

How to Cite:

Savaie, M., Baghbanian, . R., Soltani, F., Rashidi, M., MalAmir, M. D., Amiri, F., & Bakhtiari , N. The evaluation of effect of ivermectin in addition to standard COVID-19 treatment in intubated patients. *International Journal of Health Sciences*, 5764-5772. Retrieved from <https://sciencescholar.us/journal/index.php/ijhs/article/view/13390>

The evaluation of effect of ivermectin in addition to standard COVID-19 treatment in intubated patients

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Abstract---Introduction: Since the introduction of the Corona pandemic, the use of appropriate antivirals with minimal side effects has been the most important research topic. Laboratory evidence has shown that ivermectin, which has long been available as an anti-parasitic drug market, has anti-COVID19 properties. Therefore, in this study, we investigated the outcomes of this agent administration in patients undergoing mechanical ventilation. Material and method:

Intubated patients with Covid 19 who were eligible for the study were randomly divided into two groups: 1) ivermectin recipient (n = 31) and 2) placebo group (n = 29). This study was performed in Center Corona hospitals in Ahvaz from March 2020 to September 2021. Mortality event was Primary outcome; vital signs and pulmonary Compliance were as secondary outcomes of the study. Results: The results of the study did not show a significant difference between the two groups in demographic data including: age, sex, and time of intubation after the onset of symptoms, plasma levels of LDH, ESR, CRP, D-Dimer and IL-6. Survival analysis did not show a significant difference between the mortality event in the two groups. Among the variables Respiratory Rate, Heart Rate, (Systolic and Diastolic Blood pressure), O2 Saturation and Compliance (Dynamic and static), only O2 Saturation showed a significant difference (P value = 0.008) in the Repeated Measure ANOVA analysis. Conclusion: Although blood oxygen saturation is a very important variable in Covid 19 patients, this study did not show significant efficacy of ivermectin on mechanically ventilated patients and the results suggest that the addition of ivermectin is ineffective or has no synergistic effect with standard treatments Covid 19.

Keywords---Covid-19, Intubation, Ivermectin, Treatment Outcome.

Introduction

It has been almost 5 decades since the discovery of the drug ivermectin. It is an FDA approved macrocyclic lactone as an anti-parasitic treatment for onchocerciasis, strongyloidiasis, lymphatic filariasis, and scabies [1]. This drug paralyzes the parasite by stimulating chlorine channels in GABA receptors. In vitro studies showed antiviral effects against the coronavirus by mechanism of inhibition of the cytoplasmic-nuclear shuttling of viral proteins by disrupting the Import heterodimer complex (IMP α / β 1) and downregulating STAT3, thereby effectively reducing the cytokine storm [2]. There is controversy in clinical claims for its effectiveness [3, 4] and ineffectiveness [5, 6] this agent to treat covid 19 patients. [7-9]. This drug has side effects such as skin reaction (itching, edema, urticaria), lymphadenopathy, joint pain, synovitis, tachycardia, peripheral edema, facial inflammation, postural hypotension, dizziness, diarrhea, nausea, increased eosinophil levels, decreased white blood cells, Increased hemoglobin and increased liver enzymes [10-12]. Most of these studies were on the mild to the moderate clinical condition of the disease. Therefore, in this study, we investigated the consequences of this drug in patients undergoing mechanical ventilation, and considering the ethical dimension we did not deprive of using this drug alone patients from standard treatment.

Materials & Methods:

