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The effect of adding ivermectin to the standard COVID-19 treatment in intubated patients

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ABSTRACT

Introduction: Effective antiviral medications with minimal side effects has received scholarly attention since the start of the COVID-19 pandemic. Ivermectin, a long-time anti-parasitic drug, has been proven through laboratory tests to have anti-COVID-19 effects.

Objectives: This study investigated the effects of inclusion of ivermectin to the standard treatment of mechanically ventilated patients.

Patients and Methods: This study is a double-blinded, randomized, placebo-controlled clinical trial that was conducted on COVID-19 patients, in Ahvaz, Iran, from March 2020 to September 2021. Intubated COVID-19 patients who met the inclusion criteria were randomly allocated into two groups, placebo (n = 29) and the ivermectin-treated (n = 31). The primary outcome was the mortality, and the secondary outcomes were pulmonary compliance and vital signs.

Results: Two groups were similar regarding demographic characteristics such as age, gender, the length of time since the onset of symptoms before intubation, the level of lactate dehydrogenase (LDH) in the blood. Moreover, the difference in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimer, and interleukin 6 (IL-6) was not significant between the two groups. Regarding mortality rate, no significant difference between the two groups was detected. Furthermore, O2 saturation on day 5 was significantly higher in the ivermectin group as opposed to the control group (P=0.008). No statistically significant difference was found between the two groups regarding respiratory rate, heart rate, systolic and diastolic blood pressure, and lung compliance (dynamic and static).

Conclusion: Regarding the importance of blood oxygen saturation in COVID-19 patients, our results showed no significant effect of ivermectin in the treatment of ventilated COVID-19 patients, suggesting that its addition to the standard COVID-19 treatment either is ineffective or has no synergistic effect.

Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (Identifier: IRCT20190417043295N2; https://www.irct.ir/trial/57603, ethical code#IR.AJUMS.REC.1400.234).

Implication for health policy/practice/research/medical education:
Various drugs, alone or in combination with other treatments, have been tested to find an effective treatment for COVID-19. This study investigated the effectiveness of one of these drugs (i.e., ivermectin). We found that adding this agent to the standard treatments for COVID-19 is ineffective or has no synergistic effect.

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Clinical Trial

Introduction

Ivermectin was first discovered about 50 years ago. It is a macrocyclic lactone with Food and Drug Administration (FDA) approval for the antiparasitic treatment of scabies, lymphatic filariasis, onchocerciasis, and strongyloidiasis (1). This medication paralyzes the parasites by activating the chloride channels of GABA receptors. In vitro studies have shown the coronavirus-specific antiviral efficacy of ivermectin, which disrupts the import heterodimer complex (IMPα/β1) and suppresses STAT3, both of which make cytokine storms less likely and mediate the cytoplasmic-nuclear shuttling mechanism of viral

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proteins (2). Several clinical claims have been made regarding this medication's efficacy (3,4) and inefficacy (5,6) in treating COVID-19 patients. The adverse effects include urticaria, lymphadenopathy, arthralgia, synovitis, tachycardia, peripheral edema, facial swelling, orthostatic hypotension, dizziness, diarrhea, nausea, eosinophilia, and changes in the number of white blood cells in the blood. High levels of hemoglobin and liver enzymes have also been observed (7-9).

Objectives

In the present study, we compared the effects of standard treatment plus ivermectin with standard treatment alone in mechanically ventilated COVID-19 patients.

Patients and Methods

Study design

This is a double-blinded, randomized, placebo-controlled clinical trial, conducted from March 2020 to September 2021. The COVID-19 patients who were admitted to the intensive care unit, qualified for intubation, and consented to participate in the study were enrolled. Patients who met the eligibility criteria provided their informed consent. Every patient received the same level of care in accordance with the Iranian national protocol. According to this protocol, COVID-19 standard treatment for hospitalized patients includes supportive therapies (oxygen therapy and proper nutrition), antiviral medications (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 agents (bromhexine or acetylcysteine) and supplements (vitamin C, vitamin D and zinc). One-hundred eligible patients were randomly allocated into two groups. In addition to receiving the drugs recommended by the national protocol, patients in the intervention group were started on ivermectin (ivermectin TKJ 3 mg tablet-IVEKTA, Jam Tadbir Kala/Tehran, Iran; manufactured by Europhartec/France) as soon as they were admitted to the intensive care unit, then this protocol continued for a total of five days (the first day; 6 mg twice a day, and the second to fifth days; 3 mg twice a day). The patients in the control group received a placebo identical to ivermectin (starch tablet, manufactured by the school of pharmacy of this university) in addition to the drugs given by the national protocol. Meanwhile, due to ethical reasons, no patient was excluded from receiving the standard care.

