

# Effectiveness of Ivermectin among COVID-19 patients: A Randomized Controlled Trial

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## Author's Contribution

<sup>1,3</sup> Conception of study

<sup>3,5,6</sup> Experimentation/Study conduction

<sup>2,3</sup> Analysis/Interpretation/Discussion

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## Abstract

**Objective:** To determine the effectiveness of Ivermectin among COVID-19 patients in terms of mortality and biochemical/hematological attributes.

**Materials & Methods:** A Randomized Controlled Trial (RCT) was carried out in the Department of Infectious Diseases (DID) of Holy Family Hospital Rawalpindi in March 2021 through a concurrent parallel study design. Apart from seeking Ethical approval for this research, DID was also licensed by the Drug Regulatory Authority of Pakistan (DRAP) for this trial. A total of 90 PCR-positive COVID-19 patients were enrolled in this study via 1:1 randomization in an experimental and control group without blinding. The control group received Standard of Care (SOC) starting from day 1 while the experimental group was given SOC along with Ivermectin (200µg/kg) for 5 days. Study participants were assessed on days 0, 4, 7, and 10 for general symptoms through physical examination, blood oxygen saturation, and diverse hematological and biochemical indicators in addition to adverse events. Data analysis was done by means of SPSS version 25.0. Mean ± SD for age, length of hospital stay, and time to PCR negativity was calculated. Independent sample t-test was applied to determine the mean difference in age, duration of hospital stay, time to PCR negativity, SpO<sub>2</sub>, oxygen supply, serum Hemoglobin, TLC, platelet count, Clinical Severity Score (CSS), urea and creatinine levels of both groups. The difference in secondary outcome (expiry/discharge) of both groups was compared using the chi-square test. P-value ≤ 0.05 was considered significant. A 95% Confidence Interval was also computed.

**Results:** Males constituted the majority (56.7%) of our study participants. A statistically insignificant difference in mean age (P = 0.42) and mean length of hospital stay (P= 0.32) between experimental and control group subjects were observed. Mean time to PCR negativity was reported to be significantly less (P= 0.002) in the experimental group. Significant improvement was seen in PCR negativity (P<0.05), mean Clinical Severity Score (CSS) (P=0.02), mean hemoglobin level (P=0.03), and mean platelet count (P=0.03). However, the difference in health outcomes of both groups was also determined to be statistically insignificant (P>0.2, 95% CI (-0.20 - 0.12)).

**Conclusion:** Ivermectin could not be validated as effective in reducing mortality and improving the health outcome in COVID-19 patients.

**Keywords:** Ivermectin, Randomized Controlled Trial, COVID-19, PCR, Clinical Severity Score.

## Introduction

More than 3 million mortalities across the globe are attributed to COVID-19<sup>1</sup> due to resultant severe respiratory distress.<sup>2</sup> The clinical manifestations of coronavirus infection range from mild flu-like symptoms to deadly pneumonia.<sup>3</sup> Apart from grave health consequences, impending social and legal issues were also reported to be quite diverse across the regions.<sup>4</sup> These outcomes were attributed to the non-availability of potent vaccine<sup>5</sup> against COVID and incognizance of the precise regime for its management.<sup>6</sup>

National Institute of Health ensured the provision of updated guidelines to healthcare professionals, patients, and strategic planners for COVID-19 treatment by their timely revision and endorsement.<sup>7</sup> NIH is also committed to ensuring the effectiveness of new vaccines and drugs against COVID among all end users by facilitating clinical trials.<sup>8</sup> Numerous drugs have undergone multiple phases of clinical trials to test their efficacy and potential in the reduction of COVID-19-related complications and mortalities.<sup>9</sup> In addition to various regimes tested periodically for their potency amid the COVID pandemic; vitamin D was also identified as one of the efficacious remedies to manage COVID-19 at the initial stage in order to boost the immunity of infected individuals.<sup>10</sup>

COVID-19 pandemic is accounted as one of the most terrible pandemics in the world. Its infectivity has directed the efforts of all critical thinkers and researchers toward the discovery of effective medications.<sup>11</sup> Due to grave health outcomes faced in response to coronavirus infection, a combination of drugs is being recommended by US Food and Drug Administration to reduce the resultant fatalities.<sup>12</sup> Ivermectin is being used for treating cases of river blindness and lymphatic filariasis since 1987. Its efficacy in managing such pain-staking ailments and its cost-effectiveness has led scientists toward its testing against SRAS-CoV-2.<sup>13</sup>

