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Original Article

Single-dose oral ivermectin in mild and moderate COVID-19 (RIVET-COV): A single-centre randomized, placebo-controlled trial

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ABSTRACT

Introduction: Ivermectin is an antiparasitic drug which has in-vitro efficacy in reducing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) viral load. Hence, Ivermectin is under investigation as a repurposed agent for treating COVID-19.

Methods: In this pilot, double blind, randomized controlled trial, hospitalized patients with mild-to-moderate COVID-19 were assigned to a single oral administration of an elixir formulation of Ivermectin at either 24 mg or 12 mg dose, or placebo in a 1:1:1 ratio. The co-primary outcomes were conversion of RT-PCR to negative result and the decline of viral load at day 5 of enrolment. Safety outcomes included total and serious adverse events. The primary outcomes were assessed in patients who had positive RT-PCR at enrolment (modified intention-to-treat population). Safety outcomes were assessed in all patients who received the intervention (intention-to-treat population).

Results: Among the 157 patients randomized, 125 were included in modified intention-to-treat analysis. 40 patients each were assigned to Ivermectin 24 mg and 12 mg, and 45 patients to placebo. The RT-PCR negativity at day 5 was higher in the two Ivermectin arms but failed to attain statistical significance (Ivermectin 24 mg, 47.5%; 12 mg arm, 35.0%; and placebo arm, 31.1%; p-value = 0.30). The decline of viral load at day 5 was similar in each arm. No serious adverse events occurred.

Conclusions: In patients with mild and moderate COVID-19, a single oral administration of Ivermectin did not significantly increase either the negativity of RT-PCR or decline in viral load at day 5 of enrolment compared with placebo.

1. Introduction

The COVID-19 pandemic has become a major public health challenge, affecting over 175 million people globally and causing more than 3 million deaths [1]. Although most patients have a mild illness, the contagiousness of the causative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) contributes to rapid spread of infection. To date, no antiviral agent has been shown to be conclusively beneficial in

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non-severe COVID-19.

New and repurposed drugs are being trialled in mild-to-moderate COVID-19 to help suppress viral transmission and prevent disease progression. Ivermectin is one such repurposed drug which has an established safety record with over 2.5 billion doses dispensed over the past three decades [2]. Originally introduced as an anthelminthic agent, it has recently been found to possess antiviral, anti-inflammatory and anti-cancer actions as well [2]. A broad-spectrum antiviral effect against single stranded RNA viruses such as HIV-1, dengue, yellow fever, West Nile virus and others has been observed in preclinical studies [3–5]. This is attributed to a host directed action against the importin α/β protein which is used by the viral nucleocapsid to enter the host nucleus [5].

Recently, an in-vitro study by Caly et al. demonstrated that micromolar concentrations (2–2.5 μg/mL) of Ivermectin can reduce viral load by 5000-fold at 48 h in VERO/hSLAM cells [6]. Although equivalent plasma concentrations are difficult to achieve with routine antiparasitic doses of Ivermectin (150–400 μg/kg), there are inherent differences in the in-vivo and in-vitro responses to drugs. Ivermectin may act through its metabolites, get concentrated three-fold in lung tissue and have additional immunomodulatory actions at routine doses [7,8]. Till date, only a few small trials of ivermectin in COVID-19 patients have used routine clinical doses in tablet form and have shown conflicting results [9–12]. Single dose of Ivermectin was found to hasten viral load decline in the study by Samaha et al. (using 150 μg/kg) [10] but not in the study by Chaccour et al. (using 400 μg/kg) [12]. Doses higher than those approved for clinical indications (1–2 g/kg) have been shown to be well tolerated [13,14]. Hence this pilot study was designed to determine the efficacy and safety of a novel elixir formulation of ivermectin aimed to maximize oral bioavailability of ivermectin in COVID-19.

2. Methods

We conducted a randomized, placebo-controlled, three-arm, parallel group study of a single oral administration of Ivermectin elixir at two dose strengths (12 mg and 24 mg) in patients with non-severe COVID-19. The study was conducted at the COVID-19 facility at the National Cancer Institute, All India Institute of Medical Sciences, New Delhi. An independent data and safety monitoring board oversaw the conduct of the trial. The protocol was approved by the Institutional Ethics Committee vide ref No. IEC-456/22.05.2020. The trial was registered in the Clinical Trial Registry – India (CTRI) vide ref No CTRI/2020/06/026001.

