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Original Article

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The Efficacy of Famotidine in Improvement of Outcomes in Hospitalized COVID-19 Patients: A Phase III Randomized Clinical Trial

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Abstract

***Background & Aims*:** As the first randomized clinical trial, this study evaluated the effect of Famotidine on the improvement of outcomes of hospitalized patients with COVID-19.

***Materials & Methods*:** This phase III randomized clinical trial which was designed with two parallel arms, is a placebo-controlled, single-blind, and concealed allocation study, and recruited 20 patients (10 of them received Famotidine as treatment group and 10 received Placebo as control group). Oral Famotidine 160 mg four times a day was given to the COVID-19 patients until the discharge day or for a maximum of 14 days. Patients' temperature, respiration rate, oxygen saturation, lung infiltration, lactate dehydrogenase (LDH) level, and complete blood count (CBC) were measured at the baseline (before the intervention) and on day 14 after the intervention or on discharge day. Length of stay in the hospital and length of stay in the ICU were also measured as secondary outcomes of the study.

***Results*:** The results showed a significant decrease in LDH (P=0.01), mean WBC (P=0.04) and length of stay (P=0.04) of patients with COVID-19 in the group treated with Famotidine compared to the control group. There was also a significant increase in oxygen saturation (P=0.01) in the group treated with Famotidine compared to the control group. Cough improvement was also higher in the oral Famotidine group compared to the control group (P=0.02).

***Conclusion*:** This was the first clinical trial on the effect of Famotidine on the improvement of hospitalized COVID-19 patients, which indicated that high-dose Famotidine improves patients' clinical signs and reduces the severity of the disease and duration of hospitalization.

***Keywords*:** Famotidine, COVID-19, Hospitalization

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Introduction

Managing patients with COVID-19, which is caused by the SARS-CoV-2 virus, has become one of the challenges of healthcare systems today (1). Much research has recently focused on finding vaccines and medications for these patients (2). Famotidine is a low-cost, over-the-counter medication from histamine H2-receptor antagonists (H2RAs) family, which is widely used for its antiacid properties (1). The results of computer simulation studies also identified Famotidine as a possible inhibitor of 3-chymotrypsin-like protease ($3CL^{pro}$) in the SARS-Cov-2 virus (2). Famotidine can also bind to histamine 2 receptors and modify subsequent signal pathways, including regulation of antibody production by B cells, release of cytokines by Th1, T cell differentiation and division, mast cell degranulation, and dendritic cell responses (3). H2RAs have also manifested successful results against human immunodeficiency virus (HIV), papillomavirus, and hepatitis B (4).

At the time of writing the study, there has been no clinical trial to determine the effect of Famotidine on the improvement of patients with COVID-19 (5,6).

Hence, considering the possible effects of Famotidine on the immune regulation in patients with COVID-19, the antiviral effects of H2RAs, and the lack of relevant clinical trials, this study was designed to evaluate the effects of Famotidine on the recovery process, signs, and some laboratory results of hospitalized patients with COVID-19 as the first randomized clinical trial.

Materials & Methods

This phase III randomized clinical trial which was designed with two parallel arms, is a placebo-controlled, single-blind, and concealed allocation, and recruited 20 patients. It was registered at the Iranian Registry of Clinical Trials (IRCT20200509047364N2) on 17 August 2020 (https://www.irct.ir/trial/49657), which is one of the primary partner registries for clinical trials of the World Health Organization. Data were collected from Shahid Mohammadi hospital in Bandar Abbas. Due to the lack of previous studies in this field, the sample size of 20 participants was considered for the study (7).

Inclusion criteria:

The main inclusion criteria before randomization were being infected with COVID-19 confirmed by a PCR test for SARS-Cov-2 and signing a written informed consent to participate in the study.

Exclusion Criteria:

The main exclusion criteria before randomization were suffering from immunodeficiency, end-stage renal disease, moderate renal failure (creatinine clearance 30-50 ml/min), stage 4 severe chronic kidney disease, dialysis (creatinine clearance <30 ml/min), history of liver disease, history of hepatitis C infection, history of alcoholism, Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD), ALT/AST>5 times normal limits, history or evidence of prolonged QT on ECG, history of psoriasis, history of porphyria, pregnancy, taking oral contraceptive pills (OCPs), taking Dasatinib, Neratinib, Ozanimod, Pazopanib, Rilpivirine, Siponimod or Tizanidine, and allergy to any medications used in this clinical trial.