The eligibility criteria were; successful intubation, positive polymerase chain reaction (PCR) test for COVID-19, normal liver function test, and age more than 18 years old. Patients who were pregnant or had a history of drug allergies and those who withdrew from the study participants were excluded.

Permuted block randomization technique was conducted to randomly assign patients to two groups; ivermectin (cases) and placebo (control). After determining the total number of samples to be included equally in the intervention and control groups, data were submitted to an online program at https://www.sealedenvelope.com/. This software randomly determines which group A or B the references are randomly assigned to each day, respectively. For instance, the randomization could be AAABBBABBA one day and BBABABABAA the next. Despite the random order, each block contains a balanced number of As and Bs (5A, 5B). Based on the number of people in each block, the program determines and selects the order of placement A and placement B. The entire study conducted a double blind, i.e., neither the patients nor the researchers were aware of group allocation, specially designed forms were used to record the data for each patient. This included vital signs such as heart rate, blood pressure, temperature, arterial oxygen saturation and demographic data like age, gender, and any underlying illnesses. Patients received daily monitoring from the start of the study for up to 28 days. The patients' static compliance was assessed before the first medication dosage and was checked every day until the patient was weaned from ventilation for up to 28 days. The results were recorded on patient data collection forms. Accordingly, lung compliance (both dynamic and static) was assessed; since, static compliance is more realistic and calculated by creating an inspiratory pause by the ventilator.

Statistical analysis

The patients' demographic information was shown as mean ± standard deviation or as the percentage. Sidak test and chi-square test are employed to examine the differences between quantitative laboratory measures and categorical variables between two groups, respectively. Repeated measures analysis of variance (ANOVA) was employed to evaluate variables related to vital signs and pulmonary compliance. Log-rank (Mantel-Cox) analysis was used to examine mortality events. GraphPad Prism (version 8.0.2) was employed for statistical analysis. Statistical significance was defined as a P value of ≤ 0.05.

Results

The mean age of patients was 52.92 years. The mean length of stay for these patients in hospitals was four days. The mortality rate in patients receiving and not receiving ivermectin was 10.9% and 9.2%, respectively. Of all patients assessed for eligibility, 100 patients were included in the randomization while 21 patients in the control group and 19 patients in the ivermectin group were excluded (Figure 1). The mean age, the time between onset of symptoms to intubation, the length of mechanical ventilation and the plasma concentrations of lactate dehydrogenase (LDH), ESR, C-reactive protein (CRP), D-dimer, and interleukin

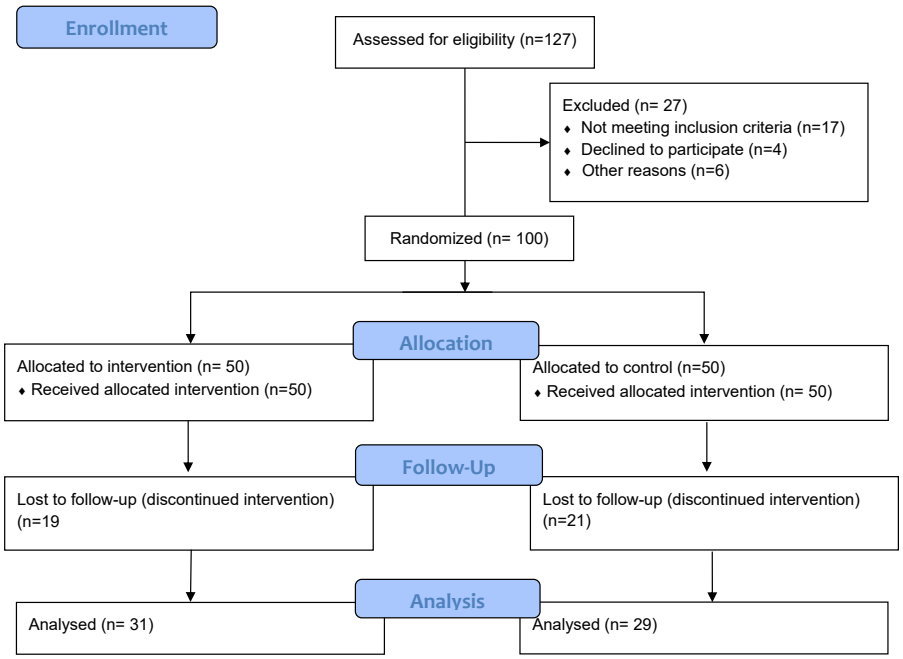

Figure 1. Consort flow chart of the study.

