Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Effect of famotidine on cognitive and behavioral dysfunctions induced in post-COVID-19 infection: A randomized, double-blind, and placebo-controlled study

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ABSTRACT

Objectives: This is an investigation of the efficacy and safety of famotidine, a selective histamine H2 receptor antagonist, on improvement of cognitive impairment, depression and anxiety symptoms developing post-COVID-19, in a 12-week, randomized controlled trial.

Methods: A total of 50 patients with a confirmed diagnosis of COVID-19 and a score ≤ 23 on the Mini-Mental State Examination (MMSE) test or a score ≤ 22 on the Montreal Cognitive Assessment (MoCA) were randomly assigned to either the famotidine (40 mg twice daily) or the placebo group. Changes in MMSE scores at weeks 6 and 12 were the primary outcome, while changes in other scales were the secondary outcomes. Participants and evaluators were blinded.

Results: At weeks 6 and 12, patients in the famotidine group had significantly higher MMSE scores ($p = 0.014$, $p < 0.001$, respectively). Regarding the MoCA scale, the famotidine group had a significantly higher score at weeks 6 and 12 ($p = 0.001$, $p < 0.001$, respectively). Considering the HAM-D scale (Hamilton Depression Rating Scale), at weeks 6 and 12, the famotidine group experienced a larger reduction ($p = 0.009$, $p = 0.02$, respectively). Additionally, comparison of the HAM-A scale scores (Hamilton Anxiety Rating Scale) at weeks 6 and 12 showed a statistically significant larger reduction in the famotidine group ($p = 0.04$, $p = 0.02$, respectively). The two groups did not differ in the frequency of adverse effects.

Conclusion: Our study supports safety and efficacy of famotidine in treating cognitive impairment, depression and anxiety symptoms induced by COVID-19.

Trial registration: This trial was registered at the Iranian registry of clinical trials (IRCT: www.irct.ir; registration number: IRCT20090117001556N138).

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the Coronavirus Disease of 2019 (COVID-19) was first detected in December 2019 in Wuhan, China and has since spread throughout the world, affecting nearly 600 million people as of August 2022 [1]. The potential neuropathogenicity of coronaviruses is well-documented [2,3].

More than one-third of patients may experience post-COVID-19 complications that persist beyond the acute illness [4,5]. Fatigue, cognitive impairment, and other neuropsychiatric disorders (such as depression) are the most common complications [6,7]. A growing body of evidence indicates that SARS-CoV-2 may cause acute and chronic neuropsychiatric symptoms by affecting the brain [8–11]. The newly

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emergent neuropsychiatric symptoms may result from direct effect of the virus on the brain, indirect immune responses, or administration of medications [11].

Famotidine, a selective histamine H2 receptor (H2R) antagonist that is widely used in treatment of gastroesophageal reflux, despite being controversial [12–15], has demonstrated promising results in alleviating symptoms in non-hospitalized COVID-19 patients and reducing mortality rates in hospitalized patients when administered in high doses [16–18]. Intriguingly, a case study demonstrated efficacy of famotidine in reducing COVID-19-induced neuropsychiatric symptoms [19]. Moreover, a small number of studies have shown beneficial effects for famotidine on cognition or improvement of symptoms in patients with schizophrenia [20–25].

Famotidine has potential benefits in reducing inflammation and preventing cytokine storm in severe cases of viral infections like COVID-19. This is due to its ability to inhibit histamine production, which can exacerbate the immune response and contribute to cytokine storm [26]. Additionally, famotidine enhances the activity of certain immune cells, such as T cells and natural killer cells, which play a crucial role in the antiviral response [27]. By boosting the immune response, famotidine may help to control viral replication and reduce the severity of infection [27]. Famotidine also has direct antiviral activity against certain viruses, including SARS-CoV-2 [27]. However, it is important to note that famotidine should not be used as a primary treatment for COVID-19 and should only be administered under the supervision of a healthcare professional.