2.1. Patients

Consecutive patients aged above 18 years admitted at the trial site were considered eligible for inclusion if they were diagnosed with non-severe COVID-19, i.e., room air saturation (SpO_2) >90%, and with no hypotension or requirement of mechanical ventilation. Diagnosis of COVID-19 was based on a positive result on either SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) or a rapid antigen test. Patients were excluded if they did not give informed consent. Other exclusion criteria included: pregnancy or lactation, known hypersensitivity to ivermectin, chronic kidney disease with creatinine clearance <30 mL/min, elevated transaminase levels (>5X upper limit of normal), myocardial infarction or heart failure within 90 days prior to enrolment, prolonged corrected QT interval (>450 ms), any other severe comorbidity as per investigator's assessment, or enrolment in another clinical trial.

2.2. Trial procedures

All included subjects underwent a detailed clinical evaluation. Comorbidities including diabetes mellitus, systemic hypertension, coronary artery disease, chronic obstructive pulmonary disease, and tuberculosis were recorded. The baseline chest radiograph was graded using the Brixia score [15]. Baseline laboratory investigations were performed, and patients were managed according to the institutional management protocol by the clinical team. The patients were followed up for a minimum of 14 days or till hospital discharge, whichever was later. All treatments administered during hospital stay were recorded.

2.3. Interventions and randomization

In preparation for the trial, our group performed a pharmacokinetic simulation study of the dosing requirements for achieving an Ivermectin lung concentration of 2–2.5 μg/mL (unpublished work). The details of the same are provided in the Supplementary Appendix. Accordingly, we found that an alcohol-based elixir formulation of Ivermectin at a dose of 400 μg/kg administered after a meal may achieve a plasma Ivermectin concentration >150 ng/mL. A 20 mL dose of elixir formulation consisted of accurately weighted ivermectin (12 or 24 mg) in ethanol (40%v/v) with syrup base which was suitability flavoured and coloured. Representative samples were subjected for the quality control to ensure the drug content and batch uniformity. It was compounded and dispensed from the in-house pharmacy by a qualified pharmacist. Similar placebos were also prepared without ivermectin and formulations were coded before delivery to the trial site. After baseline evaluation, eligible patients were randomized in a 1:1:1 ratio to receive a single dose of Ivermectin 12 mg or 24 mg elixir, or identical placebo. A variable block randomization stratified based on disease severity (mild or moderate illness) was done using a centralized telephone-based system and the patients, investigators, caregivers, and statisticians were blinded to the allocation. The intervention was given 2 h after breakfast on the day of randomization.

2.4. Virological assessment

All randomized patients underwent a baseline oropharyngeal and nasopharyngeal swab for COVID-19 RT-PCR. Samples were transported in a standardized viral transport medium at 2–8° Celsius and were processed within 24 h. RNA was extracted using an FDA-approved automated magnetic bead-based extraction system (Genolution, South Korea). For real time RT-PCR, Quantstudio™ (Thermofisher Scientific, Waltham, MA USA) was used. To determine sample adequacy and ascertain adequate extraction of RNA, an endogenous control was used for each sample as part of the assay. A reference control was run in 8 serial dilutions to make a standard curve based on cycle threshold (CT) values at each dilution. Furthermore, with each set of samples one reference each with high and low CT value was run, hence a semi-quantitative estimate of viral load (expressed as $\log_{10}$ viral copies/mL) was provided. In patients with positive baseline RT-PCR report, follow up RT-PCR was performed on days 3, 5 and 7 of enrolment to estimate the change in viral load.

2.5. Outcomes

The primary outcomes were to evaluate the efficacy of the two different doses of oral ivermectin compared with placebo in reduction of viral load (estimated from CT value) and conversion to negativity of nasopharyngeal/oropharyngeal RT-PCR on day 5 after intervention. The secondary outcomes included qualitative and quantitative results of RT-PCR on day 3 and 7 after intervention; time to clinical resolution; frequency of clinical worsening; clinical status on day 14; and hospital-free days at day 28. The clinical status was expressed using the 8-point World Health Organization (WHO) ordinal scale (Supplementary Table 1) [17]. The frequency of total and serious adverse events was documented.

2.6. Statistical analysis

As this was a pilot trial of a repurposed drug in a pandemic setting, a sample size of convenience was chosen. All randomized patients who

received a study medication were included in the intention-to-treat (ITT) analysis. Among these, patients with a positive nasopharyngeal/oropharyngeal SARS-CoV-2 RT-PCR on the day of enrolment were included in the modified intention-to-treat (mITT) analysis. The primary outcomes (viral load decline and conversion to negative RT-PCR at day 5) were assessed in the mITT population. Clinical outcomes were assessed in the mITT population, whereas the adverse effects were evaluated in the ITT population. Statistical analysis was performed using STATA (version 14). Inter-group comparisons of categorical outcome variables were performed using Fisher's exact test. Inter-group comparisons of continuous outcome variables were performed using analysis of variance (ANOVA) or Kruskal-Wallis test. The comparisons of decline of $\log_{10}$ viral copies/mL between individual study groups were performed using *t*-test and were expressed as mean difference with 95% confidence intervals (CI). In the presence of a negative RT-PCR test on a follow-up sample, the viral load was imputed to 0 on the log scale. A p-value of less than 0.05 denoted statistical significance.