6 (IL-6) in the ivermectin group were 64.03 (years), 5.28 days, 6.24 days, 1859 IU/L, 42 mm/h, 32.93 mg/L, 336.2 ng/mL and 62.9 pg/mL respectively and 62.35 years, 4.39 days, 6.54 days, 1679 IU/L, 39.61 mm/h, 35.35 mg/L, 372.1 ng/mL, and 62.70 pg/mL in the placebo group. A comparative analysis of the two groups did not show a significant difference (Table 1).

Mortality rates in both groups were compared in terms of days following hospitalization and the days following intubation. No statistically significant differences were observed based on the log-rank test (Mantel-Cox) results for post-hospital mortality (Figure 2A, $P=0.463$) and post-intubation mortality (Figure 2B, $P=0.571$). All patients in both groups were eventually died.

Secondary outcomes were examined and analyzed daily for up to six days.

According to the results of the repeated measures ANOVA, the following *P* values were respectively obtained when comparing the two groups regarding respiratory rate, heart rate, systolic blood pressure, diastolic blood pressure, oxygen saturation, and pulmonary dynamic and static compliance between the two groups of ivermectin and placebo; 0.0551, 0.008, 0.62, 0.234, 0.008, 0.186, and 0.407 (Figure 3). The heart rate showed a significant decrease in ivermectin group compared to placebo group on day two with identical post-hoc analysis values ($P = 0.040$). The SPO_2 showed a significant improvement in ivermectin group compared to placebo group on the fifth day ($P=0.0357$) and sixth day ($P=0.0231$) according to the repeated measures analysis.

Discussion

Analysis of mortality consisted of the comparing the days following hospitalization and the days following

Table 1. Demographic data of the included patients in the trial

	Ivermectin (n=31) (mean ± SD)	Control (n=29) (mean ± SD)	*P* value
Age (y)	64.03 ± 14.87	62.35 ± 14.03	0.659*
Gender/Male (n)	20 (64.52%)	21(72.41%)	0.585 **
Time between symptom onset to intubation (day)	5.28 ± 2.47	4.39 ± 4.60	0.351*
Period of ventilation (day)	6.24 ± 2.28	6.54 ± 1.90	0.574*
LDH (IU/L)	1859 ± 802.6	1679 ± 779.2	0.381*
ESR (mm/h)	42.31 ± 28.58	39.61 ± 26.56	0.707*
CRP (mg/L)	32.93 ± 24.17	35.35 ± 17.45	0.697*
D-dimer (ng/mL)	336.3 ± 431.3	372.1 ± 32.1	0.739*
IL-6 (pg/mL)	62.90 ± 29.77	62.70 ± 34.18	0.939*

SD, standard deviation; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-6, interleukin 6.
*Sidak test, **Chi-square test.

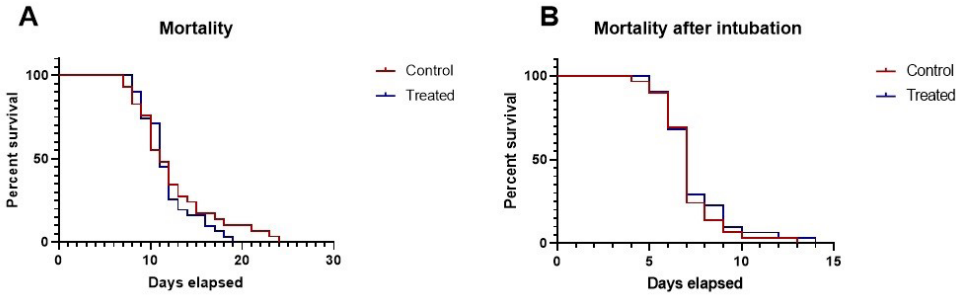

Figure 2. Mortality event (A) after hospitalization (P = 0.463), (B) after intubation (P = 0.571).

