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Clinical Trials Study

Role of H_2 receptor blocker famotidine over the clinical recovery of COVID-19 patients: A randomized controlled trial

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) is a global pandemic, causing the population at a high risk of infection-related health hazards, mortality, and a potential failure of proper medical therapy. Therefore it is necessary to evaluate the potential use of the existing drugs that could be used as options for the medical management of COVID-19 patients.

AIM

To evaluate the role of H_2 receptor blocker "famotidine" in COVID-19 illness.

METHODS

This study was done on seriously ill COVID-19 patients admitted to the intensive care unit (ICU) of different institutes in Bangladesh. Patients were divided into famotidine treatment group "A" (famotidine 40 to 60 mg oral formulation 8 hourly with other treatment as given), and control group "B" (treatment as given). National early warning

score (NEWS)-2, and sequential organ failure assessment day 1 score was calculated to evaluate the outcome. Outcomes were evaluated by time required for clinical improvement, characterized as duration required from enrollment to the achievement of NEWS-2 of ≤ 2 maintained for 24 h; time to symptomatic recovery, defined as the duration in days (from randomization) required for the recovery of the COVID-19 symptoms; mortality rate; duration of ICU and hospital stay; total period of hospitalization; the rate of supplementary oxygen requirement; the computed tomography (CT) chest recovery (%), the time required for the viral clearance, and "NEWS-2" on discharge.

RESULTS

A total of 208 patients were enrolled in this study, 104 in each group. The Famotidine treatment group had comparatively better recovery of 75% and low mortality 25% than the control 70%, and 30%. Duration of clinical improvement (group A 9.53 d, group B 14.21 d); hospitalization period among the recovered patients (group A 13.04 d, group B 16.31 d), pulmonary improvement in chest CT (group A 21.7%, group B 13.2%), and the time for viral clearance (group A 20.7 d, group B 23.8 d) were found to be statistically significant $P \leq 0.05$. However, the Kaplan Meier survival test was not significant among the two study groups, $P = 0.989$.

CONCLUSION

According to our study, treatment with Famotidine achieved a better clinical outcome compared to the control in severe COVID-19 illness, although no significant survival benefit was found.

Key Words: COVID-19; SARS-Cov-2; Famotidine; COVID-19 acute respiratory distress syndrome; COVID-19 treatment; Bangladesh

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Core Tip: Treatment with Famotidine demonstrated a comparatively better outcome in the survival. A rapid recovery time, less duration of intensive care unit (ICU) stay among the survivors, favorable improvement in the computed tomography findings, and an earlier viral clearance were observed in the Famotidine treatment group. Which differ significantly in a *t*-test ($P \leq 0.05$). The difference between the time to symptomatic recovery, ICU stay duration, and the national early warning score-2 on discharge though was not significant, but mean values were relatively less than the control. Nevertheless, survival benefit was not significant with theFamotidine as an added treatment for severe coronavirus disease 2019.

INTRODUCTION

Coronavirus disease (COVID-19) or severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has rapidly developed into a pandemic since it was first reported in December 2019 in Wuhan City of China[1]. It was first detected in Wuhan City of China, and then quickly spread all over the world. This puts the population at a high risk of infection-related health hazards and a potential failure of proper medical therapy during this pandemic[2]. Till now no pre-or post-exposure prophylactic or definite COVID-19 medical countermeasures have been found. Clinical data suggest that famotidine may mitigate COVID-19 disease, but both mechanisms of action and rationale for dose selection remain obscure. Over activation of mast cells, and histamine production plays an important role in the progress of COVID-19 illness; hypothetically, this phenomena could be inhibited by histamine target receptor activity of famotidine[3]. High-dose oral famotidine was found to be well-tolerated and associated with improved patient-reported outcomes in non-hospitalized COVID-19 cases[4]. Additionally, famotidine use in hospitalized patients was found to reduce the risk of COVID-19 mortality, lower risk of the combined outcome of mortality and intubation, and lower levels of serum markers for severe disease[5,6].