This study was permitted by the Pain Research Center of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (Pain-0004). The all-ICU hospitalized patients covid 19 hospitals, Ahvaz, Iran, from March 2020 to September 2021

that candidates for intubation and have consented to participate in the study enrolled to study. The consent forms have been collected from accompanies the patients that meet suitability criteria. All patients received standard treatments according to the Iranian national protocol. Covid 19 standard treatment in hospitalized cases according to the national protocol included supportive therapies (oxygen therapy, proper nutrition), antiviral drugs (200 mg intravenous Remdesivir on the first day and 100 mg from the second to the fifth day), corticosteroids (dexamethasone injection, Methylprednisolone injection or oral prednisolone daily for up to 10 days), injectable anticoagulants (heparin or enoxaparin), mucolytic (bromhexine or acetyl cysteine) and supplements (vitamin C, vitamin D, and zinc). All patients were randomly divided into two groups. In the case group of the patients, in addition to receiving the prescribed drugs according to the national protocol, from the time the patient enters the intensive care unit, ivermectin for patients in the intervention group begins and continues for 5 days (the first day 6 mg twice in Day and second to fifth day 3 mg twice daily). In the control group, in addition to the drugs prescribed in accordance with the national protocol, the patient receives a placebo orally in the form of a drug similar to ivermectin (starch tablets).

Inclusion criteria were positive Covid-19 PCR test, intubation, does not have an increase in liver enzymes, at least 18 years old age. Exclusion criteria include the following: history of drug allergy, pregnant women, withdrawal of the patient's family from continuing to participate in the study. Block randomization was performed to assign each treatment. In the randomized block method used in this study, first, we formed two groups ivermectin (case) and placebo (control), then according to the number of patients come, we determine how many patients will be randomized. So, by specifying the total number of samples that are in two equal groups of intervention and control, it is given to the software on www.sealedenvelope.com. This software randomly determines which group A or B the references are randomly assigned to each day, respectively. For example, randomization for one day is AAABBBABBA and the next day is BBABABABAA. Note that each block has 5 As and five Bs, maintaining a balance of the two despite the random order. This software calculates and determines the order of placement A and B based on the factorial and the number of people in each block. This study was conducted by a double-blind design. The patients and investigators were blinded. Outcomes during the study, demographic information including age, sex, underlying diseases, and vital signs including heart rate, blood pressure, body temperature, and arterial blood oxygen saturation, was recorded for each patient in individually designed forms. The patient is monitored daily for up to 28 days from the start of the study. Before receiving the first dose of the drug, the patient's static compliance is measured and will continue daily until he is separated from the ventilator for a maximum of 28 days and the results will be recorded in the patient data collection form. Dynamic and static pulmonary compliance were calculated. Static compliance is closer to reality and is calculated by creating an inspiratory pause by ventilator. For this purpose, after ensuring complete sedation with volume SIMV mode, the plateau pressure is determined by pressing the inspiratory hold button and is calculated using the following formula: static compliance = tidal volume / (Pplateau - PEEP).

Patients' demographic data were reported as a percentage or mean $\pm$ standard deviation (SD). Vital sign and pulmonary compliance variables were evaluated by repeated measure ANOVA. Mortality events were analyzed by Log-rank (Mantel-Cox) test. Graphpad Prism (ver 8.0.2) was used for statistical analyses. A P-value less than 0.05 considered as statistical significance.

Results:

Out of 16601 hospitalized patients, 15292 patients with Covid-19 were enrolled in the study by positive PCR test. The mean age of these patients was 52.92 years. In this study, 7622 patients were male and 7670 patients were female. The results showed that these patients were hospitalized for an average of 4 days. Also, 3364 patients, 22% of the total patients were admitted to the ICU. 13816 (90.34%) patients were not intubated and 1476 (9.65%) patients were intubated. 13922 (91.4%) patients survived and 1370 (8.95%) died. In intubated cases, 90.3% died. 95.7% of patients had CT scans with lung involvement. There was a significant relationship between lung involvement and intubation status and death. 91% of intubated patients, had primary arterial blood oxygen saturation below 93% and 8.5% had primary arterial saturation above 93%. A significant correlation was found between primary arterial blood oxygen saturation status and intubation as well as death. Death rates were higher in individuals with primary arterial blood oxygen saturation below 93%. There was a significant relationship between intubation status and the presence of underlying cancer, history of chemotherapy, liver disease, diabetes, AIDS, pregnancy, heart disease, chronic renal failure, history of chronic dialysis, chronic lung disease, and hypertension. Among total patients, 488 patients received ivermectin during their treatment: the death rate in patients who did not receive ivermectin was 9.2%, and the death rate in patients who received ivermectin was 10.9%. 70 patients were included in the study (Figure 1). In the ivermectin group, mean age, intubation time after the onset of symptoms, and plasma levels of LDH, ESR, CRP, D-Dimer, and IL-6 were 64.03, 5.28, 6.24, 1859, 42, 32.93, 336.2, respectively; In the placebo group, these values were 62.35, 4.39, 6.54, 1679, 39.61, 35.35, 372.1, 62.70 respectively. A comparative analysis of the two groups did not show a significant difference (Table 1).