Based on the above-mentioned findings, we hypothesized that famotidine might improve cognition and depression in newly developed cognitive impairment post-COVID-19. This double-blind, randomized, placebo-controlled trial was conducted to evaluate the efficacy and safety of famotidine in ameliorating cognitive impairment, depression and anxiety symptoms observed after COVID-19 infection.

2. Method

2.1. Trial design and setting

This was a randomized, placebo-controlled, double-blind study. Patients were recruited from September 2021 to July 2022 from hospitalized patients at Imam hospital (Tehran University of Medical Sciences, Tehran, Iran), a tertiary COVID-19 care center after discharge. Patients were randomly assigned to receive either famotidine or placebo. The institutional review board/ethics committee of Tehran University of Medical Sciences approved the trial protocol (IR.TUMS.DDRI.REC.1400.019), and it adhered to the ethical principles of the Declaration of Helsinki. We obtained patients written informed consent prior to enrollment after educating them on the potential adverse effects of the medications. Patients were instructed to call a designated helpline with any questions regarding the trial. The protocol of the trial was registered at the Iranian Registry of Clinical Trials (IRCT; http://www.irct.ir) with registration number IRCT20090117001556N138. We evaluated outcomes at three intervals: at baseline, after six weeks, and after 12 weeks.

2.2. Participants

Patients aged 18 to 65 with a history of COVID-19-related hospitalization were included in the study. Reverse transcriptase-polymerase chain reaction (RT-PCR) of nasopharyngeal samples and a lung computed tomography (CT) scan were performed for all patients. Diagnosis of COVID-19 was established upon positive RT-PCR test or compatible lung involvement along with clinical symptoms suggestive of a diagnosis of COVID-19. For inclusion in the study, at least 20 days must have had elapsed since the onset of symptoms, and at least seven days must have had elapsed since the last day of symptoms. Patients meeting the aforementioned criteria were screened for a diagnosis of cognitive impairment. Those with a score of 23 or less on the Mini-Mental State Examination (MMSE) test or a score of 22 or less on the Montreal Cognitive Assessment (MoCA) test were included in the study. Exclusion criteria included; (i) presence of other concurrent psychiatric disorder; (ii) preexisting thyroid disease; (iii) preexisting renal disease; (iv) preexisting liver disease; history of drug or alcohol abuse; (v) history of cognitive impairment or dementia; (vi) history of taking antipsychotic, antidepressant, anticonvulsant medications or any other medication that can affect cognitive performance within six months prior to enrollment; (vii) history of electroconvulsive therapy (ECT) during past two months; and (viii) pregnancy or lactation.

2.3. Intervention

Patients were randomly assigned (1:1 allocation ratio) to either the famotidine group or the placebo group. Patients received placebo or famotidine (Tablet, 40 mg) twice daily for 12 weeks. The appearance of famotidine and placebo was identical.

2.4. Randomization, allocation, concealment, and blinding

A random code was assigned to each individual patient. The randomization and allocation of treatment groups were carried out by the principal investigator of the study, who was not involved in diagnosis and follow-up. We used permuted block randomization with blocks of size four. The assignments were concealed in opaque, sealed envelopes and revealed at the end of the study for statistical analysis. The participants, care providers, and outcome assessors were blinded.

2.5. Outcomes and tools

The primary outcome was to assess changes in cognitive function using the MMSE scale. Assessment of the cognitive function using the MoCA scale and the depression and anxiety symptoms using the Hamilton Depression Rating Scale (HAM—D) and Hamilton Anxiety Rating Scale (HAM-A) scores, respectively, were the secondary outcomes. The MMSE is a tool that could quantify the severity of cognitive impairment and monitor cognitive changes over time [28]. Assessment of changes in the MoCA score as an alternative scale for evaluating cognitive deficits, evaluation of changes in the HAM-D and HAM-A were also conducted. The MoCA is a 10-min cognitive screening tool with a maximum score of 30 points [29]. Both MMSE and MoCA have been used to assess cognitive functioning post-COVID-19 [30,31]. The HAM-D is used most frequently for evaluating treatment response in cases of depression. It is a 17-item questionnaire used to determine severity of depressive symptoms, and each item is scored on a scale ranging from 3 to 5 points. The HAM-A is used most frequently for evaluating treatment response in cases of anxiety. All of the obtained measures were reported. Although all outcomes were encompassed within the trial's registration, it is important to note that the distinction between primary and secondary outcomes was not explicitly delineated.

