Role of Ivermectin in Patients with Mild to Moderate Coronavirus Disease - 2019 Admitted in Shaheed Syed Nazrul Islam Medical College Hospital, Kishoreganj: Open Label, Randomized Controlled Trial

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Abstract

Background: Covid-19 is the pandemic disease declared by world health organization (WHO) on 11th march 2020 which is potentially severe acute respiratory infection caused by a novel evolving severe acute respiratory syndrome Coronavirus 2 (sars-cov-2). To date no therapy has been shown to improve survival for patients infected with SARS-COV-2. Ivermectin has been shown to inhibit the replication of sars-cov-2 in vitro but clinical response has not been previously evaluated. In this study we would like to determine whether Ivermectin is associated with lower rate of mortality and morbidity in patients hospitalized with Covid-19.

Methods: This Open label Randomized Controlled Trial was conducted on seventy four (74) mild to moderate confirmed covid -19 patients admitted in covid ward of medicine department of Shaheed Syed Nazrul Islam Medical College Hospital, Kishoreganj during 15th June to 15th July, 2020 . Patients who fulfilled the Selection criteria (Both inclusion and exclusion criteria) were enrolled.

Results: Total 74 patients with COVID-19 were randomized into two groups- 41 patients in Ivermectin group and 33 patients in active control group. The Ivermectin group was given a single dose of Ivermectin 12 mg along with standard treatment, while in the control group only standard treatment was given. The mean age of the 74 participants was 38.1±13.1 years. The average age of Ivermectin group patients was 37.4±12.7 years which was statistically similar (p=0.632) to that of active control group 38.9±13.7 years. A male: female ratio of 4.29:1 was noted. Sex distribution was similar across groups. On the same note, distribution of other socio-demographic profiles along with history of smoking, BCG vaccination and comorbidities patients were also statistically similar between intervention and control groups. Among Ivermectin group 51.2% had history of contact with COVID-19 patients and in control group 40.6% had such a history (p=0.368). Both Ivermectin and control groups presented with statistically comparable values of signs, symptoms and laboratory investigations. The outcome of treatment of COVID-19 patients in the form of time to become asymptomatic, time to become RT-PCR negative and total hospital stay in days are almost similar in both groups. Addition of Ivermectin did not show any statistically significant variation in outcome.

Conclusion: From the present study it can be concluded that Ivermectin did not show any statistically significantly better efficacy than standard of care in the treatment of mild to moderate covid-19 patients.

[Shaheed Syed Nazrul Islam Med Col J 2021, Jan; 6 (1):77-85]

Keywords: Ivermectin, Coronavirus

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Introduction

Most people infected with the covid-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment. Older people and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness. At this time, there are no specific vaccines or treatments for covid-19. However, there are many ongoing clinical trials evaluating potential treatments.[1] Upto June 11th,2020 WHO recorded nearly 413372 people having died of covid-19 with at least 7273958 confirmed cases globally.[1]In Bangladesh, covid-19 infections are being reported from Directorate general of Health Service on daily basis. So far, we have around 78052 cases with 1049 deaths (12^{th}june, 2020)[2]. Covid-19 presents an unprecedented challenge to identify effective therapy for prevention and treatment. Currently, there is no evidence from randomized controlled trials of any potential therapy improving survival outcomes in patients with confirmed disease. In the late 1970s, Ivermectin was developed as a new class of drug to treat parasitic infections. Initially used in veterinary medicine, it was soon found to be safe and effective in humans. It has successfully been used to treat Onchocerciasis and lymphatic filariasis in millions of people worldwide as part of a global drug donation program. About 3.7 billion doses of Ivermectin have been distributed in mass drug administration campaigns globally over the past 30 years. Presently, Ivermectin is approved for use in humans in several countries to treat Onchocerciasis, Lymphatic Filariasis, Strongyloidiasis and Scabies.[3] Ivermectin has previously been studied as a therapeutic option for viral infections with in vitro data showing some activity against a broad range of viruses, including HIV, Dengue, Influenza and Zika virus.[4,5] In a recent study, Wagstaff et al, demonstrated that Ivermectin was a potent in-vitro inhibitor of SARS-COV-2, showing a 99.8% reduction in viral RNA after 48 hours.[5]In a recent study named ICON (Ivermectin In Covid Nineteen) demonstate that use of Ivermectin is associated with lower mortality in hospitalized patients with Covid19.[6]

