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Original Article

Ivermectin administration is associated with lower gastrointestinal complications and greater ventilator-free days in ventilated patients with COVID-19: A propensity score analysis

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ABSTRACT

Introduction: COVID-19 patients have been reported to have digestive symptoms with poor outcome. Ivermectin, an antiparasitic drug, has been used in COVID-19 patients. The objective of this study was to evaluate whether ivermectin has effects on gastrointestinal complications and ventilator-free days in ventilated patients with COVID-19.

Methods: COVID-19 patients who were mechanically ventilated in the ICU were included in this study. The ventilated patients who received ivermectin within 3 days after admission were assigned to the Ivermectin group, and the others were assigned to the Control group. Patients in the Ivermectin group received ivermectin 200 μg/kg via nasal tube. The incidence of gastrointestinal complications and ventilator-free days within 4 weeks from admission were evaluated as clinical outcomes using a propensity score with the inverse probability weighting method.

Results: We included 88 patients in this study, of whom 39 patients were classified into the Ivermectin group, and 49 patients were classified into the Control group. The hazard ratio for gastrointestinal complications in the Ivermectin group as compared with the Control group was 0.221 (95% confidence interval [CI], 0.057 to 0.855; p = 0.029) in a Cox proportional-hazard regression model. The odds ratio for ventilator-free days as compared with the Control group was 1.920 (95% CI, 1.076 to 3.425; p = 0.027) in a proportional odds logistic regression model.

Conclusions: Ivermectin improved gastrointestinal complications and the number of ventilator-free days in severe COVID-19 patients undergoing mechanical ventilation. Prevention of gastrointestinal symptoms by SARS-Cov-2 might be associated with COVID-19 outcome.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/COVID-19) pandemic is an emergency situation throughout the world. As treatment, dexamethasone has been used as an effective anti-inflammatory drug [1], but dexamethasone weakens host immunity [2]. Remdesivir, an antiviral drug, is a nucleoside analogue prodrug used for various viral infections and decreases the time to clinical
Table 1
Baseline patients’ clinical and demographical characteristics.

| [Original cohort] | [Weighted cohort] |
|-------------------|-------------------|
| Ivermectin        | Control           | SMD    | Ivermectin | Control | SMD    |
| N                 | 39                | 49     | 70.78      | 74.36   | 0.417  |
| Age (yr)          | 60.00 [54.00, 64.50] | 68.00 [58.00, 74.00] | 0.007 | 70.78 | 74.36 | 0.001 |
| Male              | 79.5 (31)         | 83.7 (41) | 0.017 | 85.3 (60.3) | 84.7 (63.0) | 0.016 |
| Respiratory condition | P/F ratio | 246.00 [173.00, 307.50] | 236.00 [144.00, 344.00] | 0.007 | 243.77 [144.07, 305.68] | 226.45 [138.70, 334.04] | 0.054 |
| ECMO              | 7.7 (3)           | 8.2 (4) | 0.017 | 9.7 (6.9) | 9.0 (6.7) | 0.024 |
| Comorbidities     |                  |        |           |         |        |
| Hypertension      | 148.7 (19)        | 40.8 (20) | 0.159 | 43.6 (30.8) | 40.8 (30.3) | 0.057 |
| Hyperlipidemia    | 28.2 (11)         | 24.5 (12) | 0.084 | 24.6 (17.4) | 22.3 (16.6) | 0.052 |
| Hyperuricemia     | 28.2 (11)         | 24.5 (12) | 0.084 | 24.6 (17.4) | 22.3 (16.6) | 0.052 |
| Diabetes mellitus | 20.5 (8)          | 32.7 (16) | 0.027 | 33.8 (23.9) | 32.5 (24.2) | 0.027 |
| Hypertension      | 48.7 (19)         | 40.8 (20) | 0.159 | 43.6 (30.8) | 40.8 (30.3) | 0.057 |
| Hyperlipidemia    | 28.2 (11)         | 24.5 (12) | 0.084 | 24.6 (17.4) | 22.3 (16.6) | 0.052 |
| Diabetes mellitus | 20.5 (8)          | 32.7 (16) | 0.027 | 33.8 (23.9) | 32.5 (24.2) | 0.027 |
| Hypertension      | 48.7 (19)         | 40.8 (20) | 0.159 | 43.6 (30.8) | 40.8 (30.3) | 0.057 |
| Hyperlipidemia    | 28.2 (11)         | 24.5 (12) | 0.084 | 24.6 (17.4) | 22.3 (16.6) | 0.052 |
| Diabetes mellitus | 20.5 (8)          | 32.7 (16) | 0.027 | 33.8 (23.9) | 32.5 (24.2) | 0.027 |