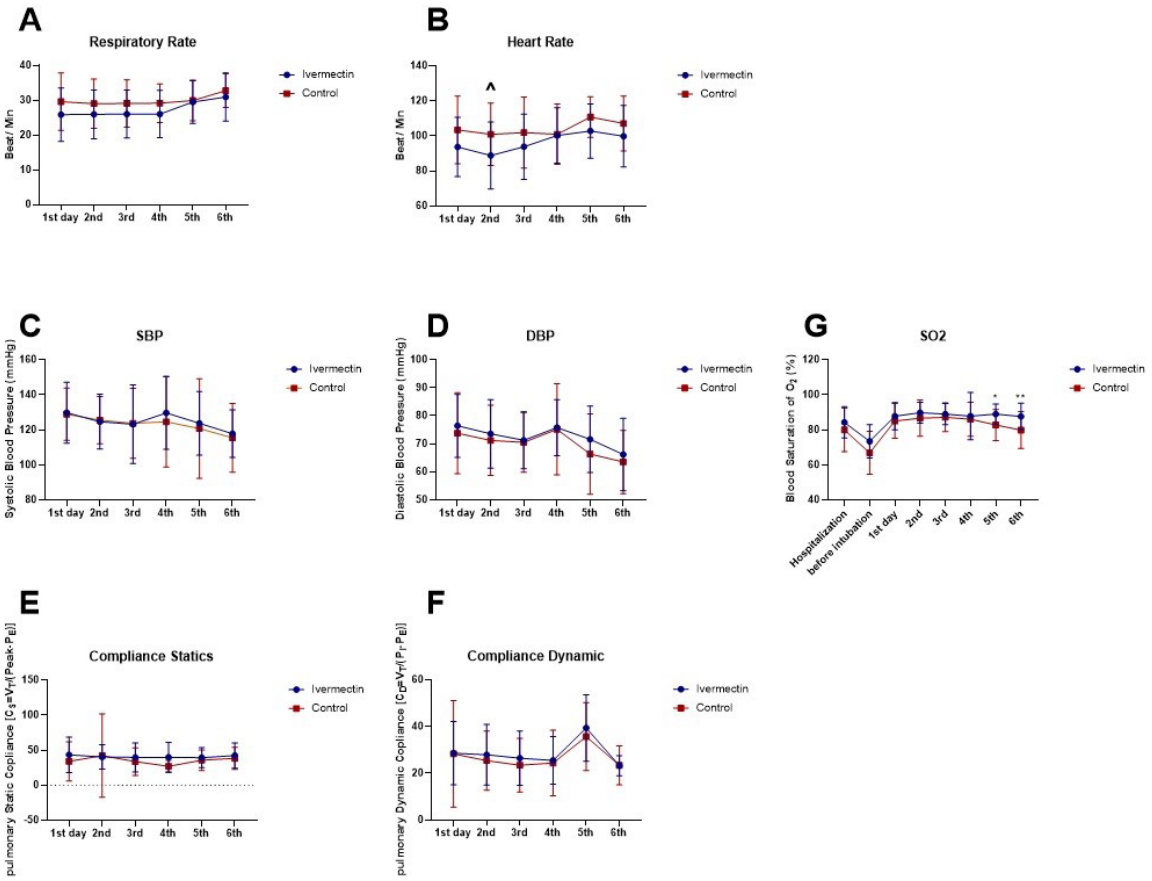

Figure 3. Secondary outcomes. (A) Respiratory rate (P = 0.05), (B) Heart rate (P = 0.008), (C) Systolic blood pressure (P = 0.62), (D) Diastolic blood pressure (P = 0.234), E) Static compliance (P = 0.186), (F) Dynamic compliance (P = 0.407) and (G) SO2 (P = 0.008).

intubation. According to the log-rank test (Mantel-Cox) results, no statistically significant differences in mortality were observed in post-hospitalization mortality (Figure 2A) versus post-intubation mortality (Figure 2B; P-values of 0.463 and 0.571 respectively). All patients in both groups eventually died. The small sample size was one of the limitations of our study. Given that no significant difference was observed between the two groups in terms of demographic variables, it could be interpreted that randomization was conducted correctly.