Methods

The study was designed and initiated by the principal investigator after the protocol was approved by the Institutional Review Board (IRB) of Shaheed Syed Nazrul Islam Medical College, Kishoreganj. This Open label Randomized Controlled Trial was conducted on seventy four (74) mild to moderate confirmed Covid -19 patients admitted in Covid ward of medicine department of Shaheed Syed Nazrul Islam Medical College Hospital, Kishoreganj during 15^{th} June to 15^{th} July, 2020. Patients who fulfilled the selection criteria (Both inclusion and exclusion criteria) were enrolled in this trial. Inclusion criteria (Male or female) were Covid-19 patient of 18-65 years of age confirmed by RT-PCR and who were mild to moderate in severity during admission.We excluded Covid-19 patient with known Co-morbidity e.g. Malignancy, CKD & CLD, who were pregnant as well as known hypersensitive to Ivermectin. We had divided the study population in two groups. One was intervention group and another one was active control group. Intervention group received Ivermectin and standard of care .Active control group received only standard of care treatment.

Patient admitted with even registration number were enrolled in intervention group & patient admitted with odd registration number were enrolled in active control group.

Main outcome variables of this study were alleviation of clinical symptoms of patients

by day-7 and negative conversion of SIRS-CoV-19 RT-PCR by day-14 .Probability of negative conversion at day 7 & 10 was specified as a secondary outcome. Confirmed case were defined as person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms. We defined negative conversion of SARS-CoV-2as two consecutive reports of a negative result for SARS-CoV-2 at least 24 hours apart without a subsequent report of a positive result by the end of the study. The definition of the alleviation of clinical symptoms was resolving from fever to an axillary temperature of 36.6°C or below, normalization of SpO2 (>94% on room air), and disappearance of respiratory symptoms including nasal congestion, cough, sore throat, sputum production, and shortness of breath. Collected data were analysed by using T-test, Fisher,s exact test and considered significant with p value less than 0.05.

Results

Total 74 patients with COVID-19 were randomized into two groups: 41 patients in Ivermectin group and 33 patients in active control group. The Ivermectin group was given a single dose of Ivermectin 12 mg along with standard treatment, while in the control group only standard treatment was given. The mean age of the 74 participants was 38.1±13.1 years. The average age of Ivermectin group patients was 37.4±12.7 years which was statistically similar (p=0.632) to that of active control group 38.9±13.7 years. A male: female ratio of 4.29:1 was noted. Sex distribution was similar across groups. On the same note, distribution of other socio-demographic profiles along with history of smoking, BCG vaccination and comorbidities patients were also statistically similar between intervention and control groups. Among Ivermectin group 51.2% had history of contact with COVID-19 patients and in control group 40.6% had such a history (p=0.368). The median interval between symptom onset to sample collection was 2 for both groups. Both Ivermectin and control groups presented with statistically comparable values of signs, symptoms and laboratory investigations (Table-V). Also, both groups were given additional therapy in a statistically similar proportion except doxycycline, amoxycillin + Clavulanic acid and meropenem (Table- VI). Table-VII shows in the outcome of treatment of COVID-19 patients in the form of time to become asymptomatic, time to become RT-PCR negative and total hospital stay in days. Addition of Ivermectin did not show any statistically significantly better efficacy than standard therapy.

Table I: Distribution of age among study population

Age groups **in years**	Ivermectin group	Active control group	P value
≤ 30	16 (39.0)	13 (39.4)	0.775
31 – 40	9 (22.0)	6 (18.2)	
41 – 50	10 (24.4)	8 (24.2)	
51 – 60	3 (7.3)	1 (3.0)	
> 60	3 (7.3)	5 (15.2)	
Mean ±SD	37.4 ±12.7	38.9 ±13.7	0.632