Table 2
Laboratory data on admission.

| Units | Ivermectin | Control | P value |
|-------|------------|---------|---------|
| Red blood cells (×10⁶/μL) | 457 ± 11.0 | 438 ± 9.6 | 0.207 |
| Hemoglobin (g/dL)         | 13.6 ± 0.3 | 13.3 ± 0.3 | 0.491 |
| Hematocrit (%)            | 39.7 ± 0.9 | 39.0 ± 0.7 | 0.565 |
| White blood cells (/μL)   | 9790 ± 947 | 9500 ± 828 | 0.840 |
| Neutrophil (%)            | 88.7 ± 1.1 | 87.3 ± 1.0 | 0.340 |
| Lymphocyte (%)            | 7.9 ± 0.9 | 9.1 ± 0.8 | 0.368 |
| Monocyte (%)              | 3.3 ± 0.3 | 3.1 ± 0.3 | 0.593 |
| Eosinophil (%)            | 0.1 ± 0.0 | 0.1 ± 0.0 | 0.335 |
| Basophil (%)              | 0.2 ± 0.0 | 0.2 ± 0.0 | 0.848 |
| Platelets (×10⁹/μL)       | 21.2 ± 12.9 | 18.5 ± 11.3 | 0.119 |

Table 3
Gastrointestinal complications and respiratory outcome.

| Units | Ivermectin (n = 39) | Control (n = 49) | P value |
|-------|----------------------|------------------|---------|
| Diarrhea | 10.3 (4) | 38.8 (19) | 0.003 |
| Regurgitation | 0 (0) | 22.5 (11) | 0.002 |
| GI complications | 10.3 (4) | 51.2 (25) | <0.001 |
| Intubation period | 8 [6, 10] | 13 [7, 38.5] | <0.001 |
| Ventilator-free days | 20 [18, 22] | 15 [0, 21] | <0.001 |
| ICU stay | 10 [7, 13] | 16 [8, 38.5] | <0.001 |
| Death within 28 days | 0 (0) | 4.1 (2) | 0.501 |

Values are expressed as median [interquartile range] or percentage [frequency]. P value = 0.001 (only for ventilator-free days).

 AFL: atrial fibrillation, ALT: alanine aminotransferase, GGT: γ-glutamyl transpeptidase, PT: prothrombin, APTT: activated partial thromboplastin time, FDP: fibrin/fibrinogen degradation products.

Values are expressed as median [interquartile range] or percentage [frequency]. GI: gastrointestinal.

AST: aspartate aminotransferase, ALT: alanine aminotransferase, γGT: γ-glutamyl transpeptidase. PT: prothrombin, APTT: activated partial thromboplastin time, FDP: fibrin/fibrinogen degradation products.

improvement in adults with severe COVID-19 [3]. However, there are limited data in patients with mechanical ventilation [4].

Ivermectin is a drug that has been used to treat parasitic infections such as onchocerciasis and lymphatic filariasis throughout the world for more than 30 years, with more than 3.7 billion doses dispensed in Africa and Central and South America to control tropical diseases [5]. Ivermectin shows in vitro activity against a broad range of viruses, including not only HIV, dengue, influenza, and Zika virus but also SARS-CoV-2 [6]. Clinical research by Rajter et al. [7] found that ivermectin treatment was associated with lower mortality in 280 COVID-19 patients in a propensity score-matching study. Contrastingly, in a randomized clinical trial of 400 patients with mild COVID-19, ivermectin administration did not decrease the time to resolution of symptoms within 21 days [8]. Thus, the effects of ivermectin are controversial, and there are few clinical data on intubated COVID-19 patients in the intensive care unit (ICU).

