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**ORIGINAL ARTICLE**

# Ivermectin A Potential Treatment in Covid-19, Related to Critical Illness

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## ABSTRACT

**Aim:** To evaluate the potential use of ivermectin with standard therapy among mild to moderate covid-19 illness.
**Methods:** This is a single-centered, prospective observational, randomized, parallel group (1:1 ratio), standard versus controlled ivermectin study recruited 210 confirmed COVID-19 positive patients who were admitted in COVID treatment center of Dr Ruth Kum Pafu Civil hospital Karachi, Pakistan from 1st November 2020 to 30th May 2021. Data were analyzed using SPSS version
**Results**: Total of 210 patients were enrolled in the study and aged matched patients were divided in two groups 105 patients received ivermectin 6 mg twice a day for five days along with standard therapy while remaining 105 patients received standard therapy as per local and international guidelines. Male were 140(66.7%) and female 70(33.3%); age ranges between 26 to 77 years and majority 140( 66.7%) were more than 50 years of age. Fever, dry cough and dyspnea were the major symptoms seen; 112(53.3%) patients had DM as a comorbid illness . Total of 21(20%) of 105 patients of ivermectin group had negative PCR for COVID 19 on day seven while the other group had positive covid test in all of 105 patients . On day 10 total of 49 more patients from ivermectin group found COVID negative along with 21 previously negative had second PCR was found negative in this way total of 70( 66.7%) of ivermectin group had negative PCR for COVID 19 while 21(20%) patients from non ivermectin got negative PCR for COVID 19 on day 10 .
**Conclusion:** Use of ivermectin with standard therapy clear the virus earlier than standard therapy in mild to moderate COVID-19 infected patients admitted in COVID treatment center of Dr Ruth Kum Pafu Civil Hospital Karachi
**Keywords:** Covid-19, Ivermectin, Standard Therapy .

## INTRODUCTION

Coronaviruses are a family of viruses that are enveloped, non segmented, positive sense RNA viruses[1]. These viruses are responsible for causing illnesses such as common cold, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS)[1]. In 2019, a new Coronavirus was identified as the cause of a disease outbreak that originated in Wuhan, China[2]. This virus is known as the Severe Acute Respiratory Syndrome Coronavirus 2. (SARS-CoV-2) and the disease it causes is called COVID-19[3]. In March 2020, the World Health Organization declared the COVID-19 outbreak, a pandemic[2]. Up to 01st July 2021, 181,930,736 cases have been confirmed globally with 3,945,832 deaths across the World[4]. At this point of time there is no proven cure of this disease and different approaches were utilized to clear the viru[5]. Several clinical trials were performed across the World to test the possible management strategies used to treat this virus by the use of antibodies to prevent the entry of virus, prevention of virus formation was assessed by inhibitors of proteases and many more were tested for cure of the illness with variable efficacy[5].

Ivermectin is an FDA-approved antiparasitic drug having variable antiviral efficacy against the number of DNA and RNA viruses. Ivermectin is a member of the Ivermectin family produced by soil microorganism streptomyces Ivermitilis and has antiviral properties against SARS CoV-2 according to a report by Caly et al[7]. Still the role of using ivermectin as an antiviral activity has not been proven clinically in vivo [8]. Robert T Kinobe et al find the use of ivermectin versus standard therapy has promising results with mean differences and 95% confidence intervals were -4.43 (-5.81, -3.04), p<0.00001[9]. Progressive workup of using ivermectin in clinical studies has been under investigation and its placement in clinical usage finds challenges against SARS-CoV-2[10]. Several studies reported antiviral effect of the broad spectrum parasiticide on RNA viruses such as Zika virus, Influenza virus, West Nile virus, Porcine Reproductive and Respiratory Syndrome virus, Newcastle disease virus, Chinkungunya virus, Human immunodeficiency virus, Yellow fever, Dengue fever, Japanese Encephalitis virus and Tick Borne Encephalitis virus[11]. Many studies with similar result suggesting antiviral effect of ivermectin against several RNA viruses is by binding with Importin α/B heterodimer which prevents its binding with viral protein and in this way it restricts entry of viral protein to nucleus which leads to inhibition of infection[12].