Description of randomization:

Before allocating each group to the eligible individuals in the study, informed consents for grouping the individuals were completed. Random sequences were prepared using online tools (https://www.sealedenvelope.com/) and block randomization method by a person who had no role in sampling or allocating individuals to random codes. Individual random allocation was done in blocks of 2 and 4 without stratification. Inclusion criteria were monitored by the recruiter and the codes in the random sequence were assigned to the patients by the treatment team who were blinded to whether each code belonged to the intervention or placebo group. Then the patients' codes for the interventions were matched with the generated random sequence information (allocation concealment was performed by the treatment team without informing the recruiter and the person who prepared the random sequence).

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Description of blinding:

In this study, all participants were aware of participating in this study and entered the study with their consent. All participants were unaware of which group they were in, and received Famotidine if they were assigned to the treatment group, and placebo if they were assigned to the control group. The first author, healthcare personnel, data collectors, and those who assessed the outcomes were aware of the patient grouping. Those who drafted the article were unaware of the grouping if they were not involved in the above processes.

Intervention groups:

Group A received standard drug therapy according to the treatment protocols of the National Committee of COVID-19 plus oral Famotidine 160 mg (Chemi Darou Co.) four times a day until the discharge day or for a maximum of fourteen days. Also, the vital signs of the patients were frequently monitored at regular intervals (Figure 1).