The present study is planned in Holy Family Hospital that is a public sector teaching hospital affiliated with Rawalpindi Medical University. It has a well-established Department of Infectious Diseases. This experimental study is initiated due to the scarcity of data about the effectiveness of ivermectin among our patients. This research would enable the concerned health authorities in advocating an efficacious regimen to curb this pandemic and improve healthcare outcomes.

## Materials and Methods

This research was a Randomized Controlled Trial (RCT). Permission for this trial was also sought from the Ethical Review Board of Rawalpindi Medical University (ERB Ref. No. 67/IREF/RMU/2021). A total of 90 patients with confirmed COVID-19 diagnosis (defined as SARS-CoV-2 Polymerase Chain Reaction (PCR) positive nasopharyngeal swab) were enrolled in this research by randomization in 1:1 ratio to receive (a) either the Standard of Care (SOC) plus ivermectin (200µg/kg) for 5 days, starting from day 1 (b) or the SOC alone for 14 days. This was a concurrent parallel study design. Participants were recruited within 2 days of admission into the COVID-19 treatment centre established within the Department of Infectious Diseases (DID) of Holy Family Hospital affiliated with Rawalpindi Medical University, Rawalpindi. DID was licensed to act as a Clinical Trial Site by the Drug Regulatory Authority of Pakistan (DRAP). Before enrollment, participants were given adequate information about the trial, the opportunity to ask questions, and sufficient time to consider participation. The allocation of participants to the groups was randomized based on sequences generated centrally at the treatment center. This was an open-label study without blinding of study participants.

Participants in the intervention group received 200µg/kg of Ivermectin with a meal once, in addition to SOC for 5 days. Assessments on enrollment and days 4, 7, and 10 included general symptoms report, physical examination, blood oxygen saturation, and chest auscultation) and adverse events.

On enrollment, as well as on days 4, 7, and 10 blood samples were obtained to measure Hb level, TLC, platelet count, and RFTs (urea, creatinine). A nasopharyngeal swab for SARS-CoV-2 PCR was also taken at enrollment and on days 4, 7, and 10.

Standard of care (SOC) was determined by the clinical team at the treatment center in line with the current National Interim Guidelines for Clinical Management of COVID-19.<sup>14</sup>

The treatment duration for participants in the intervention group was 5 days of study drug. However, SOC was continued as long as needed. Follow-up was continued until day 14 after study entry at the end of which all participants exit the study. The reason for study product discontinuation was recorded. SpO<sub>2</sub> of the participants was also measured after at least 5 minutes of resting in a sitting or supine position.

Participants were assessed for adverse events daily throughout the study period. Each morning the attending physician asked about the side effects commonly associated with Ivermectin and any additional symptoms.

The data were analyzed using SPSS version 25.0. Mean ± SD for age, length of hospital stay, and time to PCR negativity was calculated. Independent sample t-test was applied to determine the mean difference in age, duration of hospital stay, time to PCR negativity, SpO<sub>2</sub>, oxygen supply, serum Hemoglobin, TLC, platelet count, Clinical Severity Score (CSS), urea and creatinine levels of both groups. The difference in secondary outcome (expiry/discharge) of both groups was compared by means of the chi-square test. P-value ≤ 0.05 was considered significant. A 95% Confidence Interval was also computed.

## Results

Of the total 90 COVID-19 patients confirmed on RT-PCR, 45 were each from the experimental and control group. Males constituted the majority of our study participants in each group as depicted below in Figure 1.