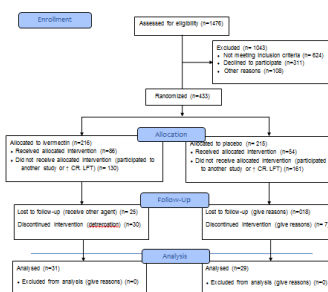


Figure 1 consort flow chart

Table 1 Demographic DATA

	Ivermectin (n=31)	Control (n=29)	P value
Age (yr, mean $\pm$ SD)	64.03 $\pm$ 14.87	62.35 $\pm$ 14.03	0.659
Gender (Male)	20 (64.52%)	21(72.41%)	0.585 *
Intubation after onset of symptom (mean $\pm$ SD)	5.28 $\pm$ 2.47	4.39 $\pm$ 4.60	0.351
Period of ventilation (mean $\pm$ SD)	6.24 $\pm$ 2.28	6.54 $\pm$ 1.90	0.574
LDH (mean $\pm$ SD)	1859 $\pm$ 802.6	1679 $\pm$ 779.2	0.381
ESR (mean $\pm$ SD)	42.31 $\pm$ 28.58	39.61 $\pm$ 26.56	0.707
CRP (mean $\pm$ SD)	32.93 $\pm$ 24.17	35.35 $\pm$ 17.45	0.697
D-Dimer	336.3 $\pm$ 431.3	372.1 $\pm$ 32.1	0.739
IL-6	62.90 $\pm$ 29.77	62.70 $\pm$ 34.18	0.939

Primary outcome assessed based on mortality analysis, data were compared for days after hospitalization and days after intubation. The results of the Log-rank (Mantel-Cox) test for post-hospital mortality (Figure 2A) and post-intubation mortality (Figure 2B) were P-values 0.463 and 0.571, respectively, which did not show a significant difference in mortality. All patients in both groups eventually died.

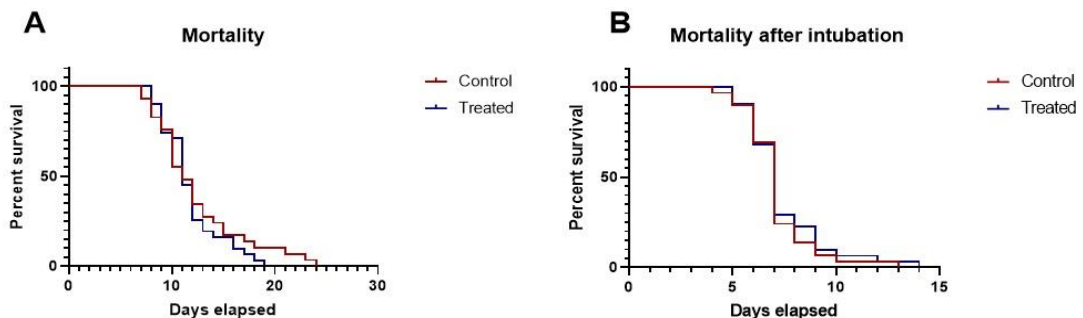


Figure 2 Mortality event, A) mortality event after hospitalization ($P= 0.463$), B) mortality event after intubation ($P= 0.571$)

Secondary outcomes were examined and analyzed daily for up to 6 days: Respiratory Rate, Heart Rate, Systolic and Diastolic Blood pressure, O₂ Saturation and dynamic and static compliance of lung. The values obtained in the Repeated Measure ANOVA analysis were P value = 0.0551, 0.008, 0.62, 0.234, 0.008, 0.186, 0.407, respectively, compared to the two groups of ivermectin and placebo (Figure 3). Due to the fact that the heart rate variable and SO₂ showed a significant difference, repeated measures analysis was performed for them, which was the oxygen concentration on the fifth day ($P = 0.0357$) and sixth day ($P =$

0.0231). The value of post hoc analysis in the heart rate variable on the second day was equal ($P = 0.0401$).

