Research Paper

Ivermectin for Management of COVID-19 in Iranian Children: Results of Two Randomized, Placebo-controlled Clinical Trials

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ABSTRACT

Background: The global search for effective COVID-19 treatments extended to the use of ivermectin, a drug with potential antiviral properties. However, evidence remains conflicting, especially for children.

Objectives: This study aimed to investigate the efficacy and safety of ivermectin for treating COVID-19 in Iranian children through two independent randomized, placebo-controlled trials.

Methods: Two multicenter, randomized, double-blind, placebo-controlled clinical trials were conducted to evaluate the efficacy of ivermectin in 195 children with COVID-19, including 66 inpatients (35 in the ivermectin group and 31 in the placebo group) and 129 outpatients (70 in the ivermectin group and 59 in the placebo group). The treatment group received a daily oral dose of ivermectin (400 µg/kg/day, 6 mg tablet) for three consecutive days, while the control group received an identical placebo. The primary outcome was disease prognosis. The secondary outcomes for inpatients included duration of hospitalization, need for pediatric intensive care unit (PICU) admission, need for oxygen, adverse events, and mortality. For outpatients, secondary outcomes were need for hospitalization, need for PICU admission, viral clearance, adverse events, and mortality.

Results: All inpatients in both ivermectin and placebo groups fully recovered from COVID-19. Among outpatients, 98.6% recovered after ivermectin use, and 100% recovered with placebo. A significant difference was found in the need for PICU admission among inpatients (2.8% in the ivermectin group and 25.8% in the placebo group; P=0.010). Additionally, viral clearance differed significantly, with more patients in the ivermectin group testing negative for COVID-19 on day six than in the placebo group (P=0.042). The length of hospital stay was similar for both groups.

Conclusions: Although ivermectin can reduce the need for PICU admission among inpatient children with COVID-19, it did not improve overall clinical recovery or length of hospital stay. For outpatients, ivermectin does not enhance recovery or reduce the need for hospitalization but showed promising viral clearance effects. Considering all aspects, the use of ivermectin in the treatment of children with COVID-19 cannot be recommended.

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Introduction

Although children were initially thought to be less susceptible than adults to COVID-19, the incidence and mortality rates among pediatric patients led to significant concerns [1, 2]. Various vaccines using different technologies such as viral vectors, mRNA, and protein subunits have been developed, but their effectiveness in reducing the disease burden and related complications is challenged by the emergence of new types of viruses and waning immunity [3]. More than five years have passed since the COVID-19 pandemic, but no single universal treatment still exists; however, several protocols for therapy and clinical management have been established to effectively manage the disease, especially in high-risk and hospitalized patients [4]. This highlights the need for effective, safe, and affordable therapeutic options, particularly for low-income countries where access to advanced treatments is limited.

Ivermectin is an Food and Drug Administration (FDA)-approved medication for certain parasitic diseases such as intestinal strongyloidiasis and onchocerciasis (river blindness). It is also used to treat enterobiasis and lymphatic filariasis in combination with other drugs, while some topical forms of it are approved for external parasites such as head lice and skin conditions such as rosacea [5-7]. Ivermectin has demonstrated multifaceted activities such as antiparasitic, antibacterial, antibuccal, anti-inflammatory, and immunomodulatory activities, but its clinical efficacy against viral infections remains unknown [8, 9]. Ivermectin is generally well-tolerated with a good safety profile at standard doses of 0.2-0.4 mg/kg for 1-2 days in children, though it is not recommended in children under 15 kg or under five years of age [10-13]. The half-life of ivermectin in humans is 12-36 hours, with metabolites persisting for several days [9]. However, as of 2025, ivermectin is not approved by the FDA for any viral infections, including COVID-19. The FDA has explicitly stated that ivermectin is not authorized or approved for preventing or treating viral diseases, and misuse or overdoses can be dangerous [14].

Despite numerous research studies demonstrating positive results of ivermectin in treating COVID-19, the findings remain inconclusive and sometimes conflicting [7, 9, 10, 13, 15-18]. Most clinical trials and studies on ivermectin for COVID-19 have focused on adult populations, and pediatric data remain very limited. The standard dose of ivermectin as a potential therapeutic for COVID-19 in children is not well studied or reported. Dosing regimens in adults vary from 200 µg/kg to 600 µg/kg for single or multiple doses, but clear, well-studied, standardized dosing guidelines for children with COVID-19 are lacking [15]. Due to insufficient clear evidence, ivermectin use in children with COVID-19 is controversial and generally restricted to clinical trial settings. Given the paucity of high-quality randomized trials in pediatric populations and the conflicting results observed in adults, a significant knowledge gap remains regarding its clinical efficacy and safety in children. To address this, we conducted two multicenter, randomized, double-blind, placebo-controlled trials to assess whether ivermectin improves disease prognosis, clinical recovery, and viral clearance in both inpatient and outpatient children with COVID-19, describing their characteristics and outcomes. We hypothesize that ivermectin administration improves clinical recovery and reduces disease progression compared with placebo in pediatric patients with COVID-19.