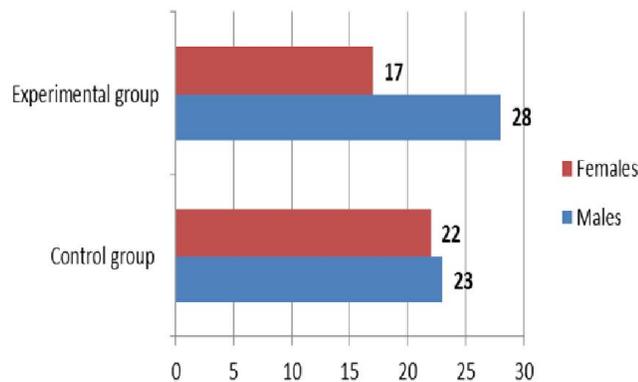


Figure 1: Gender-based distribution of COVID patients in each group of RCT (n = 90)

About 11 patients from the control group and 24 from the experimental group were not suffering from any comorbid states. The propensity of comorbidity among our study subjects is reflected below in Figure 2.

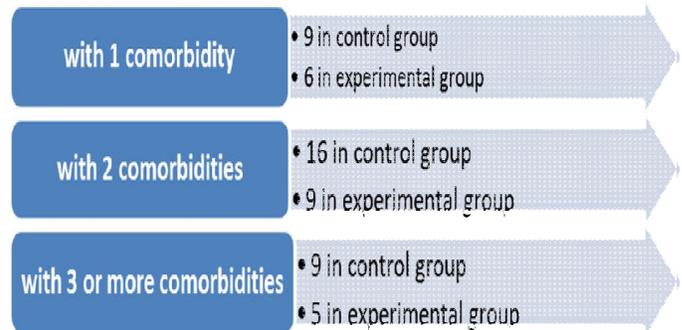


Figure 2: Comorbidity among experimental and control group participants

Hypertension was determined among the majority of our study subjects. About 62.2% and 38% of our control and experimental group patients were hypertensive. This was followed by diabetes mellitus showing 44.4% among control and 24.4% among trial subjects. However Ischemic heart disease (IHD) prevailed among 17.4% of control and 14.3% of trial patients.

Among total of 38 expired study subjects, about 10 patients did not suffer from any comorbidity. Approximately 15 expired persons were both diabetic and hypertensive while 2 and 8 subjects were only diabetic and hypertensive respectively.

Table 1: Comparison of the attributes between the experimental and control group

Attributes	Control group	Experimental group	P-value (95%CI)
Mean age	56.13 ± 17.43 years	53.3 ± 15.7 years	0.42 (-4.11-9.78)
Mean length of hospital stay	9.2 ± 5.2 days	8.3 ± 3.1 days	0.32 (-0.89 - 2.69)
Mean time to PCR negativity	8.13 ± 2.33 days	6.5 ± 2.6 days	0.002* (0.59 - 2.66)
<b>Parameters on day 0 (Admission day)</b>			
Means SPO <sub>2</sub>	91 ± 8.9	90.4 ± 11.3	0.78 (-3.66 - 4.86)
Mean CSS (Clinical Severity Score)	5 ± 0.60	5.02 ± 0.8	0.90 (-0.27 - 0.31)
Mean Oxygen supply	12.9 ± 5.1	12.2 ± 3.9	0.47 (-1.20 - 2.60)
Mean Hemoglobin	13.01 ± 3.0	13.4 ± 1.9	0.46 (-0.66 - 1.44)