3. Results

Between 28 July 2020 and 29 September 2020, a total of 278 patients with mild or moderate COVID-19 were screened, out of which 157 eligible patients were randomized. Among these, 5 patients subsequently withdrew consent. The ITT population (n = 152) included 51 patients assigned to ivermectin 24 mg, 49 patients assigned to ivermectin 12 mg, and 52 patients assigned to placebo. Among these, 125 patients had a positive SARS-CoV-2 RT-PCR on day of enrolment and were included in the mITT analysis. The mITT population included 40 patients in ivermectin 24 mg arm, 40 patients in ivermectin 12 mg arm, and 45 patients in the placebo arm. In the mITT group, 80 patients (64%) had mild illness, while 45 patients (36%) had moderate illness (Fig. 1).

The mean (SD) age of participants was 35.3 (10.4) years and majority (88.8%) were males. The proportions of asymptomatic, mild, and moderately ill patients were similar in the three groups. Baseline clinical severity by WHO ordinal scale was 3 (i.e., hospitalized, not requiring supplemental oxygen) in the majority (92%) of patients, and was 4 (i.e., hospitalized, requiring supplemental oxygen) in the remaining patients. The median duration of symptoms at the time of enrolment was 5 days (interquartile range, 3–7 days) and was similar in the three arms. There were no significant differences in the comorbidities, presenting symptoms or baseline laboratory parameters in the three arms (Table 1 and Supplementary Table 2). A minority (10%) of patients received concurrent antiviral therapies including remdesivir, favipiravir or hydroxychloroquine as decided by site physicians without any difference in the three arms (Supplementary Table 3).

3.1. Primary outcomes

The proportion of subjects who became RT-PCR negative on day 5 of enrolment was numerically higher with ivermectin 24 mg arm (47.5%) compared with ivermectin 12 mg arm (35.0%) and placebo arm (31.1%) (Table 2); however, the difference was not statistically significant (p-value = 0.30) (Fig. 2a). In subjects who received intervention early in the course of illness (within 4 days of symptom onset), Ivermectin 24 mg arm had numerically higher negativity of RT-PCR at day 5 compared with placebo arm (47.0% vs 28.6%, p-value = 0.38). The viral load at enrolment or baseline disease severity did not impact the efficacy of the therapies to achieve negative RT-PCR at day 5.

There was no significant difference in the viral load (expressed as $\log_{10}$ viral copies/mL) in the three arms, either at baseline or at day 5 of enrolment, or in the decline of viral load between the ivermectin arms and placebo at day 5 (Table 3, Supplementary Table 4 & Fig. 2b). Baseline disease severity did not affect the efficacy of ivermectin in achieving viral load decline (Supplementary Tables 5–8).

3.2. Secondary outcomes

There was no significant difference in the three arms in terms of conversion to negative RT-PCR (Table 2), or in the decline of viral load at either day 3 or day 7 of enrolment (Table 3). Secondary clinical outcomes were also similar in the three arms (Supplementary Table 9). There was no difference in the mean (SD) duration of symptom resolution in the three groups [4.26 (2.65) days in ivermectin 24 mg arm, 4.76

