inflammatory/immunomodulatory effects rather than a direct antiviral activity[16], as was proposed by other authors[17].

Likewise, several randomized clinical trials of ivermectin are carried out in humans. For instance, a recent meta-analysis of 23 randomized trials published by Hill et al.[19] compared the standard of care to ivermectin use, showing no statistically significant effect on survival, hospitalizations, hospitalization duration, or clinical recovery time. However, although this meta-analysis included six Latin American trials, only one, including 106 patients, reported a single dose of ivermectin[20]. Therefore, more studies, particularly with Latin-American patients, are required to validate cumulative results.

Consequently, the purpose of this study was to evaluate the clinical efficacy of the standard of care plus Ivermectin (single dose on day 1 of 400 µg/kg PO) compared to the standard of care plus placebo in hospitalized adults with severe COVID-19.

Patients and Methods

This report follows the recommendations of the CONSORT-2010 guidelines[21].

Trial design

A randomized, double-blind, parallel, placebo-controlled, single-center, phase II/III trial was conducted. Patients were randomly assigned in a 1:1 ratio. The study was performed at the CES Clinic in Medellin between December 10/20 and November 09/21. The CES University Human Research Ethics Board approved the study (Act 152, august 6/2020). In addition, the study protocol was prospectively registered in www.clinicaltrials.gov (code NCT04602507, on October 22/2020). Two changes to the protocol were reported after the trial started: pharyngeal swab for real-time polymerase chain reaction (RT-PCR) was initially used for disease confirmation, but later, during patient enrollment, antigen detection tests became available and increasingly used in clinical practice. Therefore, it was decided to incorporate it into the inclusion criteria to broaden eligible patients. In addition, the recruitment period had to be extended to six months because the samples could not be obtained during the initial five-month period. The CES University Human Research Ethics Board and the Colombian drug regulatory agency (INVIMA) approved these changes to the protocol.

Trial oversight

This study was conducted under the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and the Colombian legislation for human health research (resolution 8430, 1993). The CES University Human Research Ethics Board and the CES Clinic research division performed data and safety monitoring. Adverse events were reported to the CES University Human Research Ethics Board and INVIMA. In addition, the CES University Human Research Ethics Board performed an independent futility analysis (October 2021), after which approved the study continuation.

Participants

Patients were eligible if they: 1) were 18 years or older, 2) had a diagnosis of SARS-CoV-2 confirmed by RT-PCR or commercially available and approved antigen detection tests (Ag-DTs), 3) had a diagnosis of severe COVID-19 (severe pneumonia[1] or acute respiratory distress syndrome -ARDS-[1]), according to the criteria defined by the Colombian National Health Institute and the Colombian consensus on SARS-CoV-2/COVID-19[22], 4) had less than 14 days since symptoms onset and, 5) were hospitalized in a general internal medicine ward or those designated for the treatment of COVID-19 patients. Patients were excluded if they: 1) used ivermectin within two weeks before admission, 2) had diseases that may disrupt the blood-brain barrier (meningitis, head trauma, acute subarachnoid hemorrhage), 3) had a diagnosis of Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS), 4) were pregnant or nursing, 5) were unable to provide informed consent, or 6) were enrolled in a different clinical trial. ARDS was established as per Berlin definition[23], and the following criteria determined severe pneumonia: suspected respiratory infection, organ failure, and SpO_2 < 90% on room air or respiratory rate > 30 breaths per minute.

Upon admission to the internal medicine ward, potentially eligible patients were evaluated by one of the research team members (FR, VP, AR, JP), who determined whether they met the criteria for admission to the protocol. If they did, they were invited to participate and continued with the informed consent process and the signature of two witnesses, according to the Colombian ethical requirements.

Interventions

Patients were randomized to receive standard of care plus a single dose of ivermectin (400 µg/kg PO) or standard of care plus placebo; both ivermectin and placebo were administered two drops per kilo (based on actual body weight) in a glass of water (20 mL) the same day after obtaining informed consent (day 1). According to the Colombian National Health Institute and the Colombian Consensus on SARS-CoV-2/COVID-19 (22), the standard of care was defined as symptomatic measures such as analgesics, antipyretics, supplemental oxygen, bronchodilators, antidiarrheals, antibiotics, or systemic corticosteroids. Standard of care did not include any medication that explicitly targeted SARS-CoV-2.