COVID-19 causes gastrointestinal (GI) symptoms such as nausea or vomiting, diarrhea, and loss of appetite as reported in a systemic review of 6686 patients [9]. There is little research on established treatment for these GI symptoms [10]. As we have been struggling against refractory diarrhea and regurgitation in our patients with COVID-19, we planned to use an antiviral oral drug for intestinal prophylaxis, and we selected ivermectin as the drug. Therefore, the objective of this study was to evaluate whether ivermectin improved GI complications and respiratory conditions in mechanically ventilated patients with COVID-19.
Patients who were more than 20 years old, were placed on a ventilator within 3 days after admission to the ICU, and were diagnosed as having COVID-19 in the Department of Traumatology and Acute Critical Medicine and Intensive Care Unit, Osaka University Hospital during the period December 2020 to May 2021 were eligible for enrollment in this study. Patients who were less than 20 years old, or those who were placed on a ventilator within 3 days after admission to the ICU, and were diagnosed as having COVID-19 in the Department of Traumatology and Acute Critical Medicine and Intensive Care Unit, Osaka University Hospital during the period December 2020 to May 2021 were included in this study. Patients who did not receive ivermectin within 3 days after admission were assigned to the Control group. Patients in the Ivermectin group received ivermectin 200 μg/kg per 2 weeks via nasal tube. Antibiotics were administered under the same policy during the entire study period [13]. This study was approved by the institutional review board of Osaka University (approval no. 21163). Informed consent was obtained from the family of each patient.

2.3. Outcome variables

Diarrhea was defined as the acute onset of continuous loose or liquid stools occurring more than twice. Regurgitation was defined as reflux volume from the gastric tube of more than 300 mL/day. GI complications were defined as diarrhea or regurgitation. Ventilator-free days (VFD) were defined as the number of days alive and free of mechanical ventilation within 4 weeks from admission [14]. The primary outcome was VFD. The secondary outcomes included diarrhea, regurgitation, and GI complications within 4 weeks from admission.

2.4. Statistical analysis

All patient characteristics are summarized using medians with interquartile ranges (IQR) and proportions with counts for continuous variables and categorical variables, respectively. The differences in distributions of the covariates between the Ivermectin and Control groups were assessed using standardized mean differences (SMD).

We estimated the cumulative event-free probabilities of the first incidence of diarrhea, regurgitation, and GI complications using the Kaplan-Meier method. Then, we estimated the effect of ivermectin use on these events using Cox proportional-hazard regression models. Furthermore, we assessed the effect of ivermectin use on VFD and the number of ICU-free days within 28 days from ICU admission using proportional-odds logistic regression models. To reduce the biases that were introduced by the imbalances of the covariates' distributions between the groups, we used the inverse probability weighting (IPW) method. The probability of receiving ivermectin, which is referred to as the propensity score, was estimated by a multivariable logistic regression model considering the following covariates of age, sex, P/F ratio, uricemia, cardiovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, hyperuricemia, cardiovascular disease, chronic obstructive pulmonary disease, and chronic kidney disease. To avoid variance inflation due to the extreme weights, which were introduced by the extremely high and low estimated propensity scores, we trimmed the propensity scores in the unoverlapped area of the propensity score distributions in both groups.

All statistical inferences were made with a two-sided 5% significance level using R software (https://cran.r-project.org/).

3. Results

All of the patients tolerated ivermectin, and there were no clear adverse events in any patients. Patient characteristics are listed in Table 1.

The Ivermectin group contained 39 patients, and the Control group contained 49 patients. Patients in the Ivermectin group had significantly lower age and less chronic kidney disease than those in the Control group.
group. To adjust for age, sex, respiratory condition, concomitant drugs, and comorbidities, we used propensity score via the IPW method. Most patients were intubated on admission, and median time from admission to intubation had no significant differences between the Ivermectin group (median 0, IQR -0.5–0 days) and Control group (median 0, IQR -1–0 days). There were no significant differences in blood test results except for that of serum creatinine (Table 2).

The frequencies of diarrhea, regurgitation, and GI complications in the Ivermectin group were significantly lower than those in the Control group. The intubation period was significantly lower and the number of VFD was significantly greater in the Ivermectin versus Control group (Table 3). The cumulative event-free probabilities of the first incidence of GI complications and extubation using the Kaplan-Meier method are shown in Fig. 1. The mortality within 28 days did not differ significantly between the groups, but the mortality in the whole ICU stay had significantly lower in the Ivermectin group versus the Control group (0% vs. 16.3%; \( p < 0.05 \)).

In a Cox proportional-hazard regression model, the hazard ratio for GI complications for the Ivermectin group as compared with the Control group was 0.221 (95% confidence interval [CI], 0.057 to 0.855; \( p = 0.029 \)) after adjustment for covariates using propensity score with IPW method (Table 4)(Fig. 2). In the proportional odds logistic regression model, the odds ratio for VFD as compared with the control group was 1.920 (95% CI, 1.076 to 3.425; \( p = 0.027 \)) after using the same adjustment method.