But till now no clinical trial has been published regarding the role of famotidine in the severe COVID-19 disease. Therefore, an interventional study was carried out with famotidine therapy in patients with severe COVID-19 disease admitted in the intensive care unit (ICU) of the different tertiary level institutes of Bangladesh. Notably Bangladesh has an average life expectancy of 72.59 years with an easy access to healthcare facilities, though availability of the healthcare management resources is not equal in all the cities.

MATERIALS AND METHODS

This study was designed to evaluate the effect of famotidine in severe acute respiratory distress syndrome (ARDS) caused by COVID-19. COVID-19 patients admitted in the ICU of Chattogram General hospital, M. Abdur Rahim Medical College Hospital, and

250 Bed Cox's Bazar Sadar Hospital Bangladesh from July 20, 2020, onward were enrolled in this study. All these institutions are tertiary level referral hospital. The sample size was estimated 386, by $n = z^2pq/d^2$ formula. Here z = 1.96 (at 95%CI), n = sample size, p = 0.5 (prevalence), q = 1 - p, and d = 5% (margin error at standard of 0.05) COVID-19 patients [real-time reverse transcription polymerase chain reaction (RT-PCR) positive] requiring ICU support with national early warning score 2 (NEWS-2) ≥ 5 were randomly shortlisted to enroll in the study. Following enrollment patients were allocated to the study groups, A (Famotidine treatment group) and B (control group). An odd-even-ratio (1:1) was applied to hospital registration number to divide the study groups. Berlin definition was taken in consideration to define ARDS. Following primary enrollment, the cases were further confirmed by investigators. Initially, 308 patients were recruited, among them, 54 declined to enroll and 46 had uncontrolled comorbid conditions or already hospitalized for other issue; therefore, these patients were excluded. Finally, 208 COVID-19 patients were enrolled in this study (Figure 1)

Each group contains 104 patients. Group A patients received famotidine (Famotac 20 mg oral tablet formulation) every 8 hourly 30 min before the meal; 40 mg in the case of < 60 kg, and 60 mg in the case of > 60 kg body weight, and was continued for 30 d. Other treatments included remdesivir, tocilizumab, dexamethasone, a broad-spectrum antibiotic (meropenem), proton pump inhibitor, ascorbic acid, cholecalciferol, zinc, bronchodilators, and oxygen support. Additionally, treatments according to the symptomatic onset were given. Detail clinical follow-ups that included all the vitals (temperature, pulse, respiratory rate, blood pressure, oxygen saturation, percentage of supplementary oxygen use, orientation/consciousness, chief complaints, *etc*.) were obtained every 24 h interval. To evaluate the recovery "NEWS-2" was calculated accordingly. The risk of mortality in individual cases was evaluated by sequential organ failure assessment score during admission. Regular follow-ups were obtained in every twenty-four hoursinterval and noted accordingly. Outcomes were determined as: "Time to clinical improvement" characterized as the point of randomization to a maintain NEWS-2 score ≤ 2 for 24 h; "Symptomatic recovery" characterized as the time from

randomization to the recovery of the COVID-19 symptoms (recovery from the major symptoms, according to the patient's statement); mortality (%); ICU and total hospitalization duration; rate of additional oxygen usage; time require for clinical failure; on discharge NEWS-2 score; and CT chest recovery (%).

Duration of hospitalization was counted from the time from randomization to hospital discharge or "Ready for discharge", as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 4 L supplemental oxygen. Time to clinical failure was defined as the time from randomization to the first occurrence of death, mechanical ventilation, or withdrawal (whichever occurs first). The "CT chest recovery (%)" was calculated as the difference between the lung involvement in the CT findings of the initial and the CT before discharge. The CT severity score index and the average lung parenchymal involvement were calculated by an experience radiology specialist in each case. To identify the symptomatic recovery regular contacts were made every alternate day on phone following discharge. Detailed history and a sample for the re-evaluation PCR were obtained during the 5th day post-discharge physical follow-up. The PCR was repeated every 7 d interval if found positive. Time to COVID-19 recovery or viral clearance was defined as the duration (in days) from the first positive PCR to the first negative PCR that was confirmed by a repeat negative PCR after 7 d. Ethical committee approval: ERC of 250 bedded general Hospital Chattogram Ref: 980 (Date 18/07/2020). ClinicalTrials.gov ID: NCT04504240.