The progression of COVID-19 can be divided into three stages; early, pulmonary, and thrombo-inflammatory period. Within six days when the symptoms appear, patients in the early stage are frequently treated in an outpatient setting. Typical symptoms of these patients include fever, muscle pain, olfactory disturbance, headache, diarrhea, and dry cough. If not treated, COVID-19 enters the pulmonary stage, the symptoms of which are; dyspnea, hypoxemia, bilateral thoracic infiltrates, and encephalopathy. This stage lasts up to 14 days.

A ventilator is required in this stage of the disease due

to the onset of acute respiratory distress syndrome. Our results showed elevated levels of ferritin, LDL, CRP, IL-6, and D-dimer. In our study, erythrocyte sedimentation rate (ESR), LDL, CRP; IL-6, d-dimmer and ferritin at the time of intubation were assessed. Our study showed, the value of serum LDH was five times higher than normal, however plasma LDH is elevated in several diseases and is not a specific indicator, but it indicates the immune system activation state and involvement of natural killer cells (11).

These results showed that other markers like CRP, IL-6, D-dimer, and ESR are above normal limits. Acute renal injury, acute cardiac injury, myocarditis, refractory hypoxemia, and secondary infections are some of the clinical signs indicating that the disease is in its third stage. The mortality rate for the conditions mentioned above is substantial. Our clinical trial showed that administration of ivermectin had no role in both disease progression and mortality.

As mentioned earlier, the laboratory rationale for introducing ivermectin is its cytoplasm-dependent inhibition of importin (IMP) α and also by a downregulation in a three-state receptor model (12,13). This process may have a more significant effect in the first and second stages of COVID-19. Antiviral medications added to a conventional treatment do not have synergistic benefits in the second and third stages of the disease since cellular damage has already been occurred. The effectiveness of this medication in patients in their second or third stages of the disease is not supported by solid clinical data (5,6). The lack of randomized clinical trials has led to limited clinical evidence of systematic review studies considering this drug effectivity (3,4, 14-16). Studies in mild to moderate conditions showed reduced mortality, severity, and shorter time of symptom alleviation. Improved oxygen levels on days 5 and 6 could be attributed to the standard treatments, which cannot be ignored (17-19). Decreased heart rate in the ivermectin group on the second day refer to the known side effects of this drug that cause cardiomyopathy; However, this event is self-limited and it is not about to creating a crisis.

Conclusion

The results of this study indicate that adding ivermectin to the routine COVID-19 treatment either is useless or does not act synergistically with other treatments to improve the survival of the patients.

Limitations of the study

This study has some limitations including limited number of cases included, mortality of nearly all patients included in study (cases and controls) due to high mortality of COVID-19 during the surge of Delta variant outbreak period. Therefore, further studies are needed to obtain more reliable results.

Authors' contribution

Conceptualization: MS, RB, FA, MR.
Methodology: MS, RB, FA, FS, NB.
Validation: MS, NB, MR.
Formal analysis: MS, NB.
Investigation: MS, RB, MR.
Resources: MS, RB.
Data curation: MS, NB, FA, FS.
Writing–original draft preparation: MS, RB, NB.
Writing–review and editing: NB, FA, MS, MR.
Visualization: NB, RB.
Supervision: MS, NB, MD, MR.
Project administration: MS, FA, FS.
Funding acquisition: MS.

Conflicts of interest

None of the authors of this study interacted with individuals or institutions have any conflict of interest for the publication of this article. None of the authors of this study had a relationship with the company of manufacturing or distributing of ivermectin. All medications provided by hospital pharmacy were free of charge (by research grant of university hospital).

Ethical issues

The research was conducted in accordance with the Declaration of Helsinki. The Ethics Committee at Ahvaz Jundishapur University of Medical Sciences approved all study protocols (Ethical code #IR.AJUMS.REC.1400.234). Written informed consent was obtained from all participants prior to intervention. No patient was excluded from receiving the standard care. This study was extracted from the M.D. thesis of Reza Baghbanian at this university (Thesis#Pain-0004). Accordingly, the trial protocol was approved in the Iranian Registry of Clinical Trial (#IRCT20190417043295N2; https://www.irct.ir/trial/57603. Besides, publication ethical considerations (avoiding plagiarism, data fabrication, and double publication) were strictly observed by the authors.