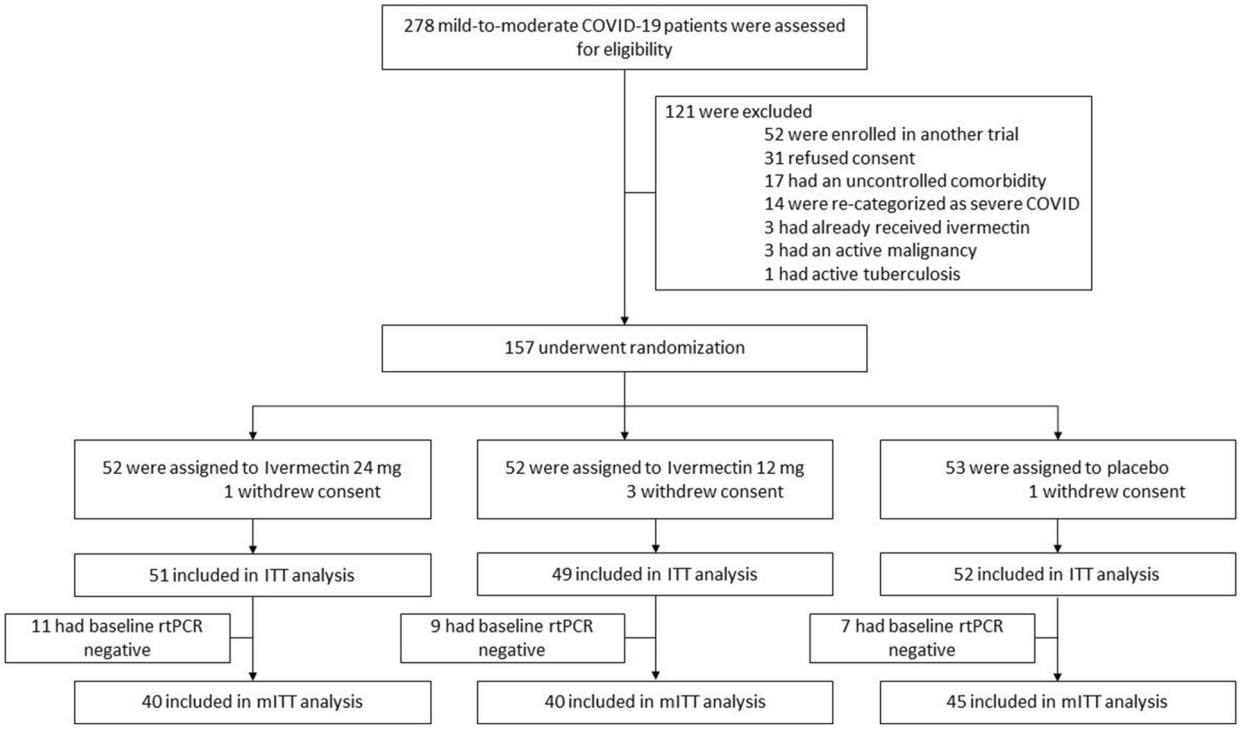

Fig. 1. Trial profile: subject enrolment, randomization and outcome assessment.

Table 1
Demographic details and baseline clinical characteristics of patients included in modified intention-to-treat (mITT) analysis.

Variable	Ivermectin 24 mg (n = 40)	Ivermectin 12 mg (n = 40)	Placebo (n = 45)	p value
Age (years), mean (SD)	34.3 (10.45)	36.3 (10.54)	35.3 (10.52)	0.64
Sex, n (%)				0.77
- Male	37 (92.5)	35 (87.5)	39 (86.7)	
- Female	3 (7.5)	5 (12.5)	6 (13.3)	
BMI (kg/m^2), mean (SD)	24.9 (3.50)	25.354 (3.53)	25.5 (3.51)	0.77
Severity, n (%)				0.80
- Mild	24 (60.0)	27 (67.5)	29 (64.4)	
- Moderate	16 (40.0)	13 (32.5)	16 (35.6)	
Comorbidities, n (%)				
- Hypertension	3 (7.5)	6 (15.0)	5 (11.1)	0.60
- Diabetes mellitus	2 (5.0)	4 (10.0)	5 (11.1)	0.63
- Post-TB sequelae	3 (7.5)	0 (0.0)	1 (2.2)	0.21
- Coronary artery disease	0 (0.0)	0 (0.0)	1 (2.2)	1.00
Smoking history, n (%)				0.68
- Active	1 (2.5)	4 (10.0)	4 (8.9)	
- Former	3 (7.5)	2 (5.0)	2 (4.4)	
Symptoms, n (%)				
- Fever	23 (57.5)	20 (50.0)	23 (51.1)	0.81
- Cough	14 (35.0)	21 (52.5)	24 (53.3)	0.19
- Breathlessness	14 (35.0)	12 (30.0)	16 (35.6)	0.89
- Sore throat	10 (25.0)	10 (25.0)	12 (26.7)	1.00
- Fatigue	8 (20.0)	7 (17.5)	6 (13.4)	0.76
- Headache	2 (5.0)	2 (5.0)	3 (6.7)	1.00
- Myalgia	12 (30.0)	7 (17.5)	13 (28.9)	0.39
- Nausea/vomiting	1 (2.5)	3 (7.5)	1 (2.2)	0.52
- Loss of taste/smell	4 (10.0)	3 (7.5)	3 (6.7)	0.92
- Chest pain	0 (0.0)	2 (5.0)	2 (4.4)	0.55
Asymptomatic at the time of enrolment, n (%)	9 (22.5)	11 (27.5)	8 (17.7)	0.53
Duration of symptoms prior to enrolment (days), median (IQR)	4 (3–7)	5 (3–7)	4 (3–6)	0.88
Early presentation (symptoms <4 days), n (%)	17 (51.5)	16 (48.5)	21 (51.2)	1.00
WHO Ordinal Scale at baseline, n (%)				
- 3	38 (95.0)	35 (87.5)	42 (93.3)	
- 4	2 (5.0)	5 (12.5)	3 (6.7)	0.50
Baseline chest radiograph severity score, n (%)[a]				
- <2	36 (90.0)	35 (89.7)	41 (91.1)	1.00
- >2	4 (10.0)	4 (10.3)	4 (8.9)	
High viral load at baseline (CT < 24), n (%)	18 (45.0)	18 (45.0)	21 (46.7)	1.00

SD – standard deviation, BMI – body mass index, TB – tuberculosis, CAD – coronary artery disease, IQR – interquartile range, WHO – World Health Organization, CT – cycle threshold.
[a] - Brixia score; data available for 124 out of 125 patients.