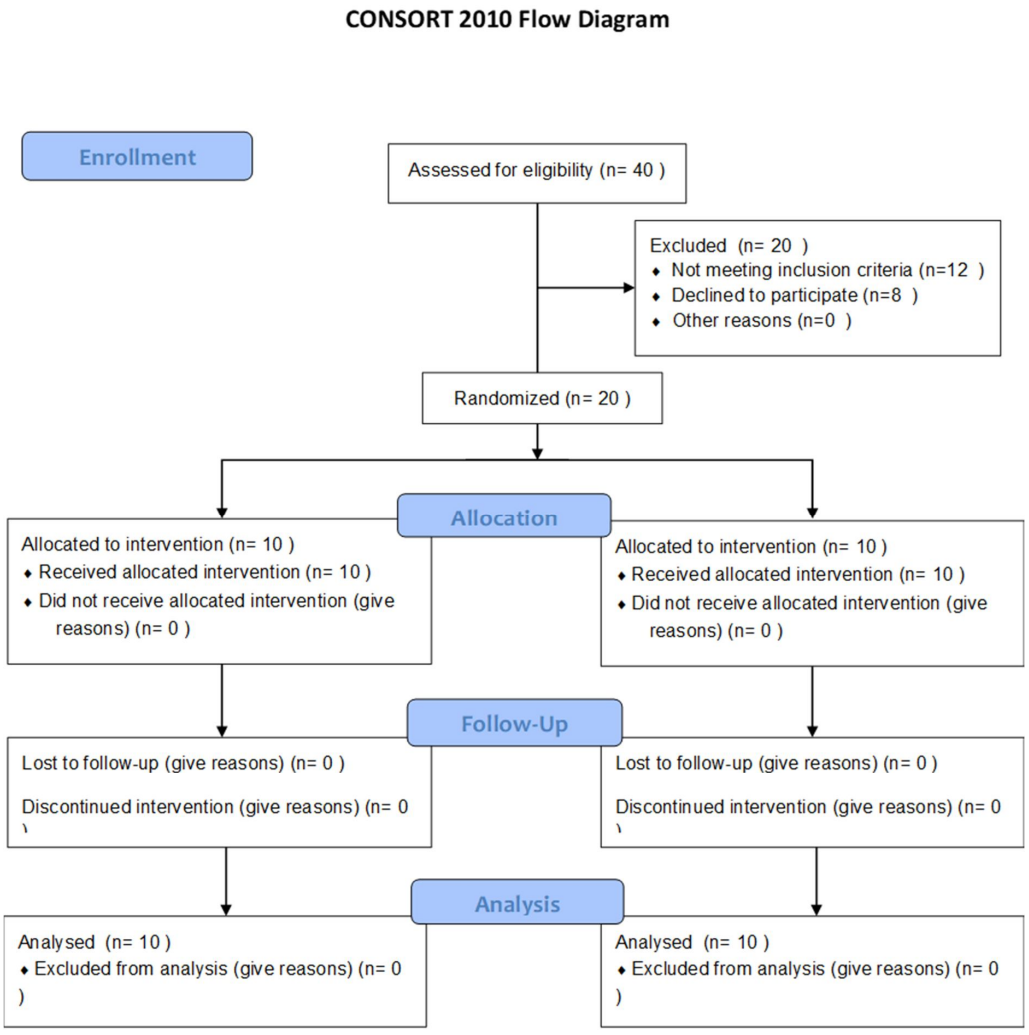

Fig. 1. CONSORT 2010 Flow Diagram of the study participants

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Standard pharmacotherapy according to the National Committee of COVID-19 treatment protocols included: (i) Hydroxychloroquine/chloroquine phosphate: Hydroxychloroquine sulfate tablets 200 mg or chloroquine phosphate tablets 250 mg (equivalent to 150 mg base amount); 2 tablets every 12 hours on the first day and then 1 tablet every 12 hours for at least 7 days and up to 14 days. (ii) One of the following medications at the discretion of the treating physician: Kaletra tablets (lopinavir/ritonavir) 200/50 mg; 2 tablets every 12 hours after meals for at least 7 days and up to 14 days. (iii) Atazanavir/Ritonavir 300/100 tablet: 1 tablet a day with food; or Atazanavir 400 mg daily for a minimum of 7 days and a maximum of 14 days.

Control group: Group B received standard therapy according to the treatment protocols of the National Committee of COVID-19 plus placebo in the form of oral tablets four times a day until the day of discharge or for a maximum of fourteen days.

Primary outcomes:

Patients' temperature, respiration rate, oxygen saturation, lung infiltration, lactate dehydrogenase, and complete blood count were measured at the baseline (before the intervention) and on day 14 after the intervention or on the discharge day.

Secondary outcomes: Length of stay in the hospital and in the ICU were measured as secondary outcomes at the baseline (before the intervention) and on days 1 and 14 after the intervention or on the discharge day.

Statistical analysis:

IBM-SPSS version 22 software was used for data analysis; independent t-test and Mann-Whitney test were used to compare the means of quantitative data.

Chi-square and Fisher's test were used to compare qualitative variables.

Results

This study examined 20 patients with COVID-19. Their mean age was 46±13 years while 12 patients were male and 8 were female.

Patients were divided into two groups of ten:

Treatment group: They were treated with Famotidine in addition to standard COVID-19 treatment.

Control group: They were treated only with the COVID-19 standard treatment and placebo.

In this study, the mean age of patients in the treatment and the control groups were 47±14 and 48±12 years, respectively; there was no statistically significant difference between the two groups (P=0.2).

Regarding gender frequency, 60% of patients were male and 40% were female in the treatment group, and 70% of patients were male and 30% were female in the control group. There was no statistically significant difference between the two groups (P=0.1).

Comparison of laboratory findings and length of stay between the two groups:

The mean WBC on the discharge day was significantly lower in the treatment group (6550±2800) than that in the control group (10640±1600) (P=0.04).

LDH on the discharge day was significantly lower in the treatment group (584±158) than that in the control group (799±147) (P=0.01). Oxygen saturation on the discharge day was significantly higher in the treatment group (94±2%) than that in the control group (92±1%) (P=0.01) (Table 1).

Length of stay was significantly shorter in the treatment group (6±3 days) than that in the control group (9±4 days) (P=0.04). Cough improvement was significantly higher in the treatment group (7 patients (70%)) than that in the control group (4 patients (40%)) (P=0.02) (Table 1).

No death or ICU admission was reported in this study in either group.

There was no significant difference between the two groups in terms of comparing lung involvement on CT Scan of patients on the discharge day. In both groups, 50% of patients had over half of their lungs involved on the fifth day of admission (Table 1).

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Table 1. Comparison of age, sex, clinical and laboratory variables between the treatment and control group

Variables		Groups		P-value
		Treatment	Control	
Gender	Male	60%	70%	0.1
	Female	40%	30%	
Age		47±14	48±12	0.2
WBC on the discharge day		6550±2800	10640±1600	0.04
Oxygen saturation on the discharge day		94±2	92±1	0.01
Length of stay		6±3	9±4	0.04
LDH on the discharge day		584±158	799±147	0.01
Cough improvement		7 patients	4 patients	0.02
More than 50% of lungs involved in CT scan on the fifth day of admission		50% 5 patients	50% 5 patients	1

Discussion

The results showed a significant decrease in LDH (P=0.01) and length of stay (P=0.04) in hospitalized patients with COVID-19 in the group treated with Famotidine compared to the control group. There was also a significant increase in oxygen saturation in the group treated with Famotidine compared to the control group. Cough improvement was also higher in the oral Famotidine group compared to the control group (P=0.02).