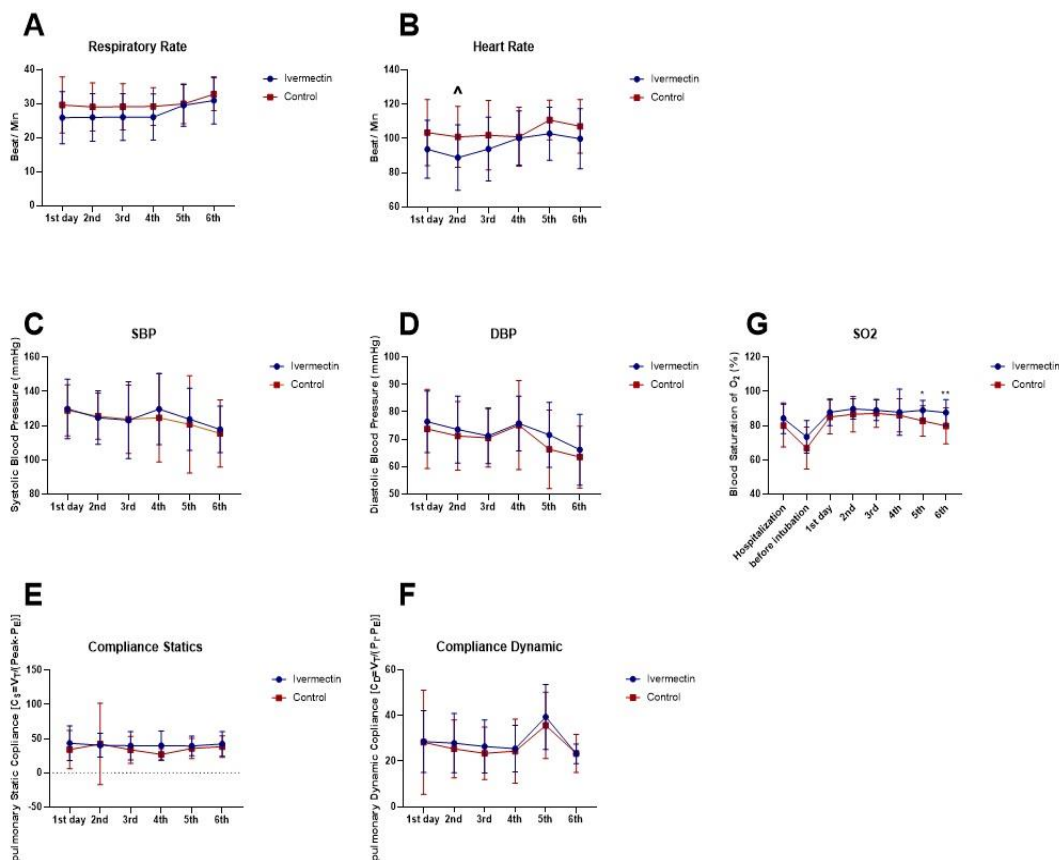


Figure 3 Secondary Outcomes, A) Respiratory Rate ($P=0.05$), B) Heart Rate ($P=0.008$), C) Systolic BP ($P=0.62$), D) Diastolic BP ($P=0.234$), E) Compliance Static ($P=0.186$), F) Compliance Dynamic ($P=0.407$) and G) SO_2 ($P=0.008$)

* $P = 0.0357$ ** $P=0.0231$ ^ $P=0.401$

Discussion

In mortality analysis, data were compared for days after hospitalization and days after intubation. The results of Log-rank (Mantel-Cox) test for post-hospital mortality (Figure 2A) and post-intubation mortality (Figure 2B) were (P value 0.463 and 0.571), respectively, which did not show a significant difference in mortality. All patients in both groups eventually died.