(2.44) days in the ivermectin 12 mg arm, and 4.58 (2.94) days in the placebo arm, p-value = 0.77]. Most patients were discharged from the hospital by day 14 of enrolment in each group (hospital discharge rate at day 14: ivermectin 24 mg, 95%; ivermectin 12 mg, 92.5%; and placebo, 86.7%; p-value = 0.42). The proportion of patients with clinical worsening (defined as an increase in the WHO ordinal score during treatment) was similar in the three groups (ivermectin 24 mg, 7.5%; ivermectin 12 mg, 5.0%; and placebo, 11.1%; p-value = 0.65).

3.3. Adverse events

There were no serious adverse events reported during the study (Supplementary Table 10). The frequency of all adverse events in the ITT population was similar in the three arms (ivermectin 24 mg, 11.8%; ivermectin 12 mg, 16.3%; and placebo, 11.5%; p-value = 0.76). The most frequent adverse event was epigastric burning sensation, which occurred in 17 (11.2%) patients.

4. Discussion

In this double-blind, randomized, placebo-controlled trial, we examined the efficacy and safety of Ivermectin at two doses (24 mg and 12 mg) in the management of non-severe COVID-19. We demonstrated that there was no statistically significant difference in the decline in viral load at day 5 between the Ivermectin arms and placebo. Patients in the Ivermectin 24 mg arm demonstrated a numerically higher rate of conversion to negative RT-PCR at day 5 compared to the placebo; however, this was not statistically significant.

Ivermectin has a plausible broad spectrum anti-viral action by inhibiting the importin α/β protein of the host [3]. The inhibition of this protein blocks the entry of the viral nucleocapsid into host nucleus for subsequent replication. In Vero/hSLAM cells, Caly et al. demonstrated that a single application of Ivermectin to achieve concentrations of 2–2.5 μg/mL enable a 5000-fold reduction in the viral load within 48 h [6]. However, these micromolar doses difficult to achieve in-vivo with the FDA-approved dose (200 μg/kg) of Ivermectin in tablet form [18]. Ivermectin bioavailability increases 2.5-fold when given alongwith a fat-rich meal or in an alcohol-based formulation [14,19], and it preferentially distribute into the lung tissue [16]. Hence, we administered a higher dose (400 μg/kg) of Ivermectin in an alcohol-based elixir after breakfast. However, even higher doses (up to 1–2 g/kg) may be required to achieve optimal therapeutic doses against SARS-CoV-2 [13,14]. Furthermore, Ivermectin may have immunomodulatory actions at nanomolar doses by inhibiting the nicotinic acetylcholine receptor (nAChR), which may act as a receptor for SARS-CoV-2 and drive dysregulated cytokine release from macrophages [20,21].

In our study, Ivermectin did not improve the time to symptom recovery or clinical status at day 14 after drug administration. Similar results were observed in the other randomized trials of Ivermectin [11, 22]. *López-Medina* et al. showed that a five-day course of ivermectin (300 μg/kg) failed to hasten symptom resolution in mild COVID-19 compared with placebo [11]. In contrast, Samaha et al. demonstrated that a single administration of Ivermectin can hasten viral load decline at day 3 [10]. We performed RT-PCR at days 3, 5 and 7 to serially evaluate decline in viral load with ivermectin compared with placebo. Our rationale was that faster viral load decline may enable non-severe COVID-19 patients to become non-infectious sooner, thereby limiting the contagion [23]. Hence, the trend towards increased viral negativity at day 5 with ivermectin 24 mg in our trial, particularly among mildly ill patients, encourages further exploration in this regard.

In a retrospective study of hospitalized patients in Florida, patients who received Ivermectin were found to have a significantly lower mortality that those who did not (15% versus 25%) [24]. The mortality benefit remained significant after propensity-matched analysis and adjusting for confounders. However, they included patients with greater illness severity than our study population, illustrated by lack of mortality in our trial. Furthermore, the greater use of concurrent therapies and retrospective design preclude drawing definitive conclusions from their data. The immunomodulatory rather than antiviral effect of Ivermectin may be hypothetically more important in moderate and severe COVID-19 [25].

There were no serious adverse events in our trial. Since we have used a novel elixir-based formulation with an aim to maximize plasma bioavailability of Ivermectin, this reassures us regarding its safety for further study. The frequency of mild adverse events was similar with

Table 2
Negativity of SARS-CoV-2 RT-PCR at various time points in the patients included in modified intention-to-treat (mITT) analysis.