The results of a computer simulation by Wu et al. showed the potential effect of Famotidine on $3CL^{pro}$ in SARS-COV-2 virus (8–10). The results of a study by Gupta et al. and other studies also showed that Famotidine could also act as a papain-like protease (PL^{pro}) inhibitor in the SARS-COV-2 virus, thereby inhibiting virus replication (5). The results of a computer study by Ortega et al. suggested administering other antiviral medications in combination with Famotidine (13). They also investigated the pharmacokinetic effects of Famotidine on SARS-COV-2 virus and reported only intravenous administration of Famotidine as effective on viral proteases (13). Loffredo et al. showed the ineffectiveness of Famotidine on the amount of $3CL^{pro}$ and PL^{pro} proteases in cultured cell lines (12). They also showed that, unlike computer studies, Famotidine had no antiviral effects on the replication of the SARS-COV-2 virus (12). In this regard, Malone et al. also showed the effects of Famotidine only on the H2R receptor (1).

The effects of Famotidine on H2R can reduce the mediators of the immune system, and can lead to a decrease in proinflammatory factors as well as a decrease in airway inflammation through TH1 lymphocytes (11). Furthermore, another effect of Famotidine on the immune system is a reduction in the histamine release from mast cells, which are major producers of histamine in respiratory viral infections (8–10). Besides, Hogan et al. applied dual histamine blockade with cetirizine and Famotidine, and reported the promising effect of Famotidine on cytokine storm and a reduction in the signs and complaints of patients with COVID-19 (11).

To date, no clinical trial has evaluated the effect of Famotidine on the improvement of inpatients with COVID-19. A retrospective study by Freedberg et al. and a case series study by Janowitz et al. were the only

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studies that have reported the effect of Famotidine on the improvement of patients with COVID-19 (2,3). The presentstudies, as the first clinical trials to examine the effect of Famotidine on inpatients with COVID-19, evaluated the effect of high-dose oral Famotidine on the improvement of these patients. (2,3).

Our results showed a significant increase in oxygen saturation in the oral Famotidine group compared to the control group (P=0.01). Oxygen saturation in the case series reported by Malone et al. over a period of 2 hours showed changes from 93% to 98% on day 15 after starting the Famotidine treatment regimen (1). Similar to the present study, Janowitz et al. also reported an increase in oxygen saturation after Famotidine administration (2). However, we cannot compare the effectiveness of Famotidine or the recovery of patients based on an antiviral medication regimen because their study did not have control groups.

The present study also showed a significant reduction in the length of stay in patients with COVID-19 in the oral Famotidine group (P=0.04). Cough improvement was also significantly higher in the oral Famotidine group compared to the control group in this study (P=0.02). In the case reported in the study by Malone et al., a similar improvement in coughs was observed after administering Famotidine (1). The improvement of cough in patients with COVID-19 has also been evaluated in the study by Janowitz et al. which was a case series study and reported a successful reduction in cough in patients after treatment with Famotidine (2).

LDH in patients with COVID-19 has been introduced as a marker for disease severity in various studies (14–18), and our results also showed a significant decrease in LDH levels in the Famotidine-treated group compared to the control group (P=0.01). Our results also showed a significant decrease in WBC in the treatment group taking Famotidine compared to the control group taking placebo (P=0.04).

The results of a retrospective study by Freedberg et al. on 1620 patients with COVID-19 showed a significant reduction in mortality and intubation risk in patients taking Famotidine (orally or intravenously, 40 or 20 mg daily); while patients taking proton pump inhibitors (PPIs) did not show a significant reduction in the above variables (3). However, our results showed a successful reduction in patients' respiratory complaints with Famotidine.

Our results regarding the gender of patients did not show a significant difference between the studied groups. We also examined lung involvement on CT Scan of patients and their age in both groups, which did not show a significant difference.

One of the limitations of our study was its small population, which presented itself in a decrease in statistical power in some tests, which did not reach a significant level. Also, it was impossible to follow up patients after discharge.

Despite the small statistical population, our results showed improvement in patients taking oral Famotidine, which can be generalized to a larger population and suggests adding Famotidine to the treatment of patients with COVID-19. Furthermore, although our study does not determine the mechanism of action of Famotidine in these patients, according to the review of literature, further studies are recommended on the effects of Famotidine on cytokine storm in patients with COVID-19.