Materials and Methods

Study design and participants

Two concurrent multicenter, randomized, double-blind, placebo-controlled clinical trials were conducted to rigorously assess the efficacy and safety of ivermectin in pediatric patients diagnosed with COVID-19. One trial was conducted in an outpatient setting, and the other in an inpatient setting. Diagnosis was confirmed in all participants via a positive result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using a highly sensitive and specific real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay performed on nasopharyngeal swab specimens. Participant recruitment started in February 2021 and was completed in August 2021.

Eligible participants were children aged 5-18 years, weighing at least 15 kg, with confirmed COVID-19. Exclusion criteria were any known hepatic or renal dysfunction, autoimmune diseases, history of hypersensitivity to ivermectin, and concurrent use of warfarin, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers (ARBs). Furthermore, outpatients who had received antiviral therapy before or during the study period were excluded to avoid confounding effects.

Inpatients were enrolled from Buali Sina Hospital, a tertiary referral center for pediatric COVID-19 cases in Sari, Iran, while outpatients were recruited from family physicians', pediatricians', and pediatric infectious disease specialists' clinics across six cities in Mazandaran

Province, Iran. During the study period, COVID-19 vaccination had not yet been introduced for children in Iran, eliminating vaccine influence on study outcomes.

Randomization

Eligible participants were randomly assigned to two groups of intervention and placebo in a 1:1 ratio. Randomization was done by a methodologist using R software (version 4.0.4). In the outpatients, from among a randomized list of 140 children, 72 were allocated to the intervention group and 68 to the placebo group. In inpatients, from among 82 children, 42 were allocated to the intervention group and 40 to the placebo group. Stratified, non-sequential assignment was used to maintain balance across groups. Allocation concealment was ensured for participants, caregivers, and clinicians to preserve blinding. The pharmacist preparing and dispensing the medication was unblinded due to operational needs, with strict protocols to prevent bias.

Interventions

Participants in the intervention group received oral tablets of ivermectin at a dose of 400 mcg/kg/day for 3 consecutive days. The tablets contained 6 mg of ivermectin (Alborz Daru Company, Iran), and the dose was determined by the participant's weight to achieve the target dose. The control group received placebo tablets identical in appearance, taste, smell, shape, and packaging. Both groups concurrently received the national standard of care (SOC) for COVID-19.

Data collection

The baseline demographic and clinical data, including age, sex, body mass index (BMI), place of residence, and preexisting medical conditions, were collected. Clinical assessments on the first intervention day included respiratory rate, oxygen saturation, chest auscultation, vital signs, symptom severity (classified as mild, moderate, or severe), medications, adverse events, and radiological findings when available. Outpatients underwent repeated RT-PCR testing six days after symptom onset to assess possible viral clearance. Daily data were recorded using standardized checklists by trained personnel.

Primary and secondary outcomes

In the inpatient group, the primary outcome was clinical recovery, defined as improvement during hospitalization, including resolution of major symptoms such as tachypnea and dry cough, along with an increase in oxygen saturation by day 7. Disease progression was defined as worsening of clinical symptoms. In the outpatient group, the primary outcomes were clinical recovery (defined as resolution of primary symptoms by day 6), disease progression requiring hospitalization due to symptom deterioration, and a negative RT-PCR result on day 5.

Secondary outcomes for both groups included length of hospital stay, requirement for admission to the pediatric intensive care unit (PICU), need for invasive or noninvasive mechanical ventilation, occurrence of drug-related adverse events, and mortality. Also, the need for hospitalization was the secondary outcome in outpatients, and viral clearance (assessed by RT-PCR on day 6) was the secondary outcome in inpatients [13].

Data analysis

Data analysis was conducted in IBM SPSS software, version 20 (IBM, Armonk, NY). The Kolmogorov-Smirnov test assessed the normality of continuous variables. Descriptive statistics included Mean±SD, frequency, percentage, median, and interquartile range (IQR). The Mann–Whitney U test compared the groups based on continuous variables such as age and hospitalization duration. Chi-square and Fisher's exact tests evaluated the differences based on categorical variables. A two-sided $P<0.05$ was considered statistically significant. Intention-to-treat analysis was also used. Missing data were handled via last observation carried forward where applicable.

Results

Inpatient characteristics

A total of 66 inpatient children were included in the study, of whom 35 were assigned to the ivermectin group and 31 to the placebo group (Figure 1). The baseline socio-demographic and clinical characteristics of inpatients are summarized in Table 1. The median length of hospital stay was 6 days, which was the same in both groups. In total, 80.3% of the patients were from urban areas. The majority were boys (n=44, 66.7%), with a median age of 11.5 years (IQR=7.75-14). Overweight or obesity was present in 57.2% of inpatients for whom BMI was available (54.9% in the ivermectin group vs 61.11% in the placebo group). Underlying comorbidities were reported in 18(27.27%) inpatients, and asthma was the most common comorbidity (7.57%, n=5). A history of contact with a confirmed COVID-19 case was reported by 56.06% of the patients. Of 39 patients who underwent computed tomography (CT) scans, 29(74.3%) showed pulmonary involvement. Among