Variable	Placebo	Ivermectin 24 mg	RR (95% CI), *p value*: Ivermectin 24 mg vs placebo	Ivermectin 12 mg	RR (95% CI), *p value*: Ivermectin 12 mg vs placebo	p value
Negative RT-PCR in mITT population, n/N (%)						
- Day 3 RT-PCR	7/45 (15.6)	3/40 (7.5)	0.48 (0.14–1.59), *0.32*	7/40 (17.5)	1.12 (0.44–2.84), >*0.99*	0.42
- Day 5 RT-PCR	14/45 (31.1)	19/40 (47.5)	1.53 (0.89–2.65), *0.18*	14/40 (35.0)	1.12 (0.61–2.05), *0.82*	0.30
- Day 7 RT-PCR[a]	16/42 (38.1)	16/36 (44.4)	1.17 (0.68–1.98), *0.65*	13/36 (36.1)	0.95 (0.53–1.68), >*0.99*	0.79
Negative RT-PCR in mild disease, n/N (%)						
- Day 3 RT-PCR	4/29 (13.8)	0/24 (0.0)	0.00 (0.00–1.07), *0.12*	3/27 (11.1)	0.80 (0.22–2.96), >*0.99*	0.18
- Day 5 RT-PCR	7/29 (24.1)	8/24 (33.3)	1.38 (0.60–3.21), *0.55*	6/27 (22.2)	0.92 (0.36–2.32), >*0.99*	0.66
- Day 7 RT-PCR	9/29 (31.0)	10/23 (43.5)	1.40 (0.69–2.86), *0.40*	7/25 (28.0)	0.90 (0.39–2.02), >*0.99*	0.52
Negative RT-PCR in moderate disease, n/N (%)						
- Day 3 RT-PCR	3/16 (18.8)	3/16 (18.8)	1.00 (0.26–3.85), >*0.99*	4/13 (30.8)	1.64 (0.48–5.71), *0.67*	0.74
- Day 5 RT-PCR	7/16 (43.8)	9/16 (56.2)	1.29 (0.64–2.68), *0.72*	8/13 (61.5)	1.41 (0.69–2.92), *0.46*	0.66
- Day 7 RT-PCR	7/13 (53.8)	6/13 (46.2)	0.86 (0.38–1.86), >*0.99*	6/11 (54.5)	1.01 (0.46–2.14), >*0.99*	1.00
Negative RT-PCR at day 5 by duration of clinical symptoms, n/N (%)[b]						
- Early presenters (<4 days)	6/21 (28.6)	8/17 (47.0)	1.65 (0.72–3.84), *0.32*	4/16 (25.0)	0.87 (0.30–2.43), >*0.99*	0.38
- Late presenters (>4 days)	7/20 (35.0)	9/16 (56.2)	1.61 (0.78–3.41), *0.31*	8/17 (47.0)	1.34 (0.62–2.95), *0.52*	0.45
Negative RT-PCR at day 5 by viral load at baseline, n/N (%)						
- High viral load (CT < 24)	2/21 (9.5)	4/18 (22.2)	2.33 (0.56–10.10), *0.39*	5/18 (27.8)	2.92 (0.74–12.07), *0.22*	0.33
- Low viral load (CT > 24)	12/24 (50.0)	15/22 (68.2)	1.36 (0.83–2.30), *0.24*	9/22 (40.9)	0.82 (0.42–1.54), *0.57*	0.19

SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2, RT-PCR – reverse transcriptase polymerase chain reaction, RR – relative risk, CI – confidence intervals, CT – cycle threshold.
[a] - RT-PCR results on day 7 available for 114 out of 125 patients included in mITT analysis.
[b] - This analysis was performed only in patients who were symptomatic at time of enrolment.