Outcomes

The primary outcome was admission to the intensive care unit (ICU), and the secondary outcomes were the requirement of invasive mechanical ventilation (IMV), length of stay at ICU, and 21-day mortality. Moreover, adverse events were actively monitored and classified as severe adverse events (tachycardia and electrocardiogram abnormalities, blood pressure changes, drowsiness and lack of muscle coordination, encephalopathy, and coma) or non-serious adverse events (abdominal pain, nausea, vomiting, dyspepsia, diarrhea/constipation, rash, weakness, drowsiness, chest discomfort, and headache). All outcomes were assessed daily from day 0 to 6 and on days 14 and 21. Administrative censoring was applied on day 21.

Sample size

The sample size was set at 50 participants per arm, providing the trial with 80% power and 95% confidence to detect an absolute risk difference of at least 25% between arms, expecting an ICU admission rate of 40% in the control group according to surveillance reports of the National Institute of Health (https://coronaviruscolombia.gov.co/Covid19/index.html) at the time of writing the protocol. However, at a sample size of 75 (intervention: 37, control: 38), patient enrolment was stopped due to the lack of COVID-19 eligible patients, as community transmission of the virus fell with the introduction of vaccination.

Randomization and implementation

A simple (unconditional) random allocation sequence was constructed with computer-generated random numbers (MS Excel). One researcher (HC) was responsible for administrative procedures, product labeling, and randomization, ensuring concealment of the allocation sequence and blinding of researchers, clinicians, and patients. Four clinician-researchers (FR, VP, AR, JP) verified eligibility criteria, obtained informed consents, enrolled participants, and assessed outcomes. After obtaining informed consent from included patients, HC verified the code according to the allocation sequence and contacted the study coordinator, who dispensed the research product to the nursing service responsible for its administration. The research products' packaging was returned to the pharmaceutical service for inspection and subsequent destruction.

Blinding

Patients, care providers, outcome assessors, and researchers were blinded to the intervention assignment (except for HC, who did not participate in outcome assessment or data analysis). Tecnoquimicas Laboratories supplied the research product (commercial brand: Ivermectina MK 0.6%) and the placebo, guaranteeing similar excipients with the single variation of containing or not the active principle. Both had the same pharmaceutical form and similar organoleptic properties (color, smell, taste). Tecnoquimicas Laboratories delivered the research product unlabeled and compliant with Good Manufacturing Practices (GMP). A second pharmaceutical laboratory certified with GMP labeled the products according to INVIMA's requirements.

Statistical methods

A blinded researcher performed statistical analyses as planned by protocol (DFRG). Before blinding was lifted, a brief report of results was sent to the CES University Human Research Ethics Board to ensure transparency.

Patient demographic and clinical baseline characteristics were summarized, according to allocated intervention, with means and standard deviations (SD) for quantitative variables and

by frequency and percentage for categorical variables. The 21-day incidence of primary and secondary outcomes were compared under intention-to-treat analysis with absolut (Risk Difference -RD-) and relative differences (Hazard ratio -HR-). Risk differences were obtained by the Generalized Linear model with binomial family and identity function. Hazard Ratios were obtained with Cox proportional hazards regression, and estimates are shown with 95% confidence intervals (95% CI) and p-values. According to Schoenfeld's residuals test, the assumption of proportional hazards was met for all outcomes and adverse events. Moreover, Nelson-Aalen cumulative hazard estimates are shown for the primary outcome. No ancillary analyses were performed. All statistical analyses were obtained with Stata version 16.1® (College Station, TX).

Results

Participant flow and recruitment

During the recruitment period, 597 patients were evaluated for eligibility, and 522 were excluded: 493 did not meet inclusion criteria or met exclusion criteria, 24 declined participation, and five for other reasons. The included 75 patients were randomly assigned to intervention (n = 37) and control (n = 38) groups. All randomized patients received the allocated interventions, and there were no losses during follow-up. Therefore, all randomized patients were included in the statistical analyses (Figure 1). Recruitment was open from December 10/20 to November 09/21, when it stopped due to a lack of COVID-19 cases meeting the eligibility criteria (no patients in two months), and it was the expiration date of the approval of the protocol.