Mean TLC	11 ± 4.6	12.2 ± 11.2	0.51 (-2.38 - 4.78)
Mean Platelet count	263.3 ± 102	261.3 ± 74.3	0.91 (-35.38-39.38)
Mean serum Urea level	71.1 ± 49.6	50.6 ± 32.4	0.02*(2.94 - 38.05)
Mean serum Creatinine level	1.67 ± 0.53	1.1 ± 0.8	0.0002* (0.28 - 0.85)
<b>Parameters on day 4</b>			
PCR Report	33 positive, 12 negative	24 positive, 21 negative	< 0.05 * (-0.09 - 0.27)
Means SPO <sub>2</sub>	92.1 ± 5.0	91.7 ± 7.2	0.8 (-2.19 - 2.99)
Mean CSS (Clinical Severity Score)	5.4 ± 1.1	5.6 ± 0.8	0.33 (-0.20 - 0.60)
Mean Oxygen supply	13.8 ± 5.1	12.9 ± 5.4	0.42 (-1.3 - 3.1)
Mean Hemoglobin	12.1 ± 2.2	12.8 ± 2.3	0.14 (-0.24 - 1.64)
Mean TLC	12.3 ± 5.4	12.1 ± 4.1	0.84 (-1.80 - 2.20)
Mean Platelet count	274.9 ± 115	303.1 ± 117.2	0.25 (-20.44 - 76.84)
Mean serum Urea level	79.9 ± 76.8	53.4 ± 34.05	0.04* (1.61 - 51.38)
Mean serum Creatinine level	2.3 ± 2.5	1.02 ± 0.7	0.001* (0.51 - 2.05)
<b>Parameters on day 7</b>			
PCR Report	29 positive, negative	16 positive, 17 negative	28 < 0.05* (-0.05 - 0.29)
Means SPO <sub>2</sub>	91.7 ± 6.1	92.4 ± 4.9	0.55 (-2.02 - 3.42)
Mean CSS (Clinical Severity Score)	5.3 ± 1.1	5.8 ± 0.9	0.02* (0.08 - 0.92)
Mean Oxygen supply	15.6 ± 9.0	10.8 ± 6.9	0.006* (1.44 - 8.16)
Mean Hemoglobin	12.6 ± 2.0	13.6 ± 2.2	0.03* (0.12 - 1.88)
Mean TLC	13.6 ± 5.5	14.3 ± 4.6	0.51 (-1.42 - 2.82)
Mean Platelet count	278.4 ± 97.5	334.7 ± 120.5	0.02* (10.38 - 102.22)
Mean serum Urea level	61.4 ± 39.1	58.9 ± 42.5	0.8 (-14.61 - 19.61)
Mean serum Creatinine level	1.8 ± 2.3	1.14 ± 0.8	0.07 (-0.06 - 1.38)

\*statistically significant

Scenario pertinent to oxygen supply among both study groups showed that only 3 subjects both from experimental and control group were on ventilator to sustain breathing till 7 days as illustrated below in Table 2.

**Table 2: Modalities of oxygen supply among COVID-19 patients**

Attributes of O <sub>2</sub> supply	Day 0		Day 4		Day 7	
	Control group	Experimental group	Control group	Experimental group	Control group	Experimental group
Room Air	12	12	11	4	6	----
Dual O <sub>2</sub>	2	1	1	3	1	1
<sup>1</sup> BiPAP	----	----	2	5	1	3
<sup>2</sup> CPAP	----	1	----	----	----	----
Ventilator	----	----	9	2	3	3

<sup>1</sup>BiPAP-Bilevel Positive Airway Pressure

<sup>2</sup>CPAP-Continuous Positive Airway Pressure

More deaths (21) were reported in the control group than those in the experimental group (17). However, this difference in mortality between the 2 arms was found to be statistically insignificant (P > 0.2) as shown below in Table 3.

**Table 3: Difference in health outcome between the experimental and control group (n = 90)**

Groups	Health outcome		Total
	Expired	Discharged	
Experimental	17	28	45
Control	21	24	45
Total	38	52	90
X <sup>2</sup> = 0.72		P > 0.2, 95% CI (-0.20 - 0.12)	

## Discussion

In the current study, ivermectin was given to COVID-19 patients in the experimental group at a dosage of 200µg/kg for 5 days. Its anti-bacterial and anti-cancer properties have already been proven.<sup>15</sup> Statistically insignificant difference ( $P > 0.2$ ) was observed in both groups with respect to mortality. In a similar study carried out in Iraq, doxycycline in addition to ivermectin was also given to the experimental group. Although this amalgamation of drugs trial by Iraqi researchers was categorized as a successful regimen for COVID; however this combination still led to deaths among 18.2% of critically ill patients.<sup>16</sup> Another research by Rajter et al verified the association of ivermectin with mortality reduction among hospitalized COVID-19 patients suffering from a severe pulmonary disorder.<sup>17</sup> Likewise another study emphasized the usefulness of ivermectin in terms of reduction in fatalities. Even the occurrence of infection among healthcare workers and household contact was also enormously minimized with ivermectin.<sup>18</sup> In a case-control study done by Behera P et al among COVID-infected healthcare workers, about a 73% reduction in SARS-CoV-2 infection was attributed to prophylactically administered ivermectin; even the antiviral effect of this drug has also been determined against Zika virus and influenza A virus.<sup>19</sup> The effectiveness of ivermectin in infection control and death reduction cannot be underestimated. However, the efficacy of other treatment regimens should also be tested.