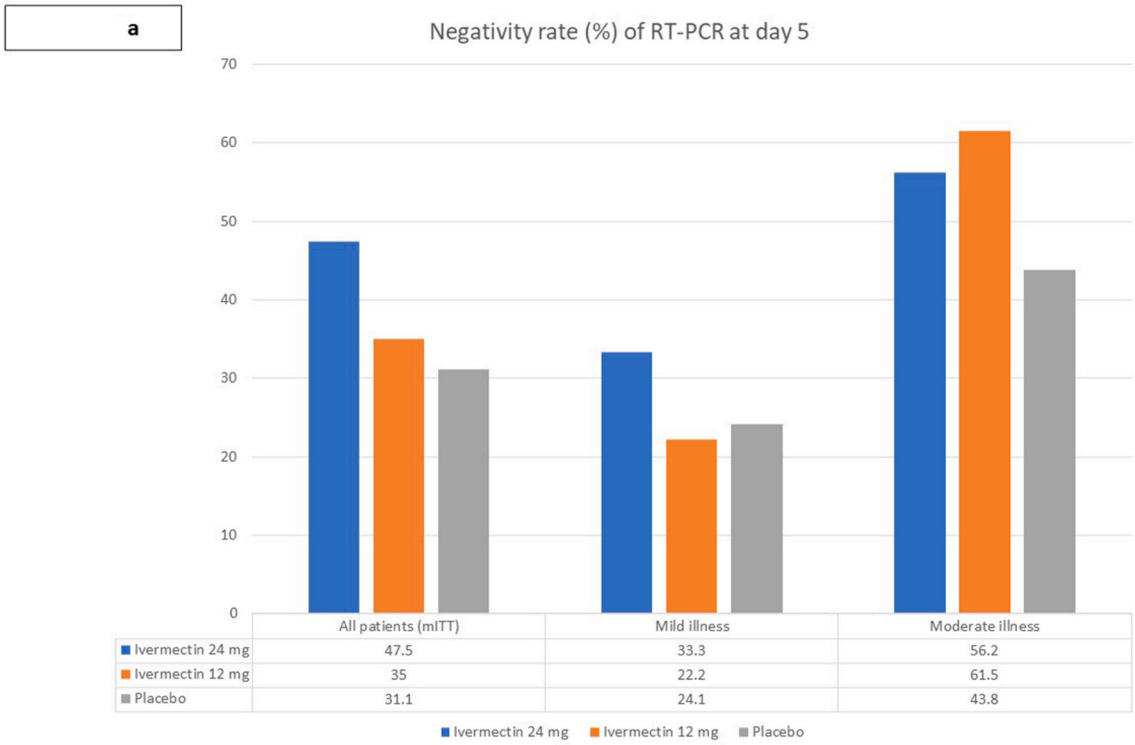

Fig. 2a. (a)Negativity rate of RT-PCR at day 5 of enrolment in the modified intention-to-treat population.

ivermectin at either dose or placebo. Other studies of Ivermectin in COVID-19 have also found a low rate of adverse events [22,26]. The predominant adverse event in our study was transient burning sensation in the epigastrium which could be attributed to the alcohol-based elixir preparation.

The major limitation of our study was that it was conducted at a single centre with a relatively small sample size. Most of our patient population was male and relatively young (mean age, 35.3 years) with

Table 3
Viral load (expressed as log_{10} viral copies/mL) by RT-PCR at various time points in all patients included in the modified intention-to-treat analysis.

Variable	Ivermectin 24 mg (n = 40)	Ivermectin 12 mg (n = 40)	Placebo (n = 45)	p value
Viral load at enrolment (log_{10} viral copies), mean (SD)	5.54 (2.02)	5.79 (1.82)	6.12 (1.73)	0.35
Viral load at day 3 (log_{10} viral copies/mL), mean (SD)				
- Absolute	3.89 (1.88)	3.85 (2.17)	3.96 (2.00)	0.97
- Decrease (day 0 to day 3)	1.65 (1.63)	1.94 (1.86)	2.16 (1.74)	0.40
Viral load at day 5 (log_{10} viral copies/mL), mean (SD)				
- Absolute	2.49 (2.50)	2.75 (2.30)	3.04 (2.44)	0.58
- Decrease (day 0 to day 5)	3.05 (2.29)	3.04 (2.05)	3.08 (1.98)	0.99
Viral load[a]at day 7 (log_{10} viral copies/mL), mean (SD)[a]				
- Absolute	1.95 (1.84)	2.30 (1.99)	2.37 (2.20)	0.62
- Decrease (day 0 to day 7)	3.56 (2.51)	3.56 (1.83)	3.88 (2.19)	0.76

[a] - RT-PCR viral load results on day 7 available for 113 out of 125 patients included in mITT analysis.

few comorbidities which reflects the demographics of the catchment area of our centre. Such a patient population is likely to have an uncomplicated disease course [27,28]. Furthermore, in the absence of previous clinical trials and considering the urgency of the research question, our sample size was exploratory. Hence, we cannot exclude the possibility that a similarly conducted study in a larger and more diverse population could have uncovered clinical efficacy of Ivermectin, if such benefit indeed exists.

Secondly, the elixir formulation of ivermectin used by us is not yet commercially available. Although our Ivermectin formulation and dosing strategy was determined by a simulation study to attain an adequate drug concentration in the lung, further pharmacokinetic studies are necessary to define the optimal therapeutic dosing of Ivermectin in COVID-19. Furthermore, Ivermectin has a plasma half-life of 18 h and does not accumulate on repeat dosing [14]. Whether multiple doses of Ivermectin in this disease may be superior to a single dose strategy is currently unknown. Hence, the translation of our findings to the use of Ivermectin tablet at various dosing strengths and frequencies in clinical practice requires caution.