4. Discussion

This study showed that the administration of ivermectin reduced the incidences of GI complications and increased VFD in patients with COVID-19 undergoing mechanical ventilation. Regarding clinical research, in a meta-analysis of 9 randomized controlled trials in 1788 COVID-19 patients, ivermectin was associated with decreased mortality [15]. However, these studies did not evaluate GI complications and VFD. In addition, most patients were not intubated when ivermectin was administered. We showed that even after patients worsened and required mechanical ventilation, administration of ivermectin via nasal tube could attenuate GI complications and shorten the duration of the intubation period.

Ivermectin has been shown to inhibit the viral replication of SARS-CoV-2 in vitro [16]. One of the presumed mechanisms is to be the inhibition of the enzyme importin \( \alpha/\beta \) in the process of translocation into the cell nucleus [6]. SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2). A deficiency in murine ACE2, which encodes a key regulatory enzyme of the renin-angiotensin system, results in highly increased susceptibility to diarrhea and intestinal inflammation induced by dextran sulfate sodium [17]. In a clinical study, fecal viral loads were detected [18], and digestive histologic and immunofluorescent staining revealed GI infection in patients with COVID-19 [19]. Previous reports showed that gastrointestinal complications occurred in about 15% of COVID-19 patients including mainly non-ventilated patients [10]. In the present study, 51.2% of COVID-19 ventilated patients in the Control group.
group experienced GI complications. The ventilated patients had a higher prevalence of GI complications than the non-ventilated patients, so the effect modification of ivermectin could be expected to be different. It may be difficult to detect the effect of ivermectin in non-ventilated patients because of the smaller incidences of GI complications. These results suggest that ivermectin could reduce SARS-CoV-2 infection in the intestine and attenuate the symptoms of regurgitation and diarrhea.

Regarding with respiratory function, a the gut has been proposed as the “motor” of multiple organ failure [20], gut dysfunction is recognized as a causative factor in the progression of diseases such as sepsis, trauma, and infection. Intestinal injury by SARS-CoV-2 could cause intestinal inflammation and alteration of the gut microbiota, which might lead to progression of the respiratory disease seen with COVID-19. In the gut microbiota of COVID-19 patients, the diversity of normal gut microbiota bacteria is decreased and the number of opportunistic bacteria is increased [21,22]. In the present study, GI complications were significantly decreased in the Ivermectin group. It is reported that the approved dose of ivermectin does not result in an adequate serum concentration to treat COVID-19 [23]. Ivermectin could have a direct effect in the intestine, and prevention of SARS-CoV-2-related GI complications might also be associated with the increase in VFD seen in the present study. The mortality in the whole ICU stay had significantly lower in this research, and we need further randomized controlled study to demonstrate that.

Anti-inflammatory drugs are essential and effective, but dexamethasone, a glucocorticoid, affects immune cells [2] and is a double-edge sword, especially in aged patients with lowered immunity who have difficulty in upregulating immunity under steroid therapy. As a result, such patients with COVID-19 have been reported to suffer from fungal disease [24] and severe cytomegalovirus infection [25,26]. It may be important to combine both an antiviral drug and an anti-inflammatory drug for SARS-CoV-2 virus in the early stage of infection to prevent prolonged respiratory failure and reduce the accumulated dose of steroids. Ivermectin might be one of the promising antiviral drugs in the treatment of COVID-19.

This study has some limitations. An imbalance in the patients’ age between the treatment groups remained after weighting. The mutant variants may be different with time, but we could not identify this. Additional well-designed studies are needed to provide further elucidation. Second, we propose that the intestinal effect of ivermectin might influence COVID-19 infection, and thus, evaluation of intestinal viral load could be a next target to confirm this supposition.

5. Conclusions

The administration of ivermectin improved GI complications and VFD in ventilated patients with COVID-19. The beneficial influence of ivermectin on the intestines may improve outcome in these patients. Further research is needed to investigate the mechanism and effects of ivermectin treatment.

Authorship statement

SK, NT, and MK reviewed the record and drafted the manuscript. HH and AU confirmed the clinical record as clinical attendants. DK, TJ and AS reviewed statistical parts and clinical application. YF and OH contributed to the discussion and managed this research. All authors read the draft and revised it critically and approved the final manuscript. All authors meet the ICMJE authorship criteria.

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Declaration of competing interest

The authors declare that they have no conflicts of interest.