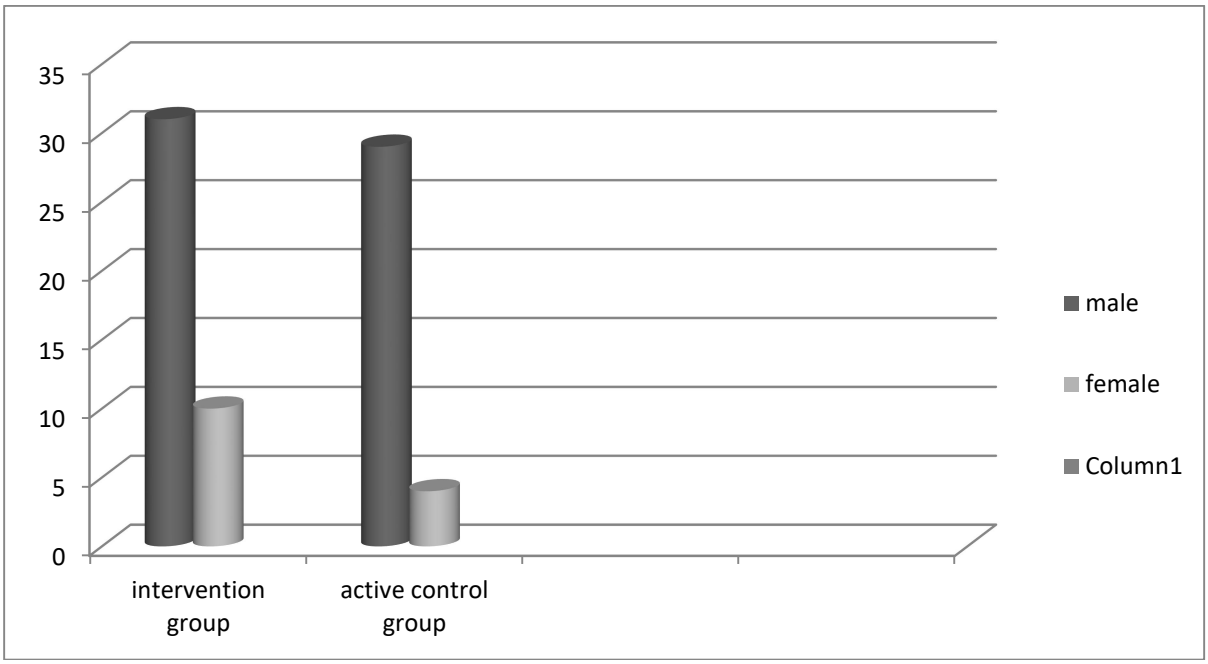

Figure 1. Distribution of study population by sex

Table II: Distribution of study population by occupation

Occupation	Ivermectin group	Active control group	P value
Service Holder	25 (65.8)	17 (54.8)	0.915
Businessman	6 (15.8)	6 (19.4)	
Housewife	3 (7.9)	3 (9.7)	
Self-employed	1 (2.6)	1 (3.2)	
Student	1 (2.6)	1 (3.2)	
Retired	2 (5.3)	3 (9.7)	