Finally, in our study we have recruited patients irrespective of the duration of illness prior to enrolment. The median duration of symptoms at randomization was 5 days in the three arms. Hence, a significant number of patients had a negative RT-PCR result at baseline and were excluded from the mITT analysis. Further, the antiviral benefits of Ivermectin may be maximal early in the disease course.

In conclusion, in this exploratory randomized placebo-controlled trial of a single oral administration of Ivermectin elixir at two different dosage strengths (12 mg and 24 mg) in patients with mild and moderate COVID-19, no significant difference in either the negativity of RT-PCR or decline in viral load at day 5 of enrolment was observed. There were no safety concerns with the use of Ivermectin at either dose. Larger studies employing different dosing regimens of Ivermectin are required to further elucidate its potential role in treatment of COVID-19.

Authorship statement

All authors meet the ICMJE authorship criteria. Anant Mohan, Pawan Tiwari, Saurabh Mittal, Ravindra Mohan Pandey and Randeep Guleria contributed to the study conception and design. Material preparation and data collection were performed by Pawan Tiwari, Tejas Menon Suri, Saurabh Mittal, Ankit Patel, Avinash Jain, Ujjalkumar Subhash Das, Tarun Krishna Boppana, Sushil Suresh Shelke, Angel Rajan Singh, Tanima Dwivedi, Biswajeet Sahoo, Anuja Pandit, Shweta Bhopale, Saurabh Vig, Ritu Gupta, Nishkarsh Gupta, Rakesh Garg, Ved Prakash Meena. Analysis was performed by Ravindra Mohan Pandey, Velpandian Thirumurthy, Shet Masih and Shelly Mahajan. The first draft

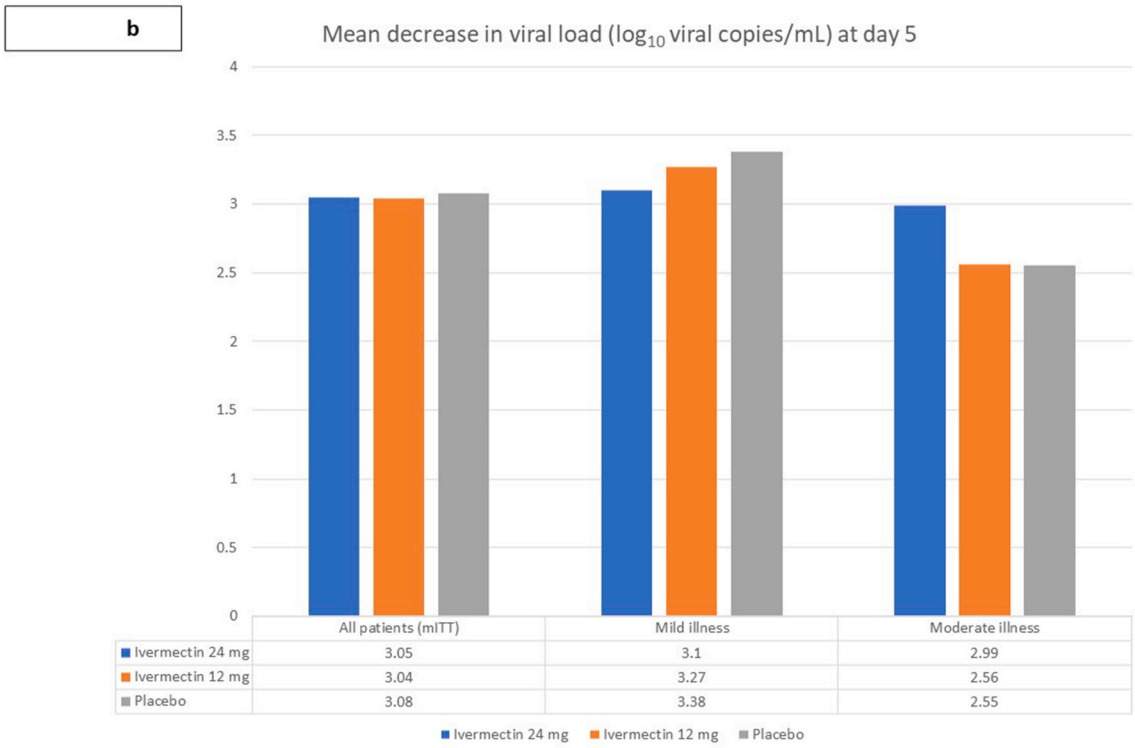

Fig. 2b. (b)Mean decrease in viral load (expressed as log10 viral copies/mL) at day 5 of enrolment.

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Declaration of competing interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2021.08.021.

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