The mean length of hospital stay among the control group was more ( $9.2 \pm 5.2$  days) than in the experimental group ( $8.3 \pm 3.1$  days). However, this difference was determined to be statistically insignificant ( $P=0.32$ ). A multicenter RCT done among mild to moderately ill COVID patients with Hydroxychloroquine revealed median time to negative PCR report equivalent till day 14 was 5 and 10 days in trial and control groups respectively.<sup>20</sup> A similar double-blind RCT by Babalola et al revealed a momentous reduction in days to COVID negativity among trial group participants ( $P=0.0066$ ).<sup>21</sup> Although ivermectin was proved to be quite effective in the United States in reducing hospitalization among COVID-19 patients or rendering them non-infective earlier; still there is a need for more interventional studies in Pakistan to prove its efficacy.

The present study illustrated that difference in mean SPO<sub>2</sub> between the control and trial groups remained statistically insignificant on day 0 ( $P=0.78$ ), day 4

( $P=0.8$ ), and day 7 ( $P=0.55$ ). The difference in mean Clinical Severity Score (CSS) of both the groups was statistically insignificant on day 0 ( $P= 0.90$ ) and day 4 ( $P= 0.33$ ). However, the CSS score was significantly higher ( $P =0.02$ ) on day 7 with a higher score ( $5.8 \pm 0.9$ ) among trial arm patients. Contrary to our results, an international RCT depicted raised SPO<sub>2</sub> among the trial group receiving ivermectin than those of the control group ( $P=0.073$ ).<sup>21</sup> More evidence should be sought to verify the association of ivermectin with oxygen saturation among COVID patients. There is a need to see the effect of other concomitant variables as well in fluctuating oxygen saturation.

The mean platelet count of our trial group participants on day 7 was higher ( $334.7 \pm 120.5$ ) than those in the control group ( $278.4 \pm 97.5$ ) and the difference in mean platelet count of both groups was also determined to be statistically significant ( $P=0.02$ ). Even the mean hemoglobin of our experimental arm patients was also raised ( $13.6 \pm 2.2$ ) as compared to those in the control arm ( $12.6 \pm 2.0$ ) on day 7 and this difference was also statistically significant ( $P=0.03$ ). Similarly, an experimental study carried out internationally revealed raised platelet ( $P=0.037$ ) count among COVID-19 patients receiving ivermectin.<sup>21</sup> Even an international RCT by Krolewiecki A et al concluded that raised plasma ivermectin concentration was positively correlated ( $r=0.47$ ) with decayed viral load.<sup>22</sup> One of the reasons for use of ivermectin among COVID-19 patients experimentally across the world is the permission granted by the World Health Organization for use of this macrocyclic lactone in clinical trials.<sup>23</sup> However, these trials should be executed with full protocol to avoid a breach of ethics.

Of the total 45 participants in the experimental group, about 17 succumbed to death while 21 out of 45 subjects from the control group expired. This difference in the outcome of the study was found to be statistically insignificant ( $P>0.2$ , 95% CI (-0.20 - 0.12)). A similar RCT carried out by Okumus et al by using ivermectin revealed 6 and 9 mortalities out of 36 experimental and 30 control arm subjects respectively<sup>24</sup> with  $P > 0.2$ . differences in PCR test negativity in our research were also determined to be statistically significant ( $P= 0.002$ , 95% CI (0.59 - 2.66)). contrary to our results, RCT done by Vallejos J et al showed statistically insignificant PCR test negativity between experimental and control group<sup>25</sup>. However, there is a need for further similar studies to establish evidence pertinent to clinical improvement associated with the use of ivermectin among COVID-19 patients

before strongly recommending it as an ideal treatment for coronavirus infection.

## Conclusion

Ivermectin was not determined to be efficacious among COVID-19 patients. Adequate pharmacovigilance should be prioritized before recommending this drug.

## Limitations

Apart from the small sample size, another limitation of our study was difficulty in generalizing the results because the studied population was suffering from a novel coronavirus disease with which our people did not suffer immensely as those reported in western countries.

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