2.6. Adverse events

The adverse events were carefully monitored by a psychiatrist at baseline and at each follow-up visit (weeks 6 and 12). We used a checklist containing 25 possible side effects of the medications, in addition to an open-ended question, to record adverse events [32–34]. In addition, one week after the study start point, participants were contacted by phone to document any adverse effects. A 24-h medical advice hotline number was also provided to patients if they experienced a side effect.

2.7. Sample size

The initial sample size of 46 was calculated using the following assumptions: (i) a mean difference of 1 between the two groups on the

MMSE with a standard deviation of 1.02; (ii) a power of 80%; and (iii) two-sided significance level of 5%. With an attrition rate of 30%, the total number of participants in the final sample was increased to sixty. A total of 30 patients were needed for each of the study's two arms based on an enrollment ratio of 1:1.

2.8. Statistical analysis

SPSS Version 26 was utilized to conduct all statistical analyses (IBM, Armonk, NY, USA). Categorical variables are presented as frequencies with percentages, while continuous variables are displayed as mean and standard deviation. Analyses were conducted on the intention-to-treat (ITT) population, which was comprised of all patients in the initial population who had a baseline and at least one post-baseline assessment by using the last observation carried forward technique. The general linear model (GLM) repeated-measures analysis was used to investigate the time, treatment, and time × treatment effects. The between-subjects factor was derived from the two treatment groups, and within-subject factors were the scores on MMSE, MoCA, HAM-D and HAM-A. We reported the Greenhouse–Geisser correction for degrees of freedom if Mauchly's test of sphericity was significant. To assess the difference in the outcome of the two groups, we calculated the mean difference in change score and respective confidence intervals (95% CI) between baseline and Week 6 and between baseline and Week 12. Independent sample *t*-test was used to compare mean changes in each score (between baseline and each point at follow-up evaluation) between the two groups. A *p*-value of <0.05 was considered statistically significant.