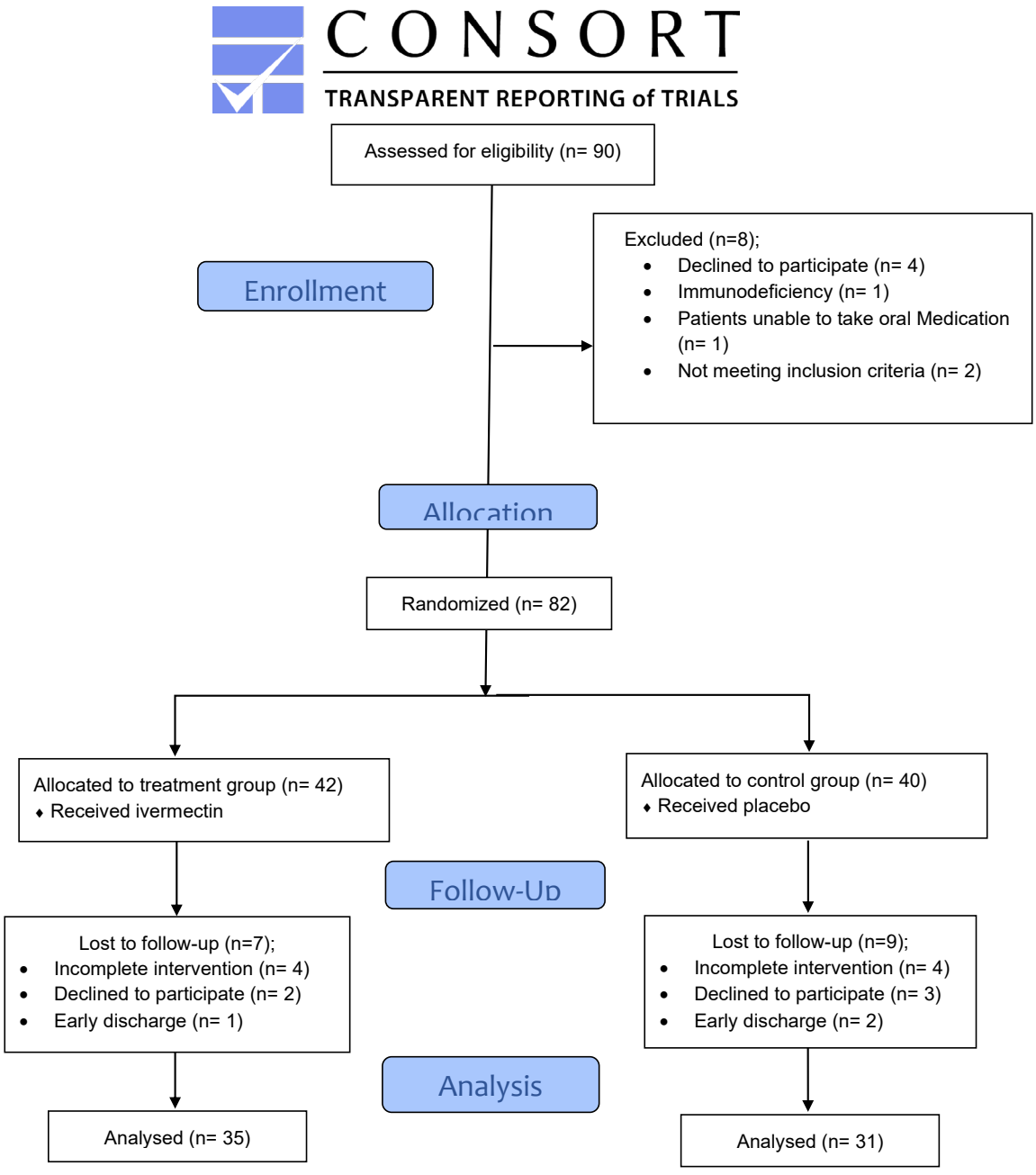

Figure 1. Flowchart of enrollment and allocation processes for inpatients

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the 66 inpatients, 9(13.63%) required admission to the PICU. Also, 19.69% of patients required oxygen during treatment, with no significant difference between the two groups. All patients with COVID-19 recovered, and no deaths occurred in either group (Table 1).