Baseline data

Table 1 presents demographics and clinical characteristics at baseline for each group. For instance, patients in the ivermectin group were aged 54.5 years on average (SD 13.2), 14 (37.8%) were male, two (5.4%) were healthcare workers, and the mean body mass index (BMI) was 29.3 kg/m^2 (SD 5.7). Although those characteristics were balanced between arms, comorbidities were more prevalent among the control group with 30 patients (78.9%) than in the intervention group with 21 patients (56.8%). Likewise, arterial hypertension (n = 18, 47.4% vs. n = 12, 32.4%) and chronic renal disease (n = 8, 21.1% vs. n = 0, 0.0%) were more frequent in the control group.

Pharmacological management

36 (97.3%) patients in the experimental group received systemic corticosteroids, and 33 (86.8%) of the control group received dexamethasone most frequently. Similarly, 36 (97.3%) and 34 (89.5%) required anticoagulants, with low-molecular-weight heparin administered most frequently. Antibiotics were administered to 7 (18.9%) and 4 (10.5%) patients, respectively. Acetylsalicylic acid was the only type of drug administered with more frequency to patients in the control group (n = 5, 13.2%) than to patients in the ivermectin group (N = 1, 2.7%) (Table 2).

Primary outcome

There was no statistically significant difference in the 21-day risk of admission to the ICU between ivermectin and placebo (RD = 5.8%; 95%CI: -11.8% - 23.5%). However, the primary outcome was more frequent among patients treated with ivermectin (n = 8, 21.6%) than among patients in the control

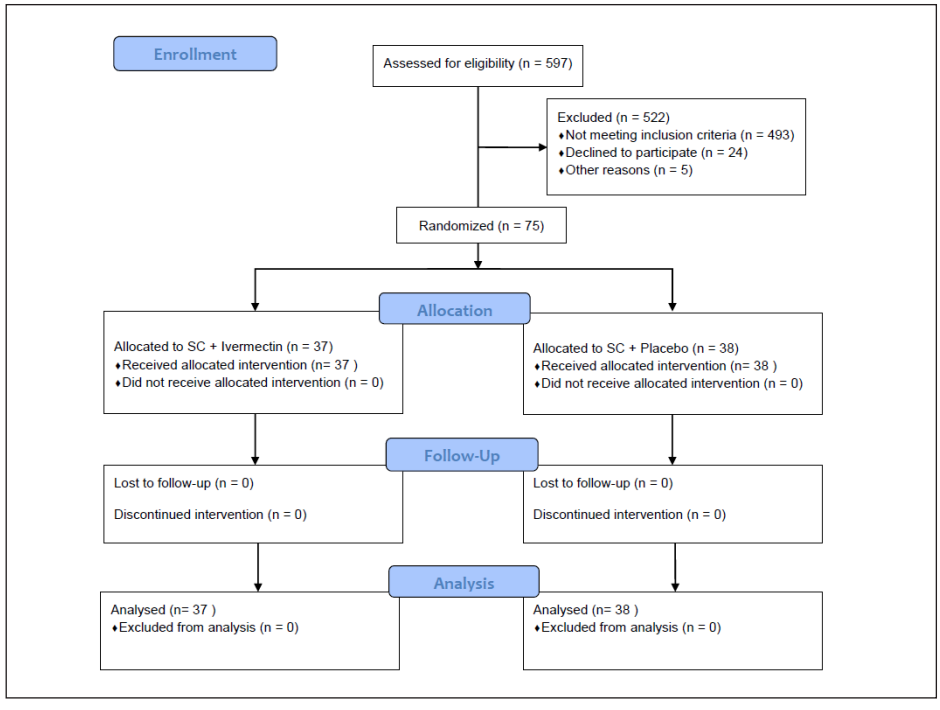

Figure 1. CONSORT flow diagram
The initial sample size was 100 (50:50). However, enrolment stopped due to the lack of COVID-19 eligible patients.