Study groups

Patients were divided into two groups: Group A (intervention group, n = 104): famotidine (Famotac 20 mg) 40-60 mg oral tablet formulation 8 hourly half an hour before a meal. In the case of < 60 kg body weight famotidine 40 mg, and the case of > 60 kg, 60 mg was given. This was continued for 30 d. Other treatments were as given; Group B (control group, n = 104): Treatment as given.

Inclusion and exclusion criteria

Severe COVID-19 patients require hospitalization under ICU (of tertiary level referral hospitals in different city of Bangladesh) with a confirmed RT-PCR were included in this study.

Patients with severe and/or uncontrolled comorbid conditions with significantly compromised organ function; patients who were hospitalized from the before due to other reasons; Contraindication/possible drug interaction; pregnant patients, severely obese patients with body mass index > 35, and critically ill COVID-19 patients in the ventilator support were not included in the study.

Statistical analysis

Statistical analyses were done by Graph Pad prism (7.2), and SPSS (V-28). Data were analyzed, mean ± SD, mean ± SEM, and frequencies were calculated. Difference among the study groups were evaluated by Chi-square, and a *t*-test. Additionally, survival benefit of the Famotidine treatment was calculated by Kaplan Meier survival analysis.

RESULTS

Number of patients (*n*) was 208; male 155 (74.5%), female 53 (25.5%); 104 patients in each group (A and B). Both the study groups have nearly similar gender distribution. Group A male 78 (75%), female 26 (25%); group B male 77 (74%), female 27 (26%). The mean age was 57.15 years, group A 57.06 years (23-83 years), and group B 57.24 years (18-85 years).

Treatment outcomes among the study groups were compared (Table 1). The recovery and death were found preferable in group A than that of group B. Recovery distribution in both study groups was comparable. The time to clinical improvement, Time to symptomatic recovery; NEWS-2 score while discharge, total ICU and hospital stay, time to viral clearance were low in the Famotidine group (A). Survivors of group A experienced a reduced duration of ICU and hospital stay. Superior improvement of the CT chest findings was observed in the Famotidine treatment group. Difference between the time to clinical improvement, total duration of hospitalization among the recovered

patients, CT chest improvement, and the time for viral clearance were statistically significant in a *t*-test ($P \leq 0.05$). However, the difference between the time to symptomatic recovery, ICU stay duration, and the time to clinical failure/death, among the groups, were not significant, $P \geq 0.05$. The CT chest involvement (%) during admission was high in group A and the values differ significantly among the groups. Additionally a significantly low level ($P \leq 0.05$) of P:F ratio, PaO_2, and O_2 saturation (finger-tip) were observed during admission in the control group than the Famotidine treatment group (Table 1).

According to the subgroup analysis of gender (Table 2), group A females had shorter ICU stay duration (≤ 10 d) compare to males. This was found reversed in group B. Duration of hospital stay in group A was almost similar among both genders. Males in group B had a higher recovery within the 21-30 d period, and females had a faster recovery in the 10-20 d, and 21-30 d period. 8% of female patients in group B required > 31 d of ICU and hospitalization stay.

Group A gained a relatively faster hospital recovery within 10 d than group B. Similarly a faster time to clinical improvement in group A than group B was observed within a 10 d period. Females in group A secured a clinical improvement during this time than the males, whereas, this was the opposite in group B. Both the males and females in group A had a fast symptomatic recovery < 10 d time. On the other hand, only a few male patients in group B had asymptomatic recovery within this period. Group A patients showed a remarkable recovery from the acute symptom during the 11-20 d period. Though the entire patient in group A gained symptomatic recovery within 30 d, some of the group B patients required > 31 d.

A better number of patients in both sexes of group A was recovered within 21 to 30 d. Although a similar number of males in both groups had a delayed viral recovery within 31 to 40 d, this number was higher in the females of group B. Group B experienced faster mortality (< 10 d) than group A. Most of the patients in group A expired within 11 to 20 d. 100% mortality was observed among the males of group B within 10 d of hospitalization. Similarly, all of the female patients died within 11 to 20 d in group A.