Ivermectin has established a safety profile for human use with fewer side effects and less toxicity[13]. Ivermectin use as a prophylactic agent in Africa is common in parasitic infections and more clinical trials are required to appraise the potential efficacy of Ivermectin[14]. Development of an effective antiviral against SARS CoV-2 will help in limiting the viral load, preventing severe disease progression and limiting person to person contact.

Therefore, we plan to evaluate the effectiveness of Ivermectin, therapy with standard therapy among mild to moderate patients with COVID-19 which may clear the virus earlier than standard therapy.

## METHODOLOGY

This is a single-centered, prospective observational, randomized, parallel group (1:1 ratio), standard versus controlled ivermectin study ; looking forward to assess the effectiveness of Ivermectin therapy with standard therapy among mild to moderate patients with COVID-19 infected patients who were admitted in the COVID-19 treatment center of Dr Ruth Kum Pafu Civil hospital Karachi, Pakistan from 1st November 2020 to 30th May 2021. after seeking approval from the Institutional Review Board. The sample size was calculated using PASS 2019 software. Keeping the prevalence of COVID-19 the confidence interval of 6.62 used with confidence level of 95% and margin of error of 5% a sample size of 210 achieves 95.085% power to detect a difference (P1-P0) of 0.1500 using a two-sided exact test with a significance level (alpha) of 0.050. These results assume that the population proportion under the null hypothesis (P0) is 0.5000.

A non-probability convenience sampling technique was used to recruit patients admitted in COVID treatment center of Dr. Ruth KM Pfau Civil Hospital Karachi, Pakistan. This study included all the patients who were given proper consent and met the following

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criteria: adults more than 18 years of age, confirmed diagnoses of COVID-19 by real-time polymerase chain reaction positive via nasopharyngeal swab technique and weight more than 48kg at the time of admission. Pregnant women and the person known to be allergic to ivermectin and to other antiviral treatment were excluded from the study. Included patients were divided into two groups ivermectin group in which along with standard treatment of COVID-19 plus 2 tablets of 6 mg ivermectin were given once daily for five days [15] and another group in which placebo standard treatment was given as per local and international guidelines [16]. Primary outcome was the time of viral clearance measured by detecting COVID-19 PCR on day 7,day 14, and day 21 in patients admitted with COVID-19 infection which were divided as ivermectin and control group and secondary outcome of development of complications such as ARDS and shock . Every participant was thoroughly examined for COVID-19 related symptoms and vitals were assessed including weight, blood pressure , pulse, temperature, respiratory rate and oxygen saturation . Venous blood samples were sent for CBC, Urea, Creatinine, Potassium, ABGs, FBS, CRP, LDH, Ferritin, Procalcitonin, LFTs, D.dimer on day one and repeat sample were done as per requirement at the time of stay in the hospital . An x-ray chest was performed to assess the severity index [17] which were held in keeping as mild and moderate COVID-19 infection and baseline ECG were performed also to evaluate cardiac lesions . A Microsoft Excel database was used to record demographics data (i.e. age and sex), comorbidities (i.e. hypertension, diabetes, chronic liver disease, and cardiovascular disease).

**Data analysis:** Data was imported into SPSS version 23.0. The Shapiro Wilk test was used to find out the normality of the data. Continuous variables were presented as median with interquartile range whereas categorical variables were presented as frequency and percentages. Moreover, the routine test results were evaluated to check if they were in the normal range. A Chi-square test was used to assess the association between ivermectin with standard therapy versus standard therapy in clearance of virus by negative PCR for COVID-19 in relation to days. Mann-Whitney U test was used to assess associations between important laboratory findings and complications . P-value<0.05 was considered significant.