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References

1. Hariyanto TI, Halim DA, Rosalind J, Gunawan C, Kurniawan A. Ivermectin and outcomes from COVID-19 pneumonia: a systematic review and meta-analysis of randomized clinical trial studies. Rev Med Virol. 2022;32:e2265. doi: 10.1002/rmv.2265.
2. Low ZY, Yip AJW, Lal SK. Repositioning Ivermectin for COVID-19 treatment: molecular mechanisms of action against SARS-CoV-2 replication. Biochim Biophys

Acta Mol Basis Dis. 2022;1868:166294. doi: 10.1016/j.bbadis.2021.166294.
3. Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis. 2021;103:214-6. doi: 10.1016/j.ijid.2020.11.191.
4. Babalola OE, Bode CO, Ajayi AA, Alakaloko FM, Akase IE, Otrofanowei E, et al. Ivermectin shows clinical benefits in mild to moderate COVID19: a randomized controlled double-blind, dose-response study in Lagos. QJM. 2022;114:780-8. doi: 10.1093/qjmed/hcab035.
5. Reis G, Silva E, Silva DCM, Thabane L, Milagres AC, Ferreira TS, et al. Effect of early treatment with ivermectin among patients with COVID-19. N Engl J Med. 2022;386:1721-31. doi: 10.1056/NEJMoa2115869.
6. Lim SC, Hor CP, Tay KH, Mat Jelani A, Tan WH, Ker HB, et al. Efficacy of ivermectin treatment on disease progression among adults with mild to moderate COVID-19 and comorbidities: the I-TECH randomized clinical trial. JAMA Intern Med. 2022;182:426-35. doi: 10.1001/jamainternmed.2022.0189.
7. Fox LM. Ivermectin: uses and impact 20 years on. Curr Opin Infect Dis. 2006;19:588-93. doi: 10.1097/QCO.0b013e328010774c.
8. Aroke D, Tchouakam DN, Awungia AT, Mapoh SY, Ngassa SN, Kadia BM. Ivermectin induced Steven-Johnsons syndrome: case report. BMC Res Notes. 2017;10:179. doi: 10.1186/s13104-017-2500-5.
9. Okumuş N, Demirtürk N, Çetinkaya RA, Güner R, Avcı İ Y, Orhan S, et al. Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients. BMC Infect Dis. 2021;21:411. doi: 10.1186/s12879-021-06104-9.
10. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395:1763-70. doi: 10.1016/s0140-6736(20)31189-2.
11. Konjević G, Jurisić V, Spuzić I. Association of NK cell dysfunction with changes in LDH characteristics of peripheral blood lymphocytes (PBL) in breast cancer patients. Breast Cancer Res Treat. 2001;66:255-63. doi: 10.1023/a:1010602822483.
12. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem J. 2012;443:851-6. doi: 10.1042/bj20120150.
13. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020;178:104787. doi: 10.1016/j.antiviral.2020.104787.
14. Chachar AZ, Khan KA, Asif M, Tanveer K, Khaqan A, Basri R. Effectiveness of ivermectin in SARS-CoV-2/COVID-19 patients. Int J Sci. 2020;9:31-5. doi: 10.18483/ijSci.2378.
15. Chowdhury AT, Shahbaz M, Karim MR, Islam J, Dan G, Shuixiang H. A comparative study on ivermectin-doxycycline and hydroxychloroquine-azithromycin therapy on COVID-19 patients. Eurasian J Med Oncol. 2021;5:63-70.
16. Bukhari KH, Asghar A, Perveen N, Hayat A, Mangat SA, Butt KR, et al. Efficacy of ivermectin in COVID-19 patients with mild to moderate disease. medRxiv [Preprint]. February 5, 2021. Available from: https://www.medrxiv.org/content/10.1101/2021.02.02.21250840v1.
17. Ottesen EA, Campbell WC. Ivermectin in human medicine. J Antimicrob Chemother. 1994;34:195-203. doi: 10.1093/jac/34.2.195.
18. Rothova A, van der Lelij A, Stilma JS, Wilson WR, Barbe RF. Side-effects of ivermectin in treatment of onchocerciasis. Lancet. 1989;1:1439-41. doi: 10.1016/s0140-6736(89)90136-0.
19. Brown KR, Ricci FM, Ottesen EA. Ivermectin: effectiveness in lymphatic filariasis. Parasitology. 2000;121 Suppl:S133-46. doi: 10.1017/s0031182000006570.