Predominant symptoms at the time of admission among hospitalized children were fever (75.75%), cough (57.57%), anorexia (42.42%), vomiting (40.9%), and shortness of breath (34.84%). No significant differences were observed between the two study groups regarding these signs and symptoms (Table 2). The most common antiviral and antibiotic administered at the time of admission were remdesivir (60.6%) and ceftriaxone (78.79%), respectively. Methylprednisolone/dexamethasone (42.4%) and heparin/enoxaparin (31.8%) were the administered corticosteroids and anticoagulants. The most commonly prescribed vitamins were zinc (72.7%) and vitamin D (71.21%). Overall, significant differences were observed between the ivermectin and

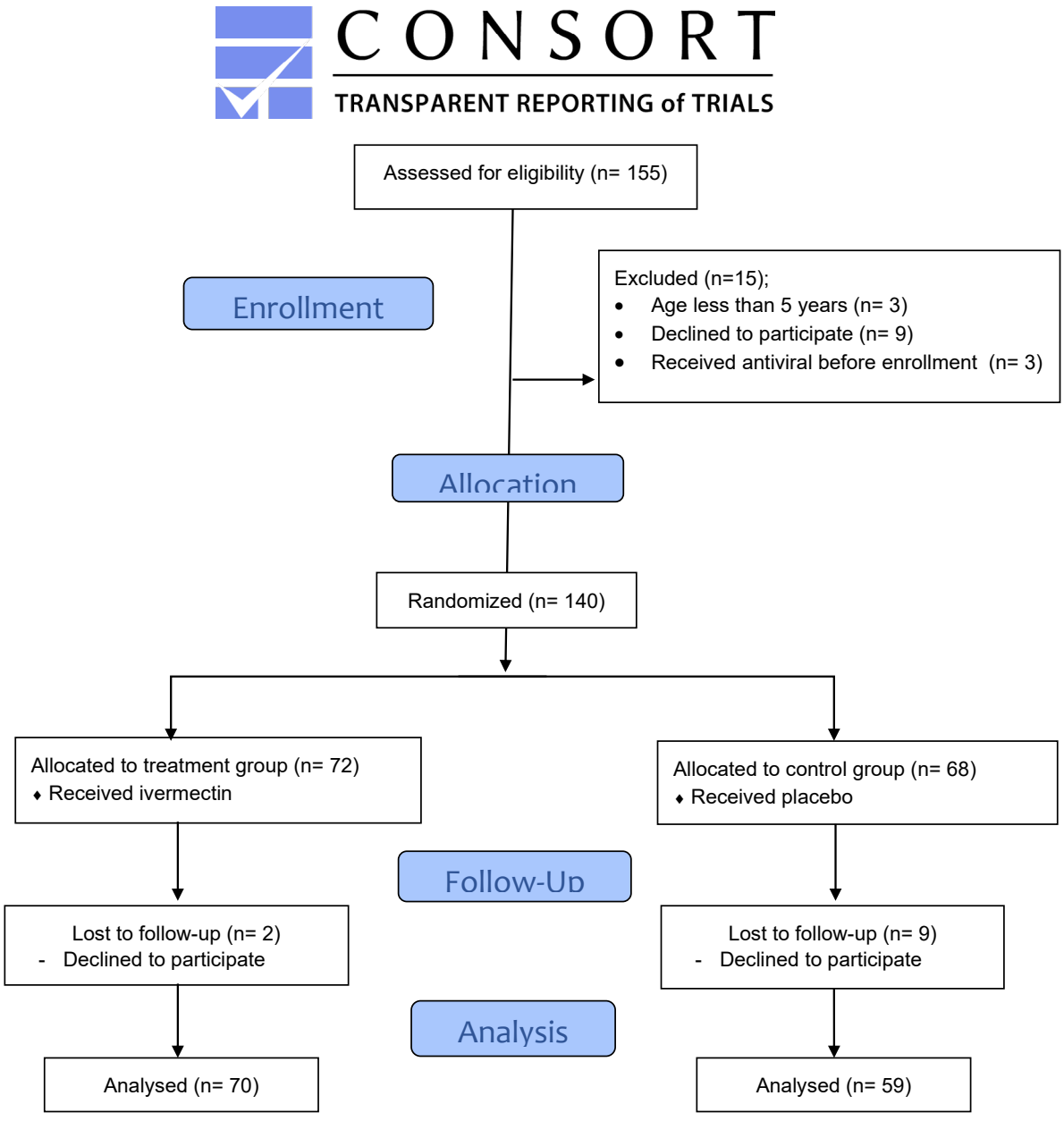

Figure 2. Flowchart of enrollment and allocation processes for outpatients

placebo groups in the use of clindamycin, meropenem, vitamin D, and vasopressin (Table 3).

Outpatient characteristics

A total of 129 outpatient children were included in the study, of whom 70 were assigned to the ivermectin group and 59 to the placebo group (Figure 2). Their baseline socio-demographic and clinical characteristics are presented in Table 4. The outpatient group included 51.16% boys (n=66) with a median age of 11 years (IQR=7–15). In total, 76.74% of the outpatients were from urban areas. Among outpatients with available BMI data, overweight or obesity was present in 27.2% of all patients (33.33% in the ivermectin group vs 18.42% in the placebo group). Underlying comorbidities were reported in 11(8.53%) patients. A history of contact with a confirmed COVID-19 case was reported by 88(68.22%) patients. Nearly all outpatients had mild COVID-19 (99.2%). Among the 44 outpatients who underwent RT-PCR testing on the 6th day, 12(27.27%) remained test positive, mostly in the placebo group; this difference was statistically significant (P=0.042). Among the outpatients, three (2.33%) required hospitalization,