The recovery percentage of the CT chest among the groups was almost equivalent. Males in group A gained a remarkable recovery during the discharge. Diversely in group B males had a lower (< 20%) and females achieve a better prognosis in the CT findings.

As stated in Table 3, Group A had a shorter hospital stay and rapid recovery, 49% of patients were discharged within 10 d time and none required > 31 d. This recovery rate was 38.5% in group B and 1.9% required > 31 d of hospitalization. Both the study groups had experienced similar ICU stay duration. Though few patients in group B required longer ICU stay. Shorter hospital stay duration (< 20 d) was observed among early (< 40 years) and the late (> 71 years) age groups of both sides. Age influence over the study groups was analyzed and outcomes were evaluated (Table 4). The middle age group of 51-70 years was the most, and the early age group of < 20 years was the least affected. Differences in the hospital recovery were observed depending on the age group. The early (< 30 years) and the late (> 81 years) age group had a full recovery in group A. Notably 51-70 year age had high mortality in both groups.

Subgroup analysis of the recovered patients against the duration of hospital stay, ICU stay, time to symptomatic recovery, time to negative PCR were evaluated (Table 5). Group A patients achieved a prompt hospital and ICU recovery within 10days; half of them were discharged within 11-20 d time. In group B the recovery was slow. Most of the patients (66%) were discharged within 11-20 d period; patients with > 61 years experienced a longer ICU stay. Similarly, viral recovery was delayed in the control group. 41 (53%) patients in the famotidine treatment group (A) gained a negative PCR within 11-20 d, 32 (41%) within 21-30 d, and 5 (6%) required > 31 d; this was 26 (36%), 35 (48%), and 12 (16%) in the group B.

Further analysis according to age group (Table 5) shows, group A showed 100% viral recovery within 20 d among patients of < 40 years age. The same trend was seen in 31-50 years, and > 81 years in group B. The 41-70 years age in group A required > 20 d for symptomatic recovery. In group B 51-80 years had a delayed improvement after 31 d.

Comorbidity was present among 58.7% of patients in group A and 44.2% in group B patients (Table 6). They were hypertension (HTN), diabetes mellitus (DM), ischaemic heart disease, chronic obstructive pulmonary disease, rheumatoid arthritis, benign prostatic hypertrophy, ischemic stroke, osteoarthritis, heart failure, hypothyroid, bronchial asthma, chronic kidney disease, inflammatory bowel disease, IBS, migraine, hepatitis-B, and carcinoma. 15.8% in group A and 21.1% in group B patients had HTN. Group A patients of ≥ 2 comorbidities had a better recovery with HTN and/or diabetes than group B. Mortality was also high in group B patients with HTN or DM and two or more comorbidity than group A.

To further evaluate and compare the survival benefit with famotidine treatment, Kaplan Meier survival analysis was done. The statistical difference involving the survival among the two study groups did not show any statistical significance (P = 0.989) (Figure 2). Log-rank hazard ratio of the group A (1.003; 95%CI: 0.59-1.69); group B (0.996; 95%CI: 0.59-1.67). Median survival: group A (27; 95%CI: 0.45-1.29), group B (35; 95%CI: 0.76-2.18).

DISCUSSION

SARS-CoV–2 infection was first detected in humans during December 2019, known to cause COVID-19 disease[3]. Patients with COVID–19 disease can present with a variety of clinical manifestations, which develop two to fourteen days following exposure to the virus. These symptoms include cough, shortness of breath, fever, chills, repeated rigor, myalgia, headache, oropharyngitis, anosmia, and ageusia[6,7]. More severe symptoms warranting hospital admission include difficulty breathing, a persistent sense of chest pain or compression, confusion or difficulty to arouse, and central cyanosis. Of hospitalized patients, 20%-42% develop ARDS. This is the most common cause of ICU admission. The mortality rate among ICU patients is still high, 39%-72%[3,8]. Different treatment options for patients with COVID-19 to reduce morbidity, mortality, and spread of the disease are an urgent global need. Trials with the repurposing of different drugs have already been published[9].