Table 1. Baseline characteristics

	Ivermectin (n = 37)		Placebo (n = 38)	
	n	%	n	%
Age, mean (SD)	54.5	(13.2)	55.9	(16.7)
Female	14	37.8	14	36.8
Health worker	2	5.4	2	5.3
Weight in kg, mean (SD)	81.0	(18.1)	81.8	(15.4)
Height in m, mean (SD)	1.67	(0.09)	1.66	(0.08)
BMI, mean(SD)	29.3	(5.7)	29.6	(5.7)
Comorbidities	21	56.8	30	78.9
Arterial hypertension	12	32.4	18	47.4
Diabetes Mellitus 2	6	16.2	7	18.4
Cancer	0	0.0	1	2.6
Chronic pneumopathy	2	5.4	3	7.9
Cardiovascular disease	3	8.1	3	7.9
Renal chronic disease	0	0.0	8	21.1
Other	13	35.1	17	44.7
Steroids				
Yes	0	0.0	2	5.3
No	22	59.5	28	73.7
No data	15	40.5	8	21.1
Immunosuppressants or immunomodulators				
Yes	0	0.0	3	7.9
No	23	62.2	27	71.1
No data	14	37.8	8	21.1
Days since onset symptoms, mean (SD)	8.8	(2.3)	8.9	(3.3)
Odynophagia	14	37.8	8	21.1
Cough	32	86.5	32	84.2
Dyspnea	35	94.6	35	92.1
Headache	16	43.2	16	42.1
Diarrhea	9	24.3	10	26.3
Loss of smell/taste	15	40.5	13	34.2
Vomiting	3	8.1	2	5.3
Edema	0	0.0	1	2.6
Arthralgia	19	51.4	17	44.7
Myalgia	25	67.6	26	68.4
Skin lesions	1	2.7	1	2.6
Fever	30	81.1	31	81.6
Rhinorrhea	4	10.8	6	15.8
Other	3	8.1	3	7.9
Temperature, mean (SD)	36.3	(0.4)	36.3	(0.8)
Heart rate, mean (SD)	78.7	(12.4)	80.8	(16.6)
Respiratory rate, mean (SD)	23.7	(6.1)	22.4	(7.4)
Systolic blood pressure, mean (SD)	120.1	(17.9)	123.4	(17.2)
Diastolic blood pressure, mean (SD)	73.8	(13.4)	71.2	(12.0)
X-ray				
Classic	29	78.4	21	55.3
Non-COVID-19 pattern	4	10.8	3	7.9
Indeterminate	4	10.8	14	36.8
Tomography				
Typical	12	32.4	14	36.8
Indeterminate	0	0.0	1	2.6
Atypical	25	67.6	23	60.5
Arterial gases	16	43.2	16	42.1

group (n = 6, 15.8%) (Table 3). Figure 2 presents the cumulative hazard estimates, 41.6% for ivermectin and 33.7% for placebo (p-value = 0.6240).

Secondary outcomes

There was no statistically significant difference in the 21-day risk of the requirement of IMV (RD = 5.7%; 95%CI: -10.8% - 22.3%) or the 21-day mortality (RD = -5.1%; 95%CI: -17.3% - 7.1%). However, IMV was more frequent among ivermectin patients (n = 7, 18.9% vs. n = 5, 13.2%), but fewer deaths were observed in the ivermectin group (n = 2, 5.4%) compared to the control group (n = 4, 10.5%) (Table 3).

Adverse events

All adverse events (n = 12, 32.4% vs. n = 11, 28.9%) and serious adverse events (n = 9, 24.3 vs. n = 7, 18.4%) were more frequent among patients treated with ivermectin than patients in the control group with RD of 3.5% (95%CI: -17.4% - 24.4%) and RD of 5.9% (95%CI: -12.6% - 24.4%), respectively. However, there was no statistically significant difference between groups (Table 3). Specifically, the most common adverse events were fever and headache.

Additional outcomes

The duration of patients in ICU and under IMV was higher among patients treated with ivermectin with mean differences of 4.1 days (95%CI -3.0 - 11.2) and 4.8 days (95%CI -1.7 - 11.4), respectively. However, there were no statistically significant differences (Table 3).

Discussion

This study aimed to evaluate the clinical efficacy of standard of care plus ivermectin (single dose on day 1 of 400 µg/kg PO) compared to standard of care plus placebo in hospitalized adults with severe COVID-19. Notably, no significant effect was observed on ICU admission, in-hospital mortality, or requirement of invasive mechanical ventilation; and no differences were observed in the rate of adverse events either.

Patients received COVID-19 clinical standard management plus ivermectin or placebo. A single dose of ivermectin of 400 ug/kg was used because while writing the research protocol based on the available literature (May 2020), we considered this dose had lower risks for the patients [24]. Nevertheless, several reports have been published with protocols using higher single doses of ivermectin or Multi-Day dosing, not showing significant benefits[19].