Table 1. Baseline sociodemographic and clinical characteristics of inpatients (n=66)

Variables		Median (IQR)/No. (%)			P
		Total (n=66)	Ivermectin (n=35)	Placebo (n=31)	
Age		11.50 [7.75 – 14]	13 [10 – 14]	10 [7 – 13]	0.086
Duration of hospitalization		6 [4.25 – 7]	6 [5 – 7]	6 [4 – 8]	0.456
Gender	Boy	44(66.7)	26(74.3)	18(58)	0.163
	Girl	22(33.3)	9(25.7)	13(42)	
Place of residence	Urban	53(80.3)	31(88.6)	22(71)	0.073
	Rural	13(19.7)	4(11.42)	9(29.03)	
Obesity or overweight	Yes	28(57.2)	17(54.9)	11(61.1)	0.669
	No	21(42.9)	14(45.1)	7(38.9)	
Underlying diseases	Asthma	5(7.57)	1(2.85)	4(12.9)	0.179*
	G6PD	4(6.06)	1(2.85)	3(9.67)	0.335*
	Diabetes	2(3.03)	1(2.85)	1(3.22)	1.000*
	Heart disease	3(4.54)	3(8.57)	0(0)	0.241*
	Hypothyroidism	2(3.03)	1(2.85)	1(3.22)	1.000*
	Malignancy	1(1.51)	0	1(3.22)	0.470*
	Pulmonary disease	1(1.51)	0	1(3.22)	0.470*
History of contact with a COVID-19 patient		37(56.06)	22(62.85)	15(48.38)	0.237
Pulmonary involvement (CT scan)	Yes	29(74.3)	18(72)	11(78.6)	0.721*
	No	10(25.7)	7(28)	3(21.4)	
Disease severity	Severe	5(7.6)	2(5.7)	3(9.7)	0.659*
Need for PICU admission		9(13.63)	1(2.85)	8(25.8)	0.010*
Need for oxygen therapy		13(19.69)	7(20)	6(19.35)	0.992*
Recovery		66(100)	35(100)	31(100)	-

G6PDd: Glucose-6-phosphate dehydrogenase deficiency.

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*Fisher's exact test.

and one was admitted to the PICU. Overall, 99.22% of the patients with COVID-19 recovered (Table 4). The most common signs and symptoms among outpatient children on the first day of admission were fever (71.32%), cough (44.19%), headache (40.31%), myalgia (35.66%), and sore throat (31.78%). No significant differences were observed between the two study groups regarding these signs and symptoms (Table 5).

The most frequently used antibiotic in the outpatients was azithromycin (53.48%). Other common medications included zinc (58.91%) and vitamin D (33.33%). Overall, no significant differences were observed between the ivermectin and placebo groups regarding the medications used (Table 6). No significant difference was observed between the two groups regarding the mean duration of symptoms (Table 7). On the 7th day of follow-up, the persistence of symptoms was low in both groups. No significant differences were observed between placebo and ivermectin in the symptoms (P>0.05) (Table 8).

Table 2. Signs and symptoms of inpatients at the first day of admission

Symptoms	No. (%)			P
	Total (n=66)	Ivermectin (n=35)	Placebo (n=31)	
Fever	50(75.75)	26(74.28)	24(77.41)	0.767
Cough	38(57.57)	21(60)	17(54.83)	0.672
Anorexia	28(42.42)	16(45.71)	12(38.7)	0.566
Vomiting	27(40.9)	14(40)	13(41.93)	0.873
Shortness of breath	23(34.84)	14(40)	9(29.03)	0.351
Nausea	20(30.3)	12(34.28)	8(25.8)	0.454
Abdominal pain	19(28.78)	11(31.42)	8(25.8)	0.615
Diarrhea	13(19.69)	8(22.85)	5(16.12)	0.493
Headache	12(18.18)	6(17.14)	6(19.35)	0.816
Body pain	9(13.63)	4(11.42)	5(16.12)	0.724*
Vertigo	8(12.12)	6(17.14)	2(6.45)	0.265*
Sore throat	8(12.12)	5(14.28)	3(9.67)	0.713*
Chills	6(9.09)	2(5.71)	4(12.9)	0.408*
Skin rash	3(4.54)	0(0)	3(9.67)	0.098*
Tachypnea	3(4.54)	0(0)	3(9.67)	0.098*
Ral	3(4.54)	2(5.71)	1(3.22)	1.000*
Wheezing	2(3.03)	1(2.85)	1(3.22)	1.000*
Anosmia	1(1.51)	0(0)	1(3.22)	0.470*
Conjunctivitis	1(1.51)	0(0)	1(3.22)	0.470*
Arthralgia	1(1.51)	1(2.85)	0(0)	1.000*
Hypotension	1(1.51)	1(2.85)	0(0)	1.000*

*Fisher's exact test.