Famotidine is a potent histamine H_2-receptor antagonist, which has widely been used in the treatment and prevention of peptic ulcer disease. After intravenous administration, the plasma famotidine concentration-time profile exhibits a biexponential decay, with a distribution half-life of about 0.18 to 0.5 h and an elimination half-life of about 2 to 4 h. Famotidine shows a low plasma protein binding (15%-22%), and steady-state drug distribution ranges from 1.0 to 1.3 L/kg. Following administration, 70% of this drug is eliminated in unchanged form into the urine. Thus total body and renal clearances (15 L/h) of famotidine correlate significantly with creatinine clearance. Famotidine is considered to be eliminated *via* glomerular filtration and renal tubular secretion[9]. Besides, famotidine is very well tolerated, free of the antiandrogenic effects infrequently reported with Cimetidine, and not associated with the altered hepatic metabolism of drugs. Thus it a popular choice for the maintenance therapy of gastric hypersecretory disorders[10].

The idea to test the usefulness of famotidine as a medical countermeasure for COVID–19 emerged from a computational molecular docking effort to identify the papain-like protease inhibitors (PLpro) of SARS-CoV–2. In addition to processing the viral polyprotein, the PLpro from corona viruses is known to remove the cellular substrates ubiquitin. The interferon-stimulated gene 15 from host cell proteins cleaves the C-terminal end of the consensus sequence LXGG, a process termed deISGylation[11-13]. Freedberg *et al*[14,15] reported that results from a retrospective study tested associations between the use of famotidine and the outcome of patients with COVID-19. They classified the use of famotidine based on COVID-19 exposure within 24 h following hospital admission and maintained a follow-up up to 30 d.

In our current study, a total of 208 ICU patients with severe COVID-19 disease were recruited. These patients were randomly divided into two groups, group A (famotidine intervention group) and group B (non-famotidine intervention group or control), where n = 104 on each side. After the intervention, group A had a recovery rate of 75% (n = 78) and a mortality rate of 25% (n = 26). On the contrary, the control group B had a relatively low recovery of 70% (n = 73) and high mortality of 30% (n = 31) (Table 1). The

time to clinical improvement, time to symptomatic recovery, duration of ICU stay and mean hospitalization duration in the famotidine treatment group were shorter than that of control. However, all these differences with group B were not statistically significant. Nonetheless, the time to clinical improvement, total hospitalization duration among the recovered patients, CT chest improvement (%), and duration of viral clearance of the famotidine group were statistically significant ($P \leq 0.05$) when compared with the control (Table 1 and Figure 3). Though, treatment with famotidine did not show a significant survival benefit against the control group in the Kaplan Meier survival analysis, $P = 0.989$ (Figure 2). The gender and age difference appeared to be an important concern in treatment outcome. The early and the late age group had a shown better percentage of COVID-19 recovery in the Famotidine treatment group. Females in the famotidine treatment group had a faster ICU/hospital and symptomatic recovery. Similar gender influence with a different outcome was seen with the non-famotidine treatment. Patients with comorbidities also showed a better recovery in the famotidine treatment group than the control (Table 6). Even the duration of death was prolonged among the patients who received famotidine (Table 2). Therefore, it appears that in contrast to the non-famotidine group, the famotidine intervention group had some clinical benefits in severe COVID-19 illness.

Our study and other famotidine studies suggest an association between the use of famotidine and improved outcomes among the hospitalized patients with COVID-19. This was also suggested by a series of famotidine studies with quantitative symptom tracking in non-hospitalized patients[5,16]. Samimagham *et al*[17] also conducted a randomized trial on the effect of famotidine on the recovery process of hospitalized COVID-19 patients, in which the intervention group received standard pharmacotherapy according to the treatment protocols of the National Committee of COVID-19 and oral famotidine four times a day until the day of discharge, for a maximum of fourteen days. However, our study was specifically focused on severe COVID-19 patients, which reduced the hospitalization duration and shortened ICU stay. Multiple other investigators had also conducted studies on famotidine[18-20].