Unfortunately, only a few studies have been performed considering the standard of care plus a single dose of ivermectin (400 µg/kg) in patients with severe COVID-19, and available reports are not comparable to our study. For instance, in India, Mohan *et al*. conducted a trial including an arm with the standard of care plus an alcohol-based elixir of ivermectin 24 mg (equivalent to 400 µg/kg). However, inclusion criteria considered non-severe COVID-19 cases, and outcomes

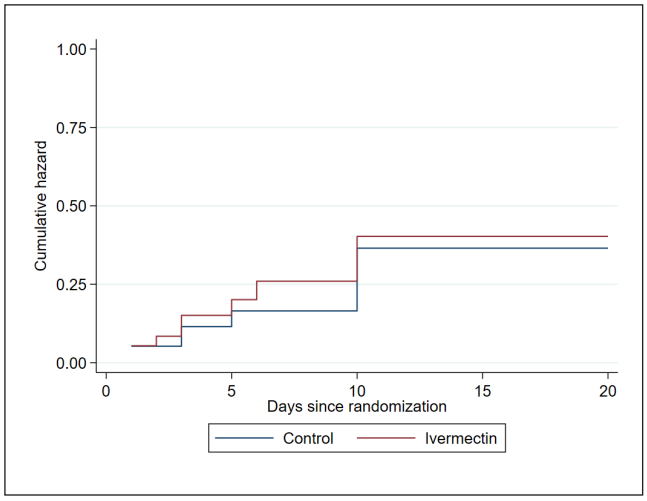

Figure 2. Nelson-Aalen cumulative hazard estimates for admission to the ICU (primary outcome)

did not include death or requirement of ICU. Their primary outcome was RT-PCR negativity on day 5 of enrollment and found no statistical significance[25]. Similarly, Chaccour *et al*. evaluated a protocol of a single dose of ivermectin (400 µg/kg) in patients with non-severe COVID-19 and no risk factors for complicated disease in Spain. However, they found no difference in the proportion of PCR positivity [26]. Additionally, the meta-analyses performed by Hill *et al*. excluding the high risk of bias studies concluded there was no benefit for ivermectin on survival (RR = 0.90; 95%CI 0.57 - 1.42, I^2 = 0%) or mechanical ventilation (RR = 1.04; 95%CI 0.63 - 1.71, I^2 = 0%), regardless of dosing or COVID-19 severity, similarly to our results[19].

Regarding adverse events, there was no difference between study arms. Specifically, the rate of adverse events was around 30%. However, the disease might have caused the most common adverse events (fever and headache), which was expected for patients with severe COVID-19, particularly given baseline characteristics such as obesity (mean BMI around 29.5) and high prevalence of comorbidities (56.8% vs. 78.9%).

Our study's main limitation was the sample size. Since the terms granted expired, administrative closure was necessary before reaching the initially planned sample of 100 patients. The small sample size is also related to the baseline imbalance in comorbidities, particularly arterial hypertension and chronic renal disease. At the protocol stage of this study, we opted for simple randomization despite the expected small sample size due to COVID-19 related restrictions like essential health personnel at hospitals and confinement. These restrictions made it difficult to implement a more efficient randomization mechanism like treatment allocation by minimization, as they would require more physical presence of administrative personnel. However, because comorbidities were relatively more frequent in the control group, the expected impact of bias derived from baseline imbalance should favor the experimental group, which was not observed in our results of no significant benefit of ivermectin in terms of clinical efficacy or safety for severe COVID-19 patients. Consequently, the risk of bias due to this imbalance is low.

Additionally, the assumption of ICU requirement around 40% for estimating sample size was not met. Along with recruitment, outcomes in COVID-19 patients improved in direct relation to increasing vaccination coverage. Even, the difficulties in achieving the proposed sample size were partly due to a decrease in severe COVID-19 patients admitted to the institution. Furthermore, at the end of recruitment, ICU requirement rounded 10% of hospitalized patients, according to surveillance data from coronaviruscolombia.gov.co, which is lower than the outcomes obtained in our study. On the other hand, early reports of ivermectin that suggested potential benefits, and motivated more robust studies as randomized trials, have been rencently identified as high-risk-of-bias[19].