Figure 2. Distribution of study population by socioeconomic condition

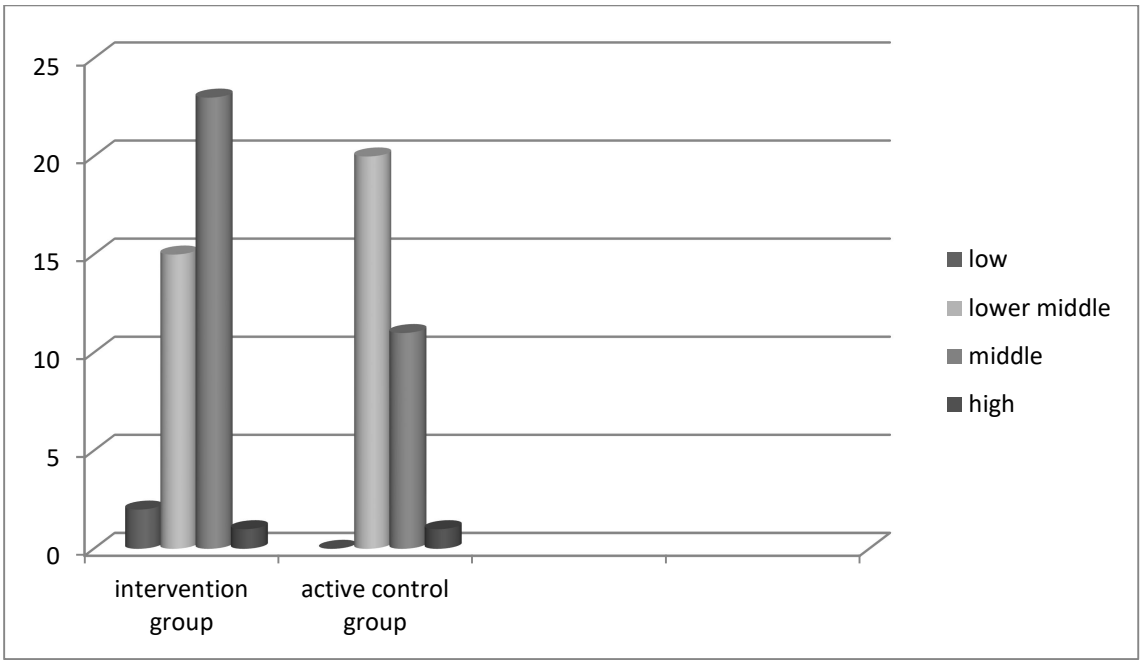

Table III: Distribution of study population by BCG vaccination status and contact with covid-19 patient

History of	Ivermectin group	Active control group	P value
Smoking	13 (35.1)	15 (45.5)	0.379
BCG vaccination	36 (100)	32 (100)	
Contact with COVID-19 patients	21 (51.2)	13 (40.6)	0.368

Table IV: Distribution of study population by co-morbidities

Comorbidities	Ivermectin group	Active control group	P value
DM	5 (12.5)	6 (18.2)	0.729
HTN	7 (17.5)	6 (18.2)	0.940
Bronchial asthma	3 (7.5)	2 (6.1)	1.000
Chronic heart disease	1 (2.5)	0	1.000
Obesity	0	1 (3.0)	0.452

Table V: Comparison of clinical features between two groups

Clinical Features	Ivermectin group	Active control group	P value
Symptoms			
Fever	24 (60.0)	13 (39.4)	0.080
Cough	22 (53.7)	24 (72.7)	0.093
Dyspnoea	20 (50.0)	18 (54.5)	0.699
Rhinorrhoea/Nasal Congestion	15 (37.5)	11 (33.3)	0.711
Sore-throat	14 (34.1)	9 (27.3)	0.525
Altered sense of smell	8 (20.0)	3 (9.1)	0.195
Altered sense of test	7 (17.5)	5 (15.2)	0.788
Vomiting	2 (5.0)	0	0.498
Diarrhoea	3 (7.5)	0	0.247
Myalgia	4 (10.0)	2 (6.1)	0.683
Headache	2 (5.0)	5 (15.2)	0.233
Fatigue	5 (12.5)	1 (3.0)	0.212
Anorexia	2 (4.9)	0	0.499
Chest pain	1 (2.5)	3 (9.1)	0.322
Signs			
Pulse (beats/min)	87.2 ±12.5	87.7 ±13.8	0.926
Systolic blood pressure (mmHg)	123.1 ±12.8	125.3 ±12.4	0.448
Diastolic blood pressure (mmHg)	76.5 ±7.3	78.9 ±8.00	0.177
Respiratory rate (/min)	19.2 ±2.9	17.6 ±3.3	0.270
SpO_2 (%)	95.59±2.93	94.61±2.42	0.979
Investigations			
Hemoglobin (g/dl)	12.3 ±1.1	11.8 ±0.8	0.085
ESR (mm)	50.4 ±21.3	43.4 ±12.0	0.178
WBC (x $10^3/cm^3$)	7.7 ± 1.6	6.6 ±1.1	0.008
Neutrophil (%)	66.3 ±13.8	53.8 ±13.7	0.003
Lymphocyte (%)	21.8 ±5.6	22.7 ±4.5	0.559
Platelet (x $10^3/cm^3$)	234.8 ±50.4	255.5 ±35.6	0.112
RBS	7.6 ±3.2	8.6 ±4.2	0.468
Serum creatinine	0.9 ±0.2	0.8 ±0.1	0.266
Disease severity			
Mild	30 (73.17%)	24 (77.41%)	
Moderate	11(26.82)	9(29.03%)	

Table VI: Comparison of drugs used as standard of care

Name of drug/therapy	Ivermectin group	Active control group	P value
Doxycycline	23 (56.09)	3 (9.6)	<0.001
Azithromycin	8(19.5)	7(22.6)	
Amoxycillin + Clavulanic acid	1 (2.5)	8 (25.8)	0.004
Cefuroxime	1 (2.5)	0	1.000
Ceftriaxone	8 (19.5)	9 (29.0)	0.388
Meropenem	0	4 (12.9)	0.035
Zinc	41 (100)	33 (100)	
Vitamin C	41 (100)	33 (100)	
Vitamin D	14 (36.8)	14 (45.2)	0.484
Enoxaparin prophylactic	7 (17.5)	12 (36.4)	0.068
Enoxaparin therapeutic	8 (20.0)	10 (30.3)	0.309
Methyl prednisolone (tab)	2 (5.0)	3 (9.4)	0.650
Methyl prednisolone (inj)	2 (5.0)	4 (12.5)	0.237
Oxygen	16 (40.0)	18 (54.5)	0.215