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Discussion

Since the onset of the COVID-19 pandemic, there has been a paucity of high-quality randomized clinical trials and comprehensive observational studies focused on treating COVID-19 specifically in children. Guidelines focusing pediatric patients have largely been adapted from guidelines for treating other viral infections or from those for adult COVID-19 patients [19, 20]. Among many investigated medications, ivermectin as a multifaceted agent has been explored as a potential therapeutic for COVID-19 in adults, albeit with contradictory findings [13, 21]. In this study, we evaluated the therapeutic potential of ivermectin in children with COVID-19 in Iran through two randomized controlled trials.

Consistent with adult studies [13, 14], our primary findings revealed that ivermectin use in children with COVID-19 did not significantly affect the course of disease; all hospitalized children and the majority of outpatients recovered regardless of ivermectin or placebo administration. Moreover, no significant differences were seen in the length of hospital stay between groups. In contrast, our previous pilot study on 69 COVID-19 patients showed that a single weight-based dose (0.2 mg/kg) of ivermectin reduced the hospitalization duration in a mixed-age COVID-19 cohort, with only 17% aged

Table 3. List of medications, vitamins and mineral supplements prescribed for inpatients

Type of Medications	Name	No. (%)			P
		Total (n=66)	Ivermectin (n=35)	Placebo (n=31)	
Antivirals	Remdesivir	40(60.6)	23(65.7)	17(54.9)	0.367
	Hydroxychloroquine	2(3)	1(2.9)	1(3.2)	1.000*
	Favipiravir	1(1.5)	1(2.9)	0(0)	1.000*
Antibiotics	Ceftriaxone	52(78.79)	26(74.23)	26(83.87)	0.342
	Clindamycin	11(16.67)	2(5.71)	9(29.03)	0.011
	Azithromycin	5(7.57)	3(8.57)	2(6.45)	1.000*
	Meropenem	5(7.57)	0(0)	5(16.13)	0.019*
	Doxycycline	3(4.54)	1(2.85)	2(6.45)	0.597*
	Vancomycin	2(3.03)	0(0)	2(6.45)	0.217*
	Imipenem	1(1.51)	0(0)	1(3.22)	0.470*
Corticosteroids	Methylprednisolone & dexamethasone	28(42.4)	14(40)	14(45.2)	0.804*
Anticoagulants	Heparin & enoxaparin	21(31.8)	12(34.3)	9(29)	0.792
NSAIDs	NSAIDs & aspirin	30(45.45)	13(37.14)	17(54.84)	0.150
Biological response modifiers	Interferon	3(4.5)	1(2.9)	2(6.4)	0.597*
Other drugs	Vasopressin	4(6)	0(0)	4(12.9)	0.044*
	Famotidine	4(6)	1(2.9)	3(9.7)	0.335*
Vitamins and minerals	Vitamin D	47(71.21)	21(60)	26(83.87)	0.033
	Zinc	48(72.7)	22(62.9)	26(83.9)	0.056
	Vitamin C	6(9)	1(2.8)	5(16.1)	0.091*

NSAIDs: Nonsteroidal anti-inflammatory drugs.

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*Fisher's exact test.

under 18 years [11]. Our other study showed that ivermectin, compared with placebo, did not have a significant potential effect on clinical improvement, reduced admission to ICU, need for invasive ventilation, and death in hospitalized patients; likewise, no evidence was found to support the impact of ivermectin on recovery, reduced hospitalization, and increased negative RT-PCR assay for SARS-CoV-2 outpatients five days after treatment. The findings did not support using ivermectin to treat mild to severe COVID-19 [13]. In these studies, participants were aged >5 years.

The need for ICU admission in severe COVID-19 cases is generally less common in children than in adults [22, 23]. However, children with severe disease and comorbidities remain prone to intensive care needs. Worldwide PICU admission rates among pediatric COVID-19 patients vary widely from 1.3% to 39% [23-26]. In our study, 13.6% of inpatients required PICU admission, with a significantly lower rate among those receiving ivermectin compared to placebo. Alsayed et al. similarly reported that early remdesivir administration in adults was associated with reduced ICU admissions [27]. Remdesivir is the FDA-approved antiviral for children ≥28 days old weighing ≥3 kg at risk of severe COVID-19 outcomes [28]. Because 60.6% of inpatients in our study received remdesivir, a potential synergistic effectiveness of ivermectin plus remdesivir in reducing PICU admission warrants consideration. Several studies have reported pronounced synergistic antiviral effects of remdesivir and ivermectin against SARS-CoV-2 [16, 29], including reduced cytokines implicated in cytokine storm [30].