Although the number of people is considered to compare the limitations of the recent study, but due to the lack of significant differences between the demographic information between the two groups, it can be concluded that randomization has been done in the best possible way. The course of Covid-19 disease can be divided into three stages: early, pulmonary and thrombo-

Inflammatory. The early stage often includes people who have received outpatient treatment less than six days after the onset of symptoms. These symptoms include: fever, myalgia, anosmia, headache, diarrhea and dry cough. If Covid-19 progresses, the disease enters the pulmonary stage. Symptoms of this stage can include: dyspnea, hypoxemia, bilateral chest infiltrate, encephalopathy, this stage lasts up to 14 days. The acute respiratory distress syndrome (ARDS) process and need to mechanical ventilation occur at this stage. In terms of the trend of laboratory changes, we can mention the increase of lactate dehydrogenase (LDL), C reactive protein (CRP), interleukin-6 (IL-6), d-dimer, ferritin. Therefore, in this study, the functions of erythrocyte sedimentation rate (ESR), LDL, CRP; IL-6, d-dimer and ferritin at the time of intubation were investigated. The LDH was 5 times higher than normal. LDH is elevated in many diseases and is not a specific indicator, but indicates an immunosuppressive state and involvement of natural killer (NK) cells [14]. Other markers, such as CRP, IL-6, d-dimer, and ESR, exceed the normal according to these findings, a favorable outflow is not predicted for patients. The third stage of disease occurs with clinical symptoms of myocarditis, refractory hypoxemia, secondary infection, acute kidney injury and acute cardiac injury. The above cases have a high percentage of mortality. The administration of ivermectin, has not prevented patients from entering higher stages of disease. Therefore, it has not had a chance to protect mortality.

As mentioned earlier, the laboratory reasons for the introduction of ivermectin are the mechanisms of inhibition of cytoplasmic dependent on the import of IMPa and downregulation of the three-state receptors model [15, 16]. This mechanism can have more effects in stages 1 and 2. In stage 2 and 3 of the disease, damage has occurred in the cellular dimension, so the addition of antiviral drug according to the standard diet does not show a synergistic effect. In the second and third stage patients, there is no strong clinical evidence of the effectiveness of this drug [5, 6]. Systematic review studies that have considered this drug effective due to the lack of randomized clinical trials (RCT) have low validity in terms of clinical evidence [3, 4, 17-19]. Studies in mild to moderate conditions have made claims such as reduced mortality, severity, and shorter time to symptom alleviation.

The trend of changes in secondary outcomes in the O₂ saturation and heart rate variables is an important issue. The improvement of oxygen concentration observed fifth and sixth days, is due to the nature of the treatment and this clinical advantage cannot be invoked. Heart rate changes in the ivermectin group refer to the side effects of this drug that cause cardiomyopathy. However, this event was observed on the second day after receiving the drug and is an event that is self-limited [20-22] and it is not about to creating a crisis.

Conclusion

Although blood oxygen saturation is a very important variable in Covid 19 patients, this study did not show significant efficacy of ivermectin on mechanically ventilated patients and the results suggest that the addition of ivermectin is ineffective or has no synergistic effect with standard treatments Covid 19.

Acknowledgments:

The budget and financial resources of this thesis research project (No. PAIN-0004) was provided by the Honorable Vice chancellor of Research and Technology of Ahvaz Jundishapur University of Medical Sciences and was approved by the ethics committee with code IR.AJUMS.REC.1400.234

This article is the result of the thesis of Dr. Reza Baghbanian to receive the degree of subspecialty in critical care medicine from Ahvaz Jundishapur University of Medical

Conflict of interest declaration:

None of the authors of this study, individuals or institutions have any conflict of interest for the publication of this article.

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