## RESULTS

Total of 210 patients were enrolled in the study and aged matched patients were divided in two groups 105 patients received ivermectin 6 mg twice a day for five days along with conventional therapy while remaining 105 patients received conventional therapy as per local and international guidelines. Male were 140 (66.7%) and female 70(33.3%); age ranges between 26 to 77 years and majority 140(66.7%) were more than 50 years of age and the median age was 55.4 years. Fever, dry cough and dyspnea were major symptoms seen in fever 189 (90%), dry cough 182(86.7%), and dyspnea in 119(56.7%); chest tightness was seen in 56(26.7%) patients. Minority of patients 14(6.7%) were having diarrhea and vomiting. The majority of 112 (53.3%) patients had DM as comorbid illness while hypertension was seen in 56 (26.75%) of patients, chronic liver disease was seen in 7 (3.3%) of patients. The median oxygen saturation at the time of arrival was 85 % (80-95%). The most common of them as shown in Table-1.

ARDS was observed in 42 (20%) patients, shock in 21 (10%) while arrhythmia was seen in 7(3.3%) patients who all had bradyarrhythmia. Ferritin, LDH, D.dimer and Procalcitonin were performed in all patients. Ferritin level was 118 to 1891 ng/dl in our patients and 175(83.3%) patients have more than 250ng/dl, LDH more than 280u/l was seen in 161(76.66%) patients and ranges from 170u/l to 871u/l. D.dimer ranges from 0.6 to 4.70 mg/l and 196 (93.33%) patients were having d.dimer more than 0.50 mg/l ,procalcitonin was less than or equal to 0.15 ng/dl seen in 119 (56.66%) patients . More than 40 u/l ALT was seen in 140 ( 66.66%). PCR for COVID 19 were done on day one, ten, fourteen and twenty days of illness and groups were observed for clearance of the virus by doing two subsequent negative PCR for COVID 19. Out of 105 patients from ivermectin with standard therapy 21 (20%) got negative PCR for COVID 19 on day seven while the patients on standard therapy alone were having positive covid tests in all 105 patients . On day 10 total of 49 more patients from ivermectin with standard found COVID negative along with 21 previously negative had second PCR was found negative in this way total of 70( 66.7%) of ivermectin with standard therapy had negative PCR for COVID 19 while 21(20%) patients from non ivermectin got negative PCR for COVID 19 on day 10 . On day 14 remaining patients of the ivermectin group were found to have negative COVID testing, while 70 ( 66.7%) from non-ivermectin got negative results and remaining 35 ( 31.81%) got negative by 21 days Table-2

When we compare the results of clearance of virus by assessing the PCR for COVID-19 on day 7,day 10, day 14 and day 21 between ivermectin with standard therapy versus standard therapy ; we found The chi-square statistic was 31.2086,the p-value is <0.00001 and the result was significant at $p < 0.05$. This shows a significant relationship between ivermectin with standard therapy versus standard therapy alone . The Mann-Whitney U test was significant in LDH comparison of both groups: the z-score was -2.28031 and the p-value was 0.0226 ( $p<0.05$) . The comparison of procalcitonin was statistically not significant and *z*-score was 0.83354 and the *p*-value was .40654( $p<0.5$) and The D.dimer was statically significant with z score was -3.72708 and the p value was 0.0002( $p<0.05$). By assessing the complications in both groups through Mann-Whitney U test we found development of shock in standard therapy was statistically significant and the z-score was 2.88116, the p-value was 0.00398(<0.05) while the chance of arrhythmia and ARDS in between groups was not statistically significant . Arrhythmia z-score was 0.083354, the p=value was 0.40654 (<0.05) and ARDS z-score was 0.00114, the p-value was 1 (<0.05) as shown in Table-3.

Table 1: Baseline characteristics of patients infected with COVID-19 (n=160)

| **Age, median (IQR),y** | **210 (26-77)** |
|---|---|
| **Gender** | |
| Female | 70 (33.3%) |
| Male | 140 (66.7%) |
| **Comorbidities** | |
| Diabetes | 112 (53..3%) |
| Hypertension | 56 (26.75%) |
| Chronic liver diseases | 07 (3.3%) |
| COPD | 07 (3.3%) |
| Cardiovascular | 14 (6.6%) |
| Systolic B.P, median (IQR), mmhg | 126 (95-180) |
| Diastolic B.P median(IQR),mmhg | 72.5(60-102) |
| Mean arterial pressure, median (IQR), mm Hg | 85 (80-95) |
| Fever | 189 (90%) |
| Dry cough | 182(86.7%) |
| Dyspnea | 119 (56.7%) |