Table 4. Baseline characteristics of outpatients (n=129)

Characteristics		Median [IQR]/No. (%)			P
		Total (n=129)	Ivermectin (n=70)	Placebo (n=59)	
Age		11 [7–15]	10. 50 [7.75–15]	11 [7–15]	0.738
Gender	Boy	66(51.1)	36(51.4)	30(50.8)	0.948
	Girl	63(48.9)	34(48.6)	29(49.1)	
Living place	Urban	99(76.7)	55(78.6)	44(74.6)	0.593
	Rural	30(23.3)	15(21.4)	15(25.4)	
Obesity & overweight	Yes	25(27.2)	18(33.3)	7(18.4)	0.113
	No	67(72.8)	36(66.7)	31(81.6)	
Comorbidities	Asthma	6(4.6)	3(4.3)	3(5)	1.000
	G6PDd	3(2.3)	0(0)	3(5)	0.093*
	Diabetes	1(0.7)	0(0)	1(1.7)	0.457*
	Hypothyroidism	1(0.7)	0(0)	1(1.7)	0.457*
Disease severity	Mild	128(99.2)	69(98.6)	59(100)	1.000*
	Moderate	1(0.8)	1(1.4)	0(0)	
History of contact with a COVID-19 patient		88(68.22)	47(67.14)	41(69.49)	0.775
Influenza vaccine		6(4.65)	6(8.57)	0(0)	0.031*
RT-PCR test (6th day) (n=44)	Positive	12(27.27)	3(13.64)	9(40.91)	0.042
	Negative	32(72.73)	19(86.36)	13(59.09)	
Need for hospitalization		3(2.33)	2(2.86)	1(1.69)	1*
Need for PICU administration		1(0.78)	1(1.43)	0(0)	1*
Recovery		128(99.22)	69(98.57)	59(100)	-

*Fisher's exact test.

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Our findings also indicated that ivermectin use was associated with a trend toward enhanced viral clearance: more outpatients in the ivermectin group were RT-PCR test negative six days after symptom onset than in the placebo group. These results align with clinical trials conducted in Bangladesh and Argentina demonstrating accelerated viral clearance with ivermectin [15, 18, 31]. However, the literature on remdesivir and ivermectin for viral clearance remains mixed, with some studies showing faster clearance and others finding no differences compared with controls [14, 15, 31-33]. Tan et al. demonstrated that the combined remdesivir and ivermectin potently suppressed SARS-CoV-2 replication in infected macrophages [30].

In our study, methylprednisolone/dexamethasone was the most commonly used corticosteroid (42.4%) in inpatients. Corticosteroid use in pediatric COVID-19 requires careful specialist consultation, balancing potential benefits against risks. When dexamethasone is unavailable, methylprednisolone serves as an alternative [20]. Also, no severe adverse drug effects or deaths occurred following ivermectin administration in both groups. This might be due to the small sample size. Nonetheless, oral ivermectin in children requires strict dosing guidance to prevent overdose and poisoning [34].

Table 5. Signs and symptoms of outpatients on the first day of admission

Symptoms	No. (%)			P
	Total (n=129)	Ivermectin (n=70)	Placebo (n=59)	
Fever	92(71.32)	49(70)	43(72.88)	0.718
Cough	57(44.19)	34(48.57)	23(38.98)	0.275
Headache	52(40.31)	30(42.86)	22(37.29)	0.521
Myalgia	46(35.66)	26(37.14)	20(33.9)	0.702
Sore throat	41(31.78)	23(32.86)	18(30.51)	0.775
Chills	31(24.03)	17(24.29)	14(23.73)	0.941
Anorexia	23(17.83)	12(17.14)	11(18.64)	0.824
Abdominal pain	18(13.95)	11(15.71)	7(11.86)	0.530
Diarrhea	17(13.18)	10(14.29)	7(11.86)	0.685
Vomiting	16(12.4)	8(11.43)	8(13.56)	0.715
Nausea	16(12.4)	10(14.29)	6(10.17)	0.480
Vertigo	10(7.75)	7(10)	3(5.08)	0.343*
Insomnia	8(6.2)	5(7.14)	3(5.08)	0.726*
Conjunctivitis	7(5.43)	5(7.14)	2(3.39)	0.453*
Shortness breath	2(1.55)	1(1.43)	1(1.69)	1*
Arthralgia	2(1.55)	1(1.43)	1(1.69)	1*
Skin rash	1(0.78)	1(1.43)	0(0)	1*
Tachypnea	1(0.78)	1(1.43)	0(0)	1*
Hypotension	1(0.78)	0(0)	1(1.69)	0.457

*Fisher's exact test.

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Table 6. List of medications prescribed for outpatients

Type of Medications	Name	No. (%)			P
		Total (n=129)	Ivermectin (n=70)	Placebo (n=59)	
Antibiotics	Azithromycin	69(53.48)	40(57.14)	29(49.15)	0.365
	Doxycycline	6(4.65)	1(1.43)	5(8.47)	0.093*
	Co-amoxiclav	1(0.78)	1(1.43)	0(0)	1*
	Cefuroxime	1(0.78)	1(1.43)	0(0)	1*
Other drugs	Zinc	76(58.91)	46(65.71)	30(50.85)	0.087
	Vitamin D	43(33.33)	27(38.57)	16(27.12)	0.169
	Vitamin C	32(24.81)	17(24.29)	15(25.42)	0.881
	Famotidine	14(10.85)	9(12.85)	5(8.47)	0.425

*Fisher's exact test.