Conclusion

This was the first clinical trial on the effect of Famotidine on the recovery of inpatients with COVID-19, which indicated that high-dose Famotidine improves patients' clinical signs and reduces the severity of the disease and duration of hospitalization.

Declarations:

Ethics approval and consent to participate:

The protocol was approved by the ethics committee of Hormozgan University of Medical Sciences on August 2, 2020, with the code IR.HUMS.REC.1399.255. (https://ethics.research.ac.ir/ProposalView.php?id=143967)

Authors certify that this trial has received ethical approval from the appropriate ethical committee as

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described above. Informed consent will be obtained in Persian language, where the harms and benefits of the oral Famotidine and the placebo were described.

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Authors' contributions

M KJ. and HR S. designed the study. All the authors contributed in data collection and manuscript writing. M KJ supervised the study.

Conflict of interest

The authors have no conflict of interest in this study.

References

1. Malone RW, Tisdall P, Fremont-Smith P, Liu Y, Huang XP, White KM, et al. COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms. Front Pharmacol 2021;12:633680.
2. Janowitz T, Gablenz E, Pattinson D, Wang TC, Conigliaro J, Tracey K, et al. Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalised patients: a case series. Gut 2020;69(9):1592-7.
3. Freedberg DE, Conigliaro J, Wang TC, Tracey KJ, Callahan MV, Abrams JA, et al. Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Cohort Study. Gastroenterology 2020;159(3):1129-31.
4. Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B 2020;10(5):766–88.
5. Sen Gupta PS, Biswal S, Singha D, Rana MK. Binding insight of clinically oriented drug famotidine with the identified potential target of SARS-CoV-2. J Biomol Struct Dyn 2021;39(14):5327-33.
6. Shaffer L. 15 drugs being tested to treat COVID-19 and how they would work. Nat Med [Internet]. 2020 May 15; Available from: https://pubmed.ncbi.nlm.nih.gov/32415251/
7. Samimagham HR, Hassani Azad M, Haddad M, Arabi M, Hooshyar D, KazemiJahromi M. The Efficacy of Famotidine in improvement of outcomes in Hospitalized COVID-19 Patients: A structured summary of a study protocol for a randomised controlled trial. Trials 2020;21(1):1-3.
8. Hu Y, Jin Y, Han D, Zhang G, Cao S, Xie J, et al. Mast Cell-Induced Lung Injury in Mice Infected with H5N1 Influenza Virus. J Virol 2012;86(6):3347-56.
9. Marshall JS, Portales-Cervantes L, Leong E. Mast Cell Responses to Viruses and Pathogen Products. Int J Mol Sci 2019;20(17):4241.
10. Thangam EB, Jemima EA, Singh H, Baig MS, Khan M, Mathias CB, et al. The role of histamine and histamine receptors in mast cell-mediated allergy and inflammation: The hunt for new therapeutic targets. Front Immunol 2018;9:1873.
11. Hogan RB, Hogan RB, Cannon T, Rappi M, Studdard J, Paul D, et al. Dual-Histamine Blockade with Cetirizine - Famotidine Reduces Pulmonary Symptoms in COVID-19 Patients. Pulm Pharmacol Ther 2020; 63:101942
12. Loffredo M, Lucero H, Chen DY, O'Connell A, Bergqvist S, Munawar A, et al. The Effect of Famotidine on SARS-CoV-2 Proteases and Virus Replication [Internet]. bioRxiv; 2020 [cited 2022 Jun 29]. p. 2020.07.15.203059. Available from: https://www.biorxiv.org/content/10.1101/2020.07.15.203059v1
13. Ortega JT, Serrano ML, Jastrzebska B. Class A G Protein-Coupled Receptor Antagonist Famotidine as a Therapeutic Alternative against SARS-CoV2: An In Silico Analysis. Biomolecules 2020;10(6):954.
14. Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis. 2020; ciaa270.
15. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect 2020;81(2):e16-25.

[DOI: 10.52547/rabms.8.2.75]

16. Zhao D, Yao F, Wang L, Zheng L, Gao Y, Ye J, et al. A Comparative Study on the Clinical Features of Coronavirus 2019 (COVID-19) Pneumonia with Other Pneumonias. Clin Infect Dis. 2020 Jul 28;71(15):756–61.
17. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020 Jul 1;146(1):110–8.
18. Ji D, Zhang D, Xu J, Chen Z, Yang T, Zhao P, et al. Prediction for Progression Risk in Patients with COVID-19 Pneumonia: The CALL Score. Clin Infect Dis. 2020 Sep 12;71(6):1393–9.

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