Table VII: Comparison of outcome variables between two groups

Outcome variable	Ivermectin group Mean ±SD	Active control group Mean ±SD	P value
Time to become asymptomatic (days)	10.7 ±5.5	10.6 ±6.5	0.921
Time to become RT-PCR negative for COVID-19 (days)	8.4 ±2.9	8.3 ±3.6	0.891
Hospital stay (days)	8.7 ±2.2	9.8 ±3.4	0.075

Discussion

Corona virus disease-2019(COVID-19) pandemic declared by the World Health Organization (WHO) on 11th March 2020, caused by SARS-CoV2 virus is at exponentially rising state across the globe. Bangladesh is also facing the toll of this highly transmissible zoonotic disease with community transmission across the country.[7] The treatment methods for COVID-19 are emerging and rapidly evolving because of ongoing research being done worldwide by a record number of investigators. Due to the uniqueness of each medical and research facility, the approach to the care of patients with COVID-19 varies from institution to institution. In Bangladesh, many patients with mild to moderate disease were being treated with Ivermectin. New concerns about Ivermectin has led us to seek its role to reduce morbidity and mortality of Covid -19 patients. Thus, we have undertaken a comparative therapeutic analysis, comparing standard drugs with Ivermectin and Standard drugs according to national guideline.

Ivermectin is a relatively safe and well-tolerated anti-parasitic drug for Head Lice, Scabies, Onchocerciasis, And Strongyloidiasis that acts by inhibiting nuclear transport activity.[8] In-vitro studies have shown its function against Human Immunodeficiency Virus (HIV), Dengue, Influenza, and most recently, against SARS-CoV-2. This effectiveness against SARS-CoV-2 infection is due to its critical interaction of RNA viruses responsible for integrase protein nuclear import.[9,10] A recent report suggests that Ivermectin reduces mortality rates in hospitalized patients with COVID-19.[11] However, it is not known if antiviral levels are attainable while using known dosing regimens of Ivermectin therapy in patients with COVID-19.[12,13] Thus, it is vital to investigate the dose regimens of Ivermectin for COVID-19

treatment or to determine if there is appropriate synergism using combination therapy with another drug.

In this randomized controlled study, we had divided the study population ino two groups. One was Intervention group and another was active control group. Intervention group received Ivermectin and standard of care. Active control group received only standard of care treatment.

The presenting symptoms of the COVID19 patients were fever, cough, dyspnoea, rhinorrhoea,nasalcongesion, sore throat, altered sense of smell, altered sense of taste, fatigue, mayalgia, diarrhoea, vomiting, headache, anorexia and chest pain. To avoid the influence in the recovery duration, we solely selected the cases devoid of any severe comorbidities. Only patients with mild to moderate diseases that were included. The difference in recovery to negative PCR duration was not significant (P = 0.891) among the two groups. Still, the mean duration of recovery is shorter 8.3days in the case of active control group than that of Ivermectin group 8.4 days. The difference in recovery to becoming symptom-free was 10.7 days (5 to 16 days) in Ivermectin group and 10.6 (4 to 17 days) in active control group. This difference was not statistically significant. Addition of Ivermectin did not show any statistically significantly better efficacy than standard therapy. In our study there was significant difference in the proportion of male and female patients, and infection in children is rare, which was consistent with the results of a study performed by Zhong et al.[14] Their results showed that males were more likely to be infected than females.[8]According to this study, both the Ivermectin group and active control group regimens were tolerated and may have been an effective treatment for mild to moderate SARS-CoV-2 infection. Our study has limitations; these include relatively small sample size, the dose of Ivermectin, case selection, also the outcome may be biased by additional factors like severity of the disease, lack of cooperation of some participants, and unknown comorbidity.

Conclusion

From the present study it can be concluded that Ivermectin did not show any statistically significantly better efficacy than standard of care in the treatment of mild to moderate covid-19 patients. Still, it is very difficult to comment on this because sample size was small and study period was short. Further multicentre double blind randomized controlled trials are needed involving larger sample size.

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