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Table 7. Mean duration of COVID-19 symptoms in outpatients using the Kaplan-Meier estimator

Duration of Symptoms	Group	Mean±SE	95% CI	P
Fever	Ivermectin	1.24±0.15	0.95, 1.52	0.090
	Placebo	1.71±0.23	1.26, 2.16	
Chills	Ivermectin	0.45±0.11	0.24, 0.66	0.956
	Placebo	0.46±0.13	0.2, 0.72	
Cough	Ivermectin	1.81±0.28	1.27, 2.36	0.777
	Placebo	1.98±0.31	1.38, 2.59	
Anorexia	Ivermectin	0.62±0.19	0.25, 0.99	0.589
	Placebo	0.8±0.23	0.35, 1.25	
Sore throat	Ivermectin	1.04±0.2	0.64, 1.44	0.708
	Placebo	1.1±0.24	0.64, 1.56	
Abdominal pain	Ivermectin	0.48±0.14	0.21, 0.74	0.852
	Placebo	0.42±0.16	0.11, 0.74	
Vertigo	Ivermectin	0.3±0.1	0.10, 0.5	0.333
	Placebo	0.15±0.1	0, 0.34	
Headache	Ivermectin	1.05±0.19	0.67, 1.42	0.369
	Placebo	0.83±0.18	0.47, 1.19	
Nausea	Ivermectin	0.36±0.1	0.16, 0.57	0.569
	Placebo	0.29±0.14	0.01, 0.57	
Vomiting	Ivermectin	0.22±0.09	0.05, 0.4	0.962
	Placebo	0.24±0.09	0.06, 0.42	
Diarrhea	Ivermectin	0.31±0.09	0.13, 0.49	0.930
	Placebo	0.32±0.11	0.11, 0.54	
Body pain	Ivermectin	1.02±0.2	0.63, 1.41	0.693
	Placebo	0.9±0.21	0.49, 1.31	
Conjunctivitis	Ivermectin	0.15±0.06	0.03, 0.27	0.390
	Placebo	0.34±0.12	0.01, 0.47	
Anosmia	Ivermectin	0.46±0.15	0.17, 0.76	0.250
	Placebo	0.25±0.1	0.06, 0.45	

SE: Standard error.

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Table 8. The symptoms persisted in outpatients on the 7th day of follow-up

Symptoms	No. (%)			RR	95% CI	P
	Total (n=129)	Ivermectin (n=70)	Placebo (n=59)			
Fever	4(3.1)	1(1.4)	3(5.1)	3.56	0.37, 36.5	0.331
Cough	12(9.3)	6(8.6)	6(10.2)	1.2	0.36, 3.96	0.756
Anorexia	4(3.1)	2(2.9)	2(3.4)	1.19	0.16, 8.73	1
Nausea	1(0.8)	0(0)	1(1.7)	-	-	0.457
Abdominal pain	2(1.6)	1(1.4)	1(1.4)	1.19	0.07, 19.44	1
Headache	3(2.3)	3(4.3)	0(0)	-	-	0.250
Body pain	3(2.3)	2(2.9)	1(1.7)	0.59	0.52, 6.63	1
Sore throat	4(3.1)	2(2.9)	2(3.4)	1.19	0.16, 8.73	1
Conjunctivitis	1(0.8)	0(0)	1(1.7)	-	-	0.457

RR: Risk ratio.

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Note: Ivermectin was the reference group for RR calculations.

This study had some limitations. The small sample size limited evaluation of ivermectin's impact on mortality. The lack of long-term inpatient follow-up limits assessment of symptom resolution. Plasma ivermectin levels were not measured, preventing correlation between pharmacokinetics and antiviral effects. Viral clearance was only assessed in outpatients. Also, laboratory safety parameters, including liver function tests, and formal neurological assessments were not systematically evaluated. Future studies should include detailed laboratory and neurological safety assessments to comprehensively evaluate the safety profile of ivermectin in pediatric populations.

Conclusion

In conclusion, ivermectin does not improve clinical recovery, disease progression, hospitalization duration, or mortality in children with COVID-19 in either inpatient or outpatient settings. Although outpatient children who received ivermectin had a higher rate of RT-PCR negativity than those who received placebo, this did not translate into significant clinical benefit. Therefore, based on the overall evidence from this study, ivermectin cannot be recommended for the treatment of pediatric COVID-19. Our findings provide valuable pediatric-specific evidence but emphasize the critical need for further rigorous research to establish ivermectin's efficacy and safety in this population.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them. A written informed consent has been obtained from parents or legal guardians before enrollment. All procedures adhered to the Declaration of Helsinki and Good Clinical Practice guidelines.

The study protocols for both trials were approved by the ethics committee of Mazandaran University of Medical Sciences, Sari, Iran (Codes: IR.MAZUMS.REC.1399.915 and IR.MAZUMS.REC.1399.869), and the trials were registered by the Iranian Registry of Clinical Trials (IRCT) (Codes: IRCT20111224008507N5 and IRCT20111224008507N4).

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Conflicts of interest

The authors declared no conflict of interest.

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