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References

[1] Group RC, Horby P, Lim WS, Embleton JR, Madham M, Bell JI, et al. Dexamethasone in hospitalized patients with covid-19. N Engl J Med 2021;384:693-704.
[2] Salem MA. A response to the recommendations for using dexamethasone for the treatment of covid-19: the dark side of dexamethasone. J Pharm Pract 2021;34:179-80.
[3] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe covid-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1560-8.
[4] Beigel JH. What is the role of remdesivir in patients with covid-19? Curr Opin Crit Care 2021. https://doi.org/10.1097/MCC.0000000000000866.
[5] Yaginuma M, Foster P, Hanaki H, Omura S. Global trends in clinical studies of ivermectin in covid-19. Jpn J Antibiot 2021;74:44-55.
[6] Wehbe Z, Wehbe M, Izzani R, Pintus G, Zaraket H, Yassine HM, et al. Repurposing ivermectin for covid-19: molecular aspects and therapeutic possibilities. Front Immunol 2021;12:655868.
[7] Rajer JC, Sherman MS, Fettke N, Vogel F, Sacks J, Rajter JJ. Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: the ivermectin in covid nineteen study. Chest 2021;159:85-92.
[8] Lopes-Medina E, Lopes P, Hurtado IC, Davalos DM, Ramos O, Martinez E, et al. Effect of ivermectin on time to resolution of symptoms among adults with mild covid-19: a randomized clinical trial. JAMA 2021;325:426-35.
[9] Mao R, Qiu Y, He JS, Tan JY, Li XH, Liang J, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with covid-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5:667-78.
[10] D’Amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea during covid-19 infection: pathogenesis, epidemiology, prevention, and management. Clin Gastroenterol Hepatol 2020;18:1663-72.
[11] Bone RC, Balla RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions of sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The accp/ccm consensus conference committee. American college of chest physicians/society of critical care medicine. Chest 1992;101:1644-55.
[12] Shimizu K, Hibino S, Biros MH, Israwa T, Shimazu T. Emergency medicine in Japan: past, present, and future. Int J Emerg Med 2021;14:2.
[13] Mikana K, Aoki N, Aoki Y, Abe S, Iwata S, Ouchi K, et al. JAID/JSC guidelines for the treatment of respiratory infectious diseases: the Japanese association for infectious diseases/Japanese society of chemotherapy - the JAID/JSC guide to clinical management of infectious disease/guideline-preparing committee respiratory infectious disease wg. J Infect Chemother 2016;22:51-65.
[14] Schoenfeld AD, Bernard GR, Network A. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med 2002;30:1772-7.
[15] Zein A, Salistyiana CS, Raffaele WM, Pranata R. Ivermectin and mortality in patients with covid-19: a systematic review, meta-analysis, and meta-regression of randomized controlled trials. Diabetes Metab Syndr 2021;15:102186.
[16] Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of sars-cov-2 in vitro. Antivir Res 2020;178:104787.
[17] Hashimoto T, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paulino M, et al. Ace2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature 2012;487:477-81.
[18] Wu Y, Cheng X, Jiang G, Tang H, Ming S, Tang L, et al. Altered oral and gut microbiota and its association with sars-cov-2 viral load in covid-19 patients during hospitalization. NPJ Biofilms Microbiomes 2021;7:61.
[19] Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of sars-cov-2. Gastroenterology 2020;158:1831-1833 e3.
[20] Clark JA, Coopersmith CM. Intestinal crosstalk: a new paradigm for understanding the gut as the ‘motor’ of critical illness. Shock 2007;28:384-93.
[21] Zhao T, Zhang F, Lai GY, Yeoh YK, Li AYL, Zhan H, et al. Alterations in gut microbiota of patients with covid-19 during time of hospitalization. Gastroenterology 2020;159:944-955 e8.
[22] Lv L, Gu S, Jiang H, Yan R, Chen Y, Chen Y, et al. Gut mycobiota alterations in patients with covid-19 and b1n1 infections and their associations with clinical features. Commun Biol 2021;4:480.
[23] Schmitt VD, Zhou JJ, Lohmer LRL. The approved dose of ivermectin alone is not the ideal dose for the treatment of covid-19. Clin Pharmacol Ther 2020;108:762-5.
[24] White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, et al. A national strategy to diagnose covid-19 associated invasive fungal disease in the icu. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa1298.

[25] Amiya S, Hirata H, Shiroyama T, Adachi Y, Niitsu T, Noda Y, et al. Fatal cytomegalovirus pneumonia in a critically ill patient with covid-19. Respirol Case Rep 2021;9:e00801.

[26] Niitsu T, Shiroyama T, Hirata H, Noda Y, Adachi Y, Enomoto T, et al. Cytomegalovirus infection in critically ill patients with covid-19. J Infect 2021. https://doi.org/10.1016/j.jinf.2021.07.004.