Almost all of these studies, including ours, showed clinical benefits and accepted levels of tolerance of famotidine in the treatment of severe COVID-19 disease.

This study has limitations. The small sample size is a matter of concern. Also, the exclusion of the critically ill COVID-19 patients in the ventilator support, and moderate degree of hospitalized patients might have an influence on the outcome. But to the best of our effort, we selected the study group patients, devoid of serious or uncontrolled comorbidity without compromised organ function to ensure the proper comparison and outcome among the study groups without influence.

CONCLUSION

According to this study, the famotidine treatment group demonstrated a comparatively better outcome in the survival and death rate. A rapid recovery time, less duration of ICU stays among the survivors, favorable improvement in the CT findings, and an earlier viral clearance were observed in the famotidine treatment group. These values were statistically significant in a *t*-test. The difference between the time to symptomatic recovery, ICU stay duration, and the NEWS-2 on discharge though was not significant, but mean values were relatively less than the control. However, the survival benefit was not significant with the Famotidine treatment for severe COVID-19 disease. All these suggest that H_2 receptor blocker Famotidine might have a favorable role in the prognosis of the COVID-19 illness.

ARTICLE HIGHLIGHTS

Research background

Famotidine is a histamine-2 receptor antagonist that suppresses gastric acid production. *In vitro*, famotidine inhibits human immunodeficiency virus replication. Recently, Wu *et al* used computational methods to predict structures of proteins encoded by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) genome and identified famotidine as one of the drugs most likely to inhibit the 3-chymotrypsin-like protease which processes proteins essential for viral replication. Famotidine use was associated

with a reduced risk of intubation and mortality among the patients hospitalized with coronavirus disease 2019 (COVID-19). Therefore it is necessary to evaluate the potential use of the existing drugs like famotidine that could be used as options for the medical management of COVID-19 patients.

Research motivation

COVID-19 is a worldwide pandemic. Hence SARS-CoV-2 is a novel virus; there is no specific medication against it. Thus clinicians and scientists all over the world are struggling with the treatment of this disease. Besides antiviral drugs, immunosuppressive agents, and symptomatic therapy like H_2 receptor blocker famotidine came to the limelight due to its role in reducing the symptoms of COVID-19 patients.

Research objectives

To evaluate the role of H_2 receptor blocker "famotidine" in COVID-19 illness.

Research methods

COVID-19 patients admitted in the intensive care unit (ICU) of Chattogram General hospital, M. Abdur Rahim Medical College Hospital, and 250 bed Cox's Bazar Sadar Hospital Bangladesh from July 20, 2020, onward were enrolled in this study. Patients were divided into famotidine treatment group "A" (famotidine 40 to 60 mg oral formulation 8 hourly with other treatment as given), and control group "B" (treatment as given). National early warning score (NEWS)-2, and sequential organ failure assessment day 1 score was calculated to evaluate the outcome of the patients.

Research results

(1) The recovery (75% in group A and 70% in group B and death (25% in group A, and 30% in group B) were found preferable in group A than that in group B; (2) Superior improvement of the computed tomography (CT) chest findings was observed in the

Famotidine treatment group; (3) Among the group A survivors, the duration of ICU and hospital stay were low; (4) However, the difference between the time to symptomatic recovery, ICU stay duration, and the time to clinical failure/death, among the groups, were not significant, $P \geq 0.05$; (5) Group A achieved reduced of hospital stay and rapid recovery; (6) Viral recovery was delayed in the control group; (7) The Kaplan Meier survival analysis was performed. The difference involving survival among the two study groups did not show any statistical significance ($P = 0.989$).

Research conclusions

The famotidine treatment group demonstrated a comparatively better clinical outcome than the control. A rapid recovery time, less duration of ICU stay among the survivors, favorable improvement in the CT findings, and an earlier viral clearance was observed in the Famotidine treatment group; and were statistically significant in a T-test with the control. However, survival benefit was not significant with the Famotidine treatment for severe COVID-19 disease.

Research perspectives

The results of this study will add up to an important point in treating the SARS-CoV-2 infection during this time of desperate need which will have an overall effect in the long run from every perspective.

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