Table 2. Management in standard care

	Ivermectin (n = 37)		Placebo (n = 38)	
	n	%	n	%
Steroids	36	97.3	33	86.8
Prednisone	0	0.0	1	2.6
Deflazacort	0	0.0	0	0.0
Dexamethasone	35	94.6	32	84.2
Betamethasone	0	0.0	0	0.0
Hydrocortisone	0	0.0	0	0.0
Methylprednisolone	1	2.7	1	2.6
Antibiotics	7	18.9	4	10.5
Ampicillin	1	2.7	1	2.6
Piperacillin	5	13.5	2	5.3
Moxifloxacin	0	0.0	0	0.0
Ceftriaxone	0	0.0	0	0.0
Amoxicillin clavulanic acid	1	2.7	0	0.0
Cefepime	1	2.7	0	0.0
Ceftaroline	1	2.7	0	0.0
Ciprofloxacin	1	2.7	0	0.0
Meroperem	1	2.7	0	0.0
Linezolid	1	2.7	0	0.0
Anticoagulants	36	97.3	34	89.5
Low weight heparin	34	91.9	34	89.5
Fondaparinux	0	0.0	0	0.0
Unfractionated heparin	0	0.0	1	2.6
Rivaroxaban	1	2.7	0	0.0
Warfarin	2	5.4	0	0.0
Anti-aggregants	1	2.7	5	13.2
ASA	1	2.7	5	13.2
Clopidogrel	0	0.0	0	0.0

Non-exclusive

Table 3. Intention-to-treat analysis of clinical outcomes and adverse events

Outcome	Ivermectin (n = 37)	Placebo (n = 38)	Absolute difference (95%CI)	Hazard Ratio (95%CI)	p-value
Primary outcome					
Admission to the ICU	8 (21.6%)	6 (15.8%)	5.8% (-11.8% - 23.5%)	1.37 (0.53 - 3.57)	0.520
Secondary outcomes					
Invasive mechanical ventilation	7 (18.9%)	5 (13.2%)	5.7% (-10.8% - 22.3%)	1.34 (0.42 - 4.23)	0.619
Deaths	2 (5.4%)	4 (10.5%)	-5.1% (-17.3% - 7.1%)	0.43 (0.07 - 2.50)	0.348
Adverse events					
All adverse events	12 (32.4%)	11 (28.9%)	3.5% (-17.4% - 24.4%)	1.07 (0.46 - 2.47)	0.873
Serious adverse events	9 (24.3%)	7 (18.4%)	5.9% (-12.6% - 24.4%)	1.37 (0.51 - 3.69)	0.530
Other outcomes					
Days of ICU, mean	9.8	5.7	4.1 (-3.0 - 11.2)		
Days of IMV, mean	10.4	5.6	4.8 (-1.7 - 11.4)		

For primary, secondary, and harm outcomes, absolute differences correspond to risk differences. For other outcomes, the absolute difference corresponds to mean differences. **SC:** Standard of care, **ICU:** Intensive Care Unit, **IMV:** Invasive Mechanical Ventilation.

Low-risk-of-bias studies conclude no benefit of ivermectin which is in accordance with our findings. However, these limitations affected the statistical power and consequently the precision of effect estimates.

Lastly, many patients could not be included during the recruitment period because they had consumed ivermectin, likely because some clinical practice guidelines recommended its use as the antiparasitic agent of choice prior to starting systemic corticosteroids standard treatment for COVID-19. Besides, the dosage was not specified for anticoagulation or prophylaxis management, and some baseline characteristics could not be determined for all patients as para-clinical examinations were obtained as a secondary source from medical records. Lastly, vaccination status was not considered as a baseline variable, because in Colombia, the eligibility to COVID-19 vaccine was introduced by stages depending on risk level (health personnel, comorbidity, and age); hence, not all patients eligible in this study could access to COVID-19 vaccine at the time of disease onset.

Despite these limitations, our results align with the recently published evidence of higher methodological quality, provide data on Latin-American patients and contribute to cumulative efforts to evaluate ivermectin and other potential repurposed drugs for COVID-19. Remarkably, as a strength of our study, there were no failures in randomization or blinding, which provides security in data integrity and protection against potential biases.

In conclusion, we found that ivermectin in a single dose on day 1 of 400 µg/kg PO showed no significant benefit in reducing the requirement of ICU, IMV, or mortality for severe COVID-19 patients.

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Data availability. The data required to reproduce these findings is available upon reasonable request to the correspondence author

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Abbreviations

- ICU: Intensive Care Unit
- IMV: Invasive Mechanical Ventilation
- RD: Risk Differences
- HR: Hazard Ratio
- SD: Standard Deviation
- EC50: Half Maximal Effective Concentration
- INVIMA: Instituto Nacional de Vigilancia de Medicamentos y Alimentos
- ARDS: Acute Respiratory Distress Syndrome
- GMP: Good Manufacturing Practices

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