Table 2: Complications, severity of markers and clearance of PCR days in patients infected with COVID-19 (n=210)

| **Complications** | |
|---|---|
| ARDS | 42 (20%) |
| Shock | 21 (10%) |
| arrhythmia( brady) | 7 (3.3%) |
| **Raised markers** | |
| Ferritin | 118-1891 ng/dl |
| LDH | 170-871 u/l |
| D.dimer | 0.6-4.70 |
| Procalcitonin | Less than 0.15 ng/dl(56.66%) |
| **ivermectin with standard therapy 105** | **Standard therapy 105** |
| Day 7 21(20%) | 0 |
| Day 10 70(66.7%) | 21(20%) |
| Day 14 105(100%) | 70(66.6) |
| Day 21 | 105(110%) |

Table 3. Statistical analysis of ivermectin with standard therapy versus standard therapy alone of patients infected with COVID-19 (n=210)

| **ivermectin with standard therapy** | **standard therapy** |
|---|---|
| Chi-square 31.2086 p-value <0.0001(<0.05) | |
| Mann-whitney U test in LDH z-score -2.28031 p-value 0.0226(p<0.05) | Development of shock z-score 2.88116 p-value 0.00398(p<0.05) |
| D.dimer z-score -3.72708 p-value 0.0002(p<0.005) | |

## DISCUSSION

To our knowledge, this is the first and largest single -centered, prospective observational, parallel group(1:1 ratio), standard versus controlled ivermectin study from Pakistan of 210 hospitalized patients with mild to moderate infected patients with COVID-19 looking forward to assess the effectiveness of ivermectin with standard therapy versus standard therapy alone . Pierre Kory et al did a Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin and found statistically significant effects of ivermectin by reducing mortality, early clinical recovery, and viral clearance by time measuring in 18 randomized clinical trials in patients with COVID-19 infection [18] and we also found same promising results of early clearance and less chance of development of complications in ivermectin versus standard therapy . A study on prophylactic use of ivermectin in C0VID-19 infection found that ivermectin had the ability of inhibiting the COVID-19 replication in this way it possibly supports to lower the infection rate and mortality which is in favour of our results [14]. A study from Bangladesh on 5 days treatment of ivermectin versus placebo in mild COVID-19 infection proves to limit viral replication and significant drop in CRP and LDH on day 7 which also favouring our results of statistically significant relationship of LDH and D. dimer in ivermectin versus standard therapy [15]. A randomized trial on ivermectin and doxycycline versus azithromycin and hydroxychloroquine found early improvement in symptom relief and less side effects but had no effect on early clearance of the virus [19] . A study by Leon Caly found the use of ivermectin in vitro can reduce the 5000 fold in viral RNA of SARS-CoV-2 in 48 hours which supports its use in humans for early clearance and better symptom relief [20]. Ivermectin's molecular study found promising interaction of ivermectin with protein targets which were found to be the leading n-protein in SARS-CoV-2 infection [21]. A study by Saiful Islam Khan also found the rapid clearance of SARS-Co-V 2 virus by ivermectin usage with control of the course of illness which is comparable to our results [22]. The ivermectin COVID-19 study demonstrates decreasing mortality in hospitalized COVID-19 infected patients with significant pulmonary involvement [23]. A white paper on ivermectin concludes the use of ivermectin in COVID-19 infection is a potential molecule to be used for prophylaxis and treatment of patients infected with COVID-19 [24]. A randomized clinical trial of 397 patients who were using ivermectin in patients infected with COVID-19 found significant clinical improvement in comparison to the usual therapy [25].

## CONCLUSION

In this single-center case series of 210 PCR for COVID-19 positive admitted patients with mild to moderate COVID-19 found significant improvement in severity markers LDH and D. dimer and Ivermectin with standard therapy also proves to reduce the clearance timing of SARS-Co-V-2 virus in comparison to standard therapy . Standard therapy is found to be associated with increased risk of shock in patients with COVID-19 versus ivermectin with standard therapy which supports its early use for the better symptom relief and timely virus clearance which will ultimately improve mortality.

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