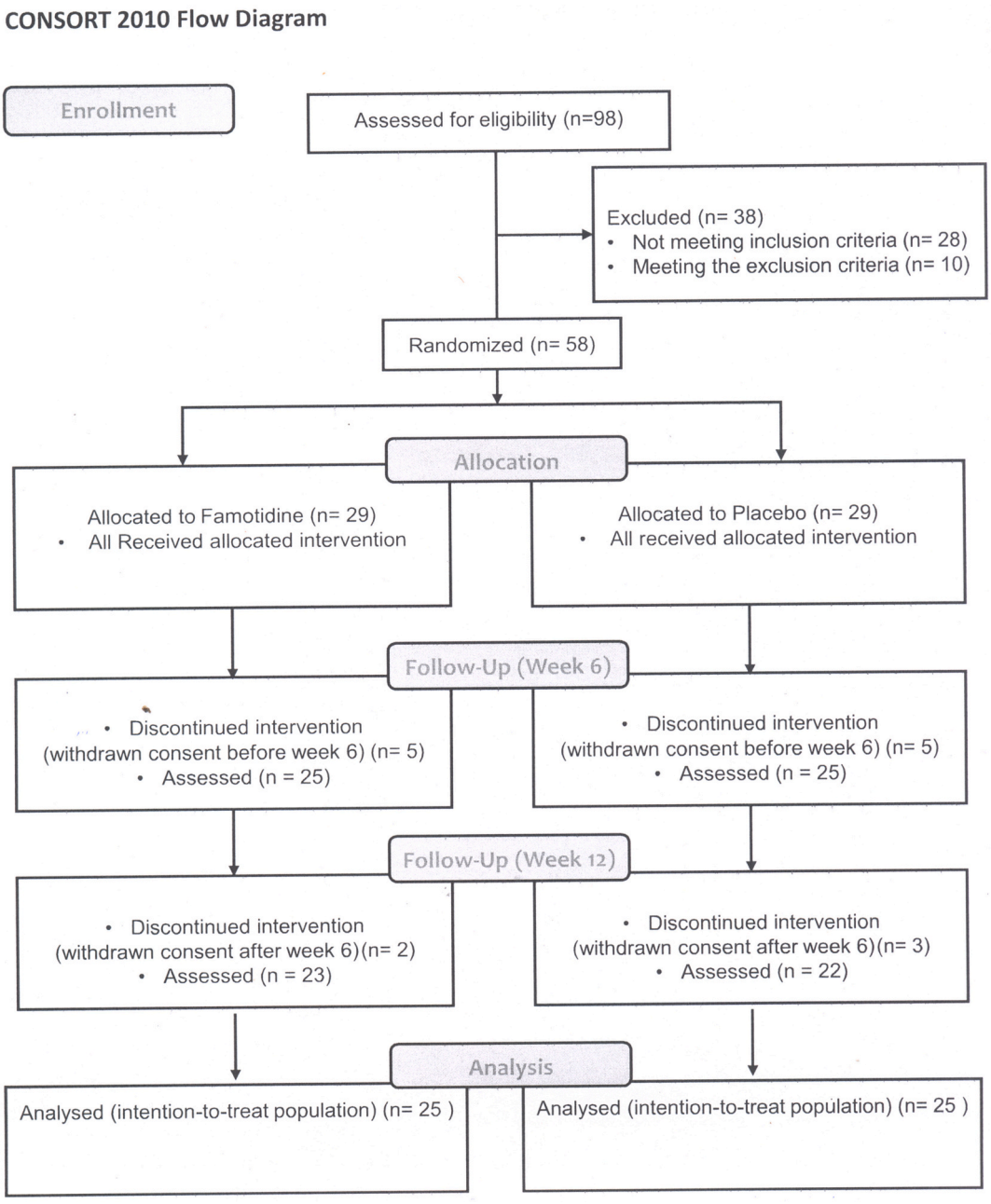

Fig. 1. Flow diagram of the study.

3. Results

3.1. Participants

We screened 98 potential cases with a history of hospitalization due to COVID-19 infection for study eligibility. Twenty-eight patients did not meet the inclusion criteria, and ten patients met the exclusion criteria. Sixty patients were enrolled in the study and randomized into treatment groups with an allocation ratio of 1:1: (i) famotidine 40 mg twice daily and (ii) placebo twice daily (Fig. 1). Before the first clinical assessment visit, ten patients (five patients from each arm) dropped out due to consent withdrawal due to problems with commuting. Fifty patients completed the first post-baseline assessment and were included in the intention-to-treat population, among whom 45 completed the trial and five (two from the famotidine group and three from the placebo group) dropped out of the study between weeks 6 and 12 due to problems with commuting.

3.2. Baseline characteristics

Baseline demographic and clinical characteristics of study participants are described in Table 1. Patients in the famotidine and placebo groups were comparable based on age, gender, education, marital status, COVID-19 diagnostic method, duration of hospitalization, days elapsed since the last day they had symptoms, oxygen therapy, whether they required administration of remdesivir, and associated comorbidities and past medical history. There was no significant difference between the two trial groups based on baseline MMSE, MoCA, HAM-D and HAM-A scores (Table 2).

Table 1
Baseline demographic and clinical characteristics of the patients in the two study groups.

Variable	Famotidine ($N = 25$)	Placebo ($N = 25$)
Age (years), mean (SD)	37.32 (9.59)	35.16 (8.24)
Sex, n (%)		
Females	11 (44.0%)	12 (46.0%)
Males	14 (56.0%)	13 (54.0%)
Marital status, n (%)		
Single	10 (40.0%)	8 (32.0%)
Married	14 (56.0%)	17 (68.0%)
Divorced	1 (4.0%)	0
Education, n (%)		
Primary	0	3 (12.0%)
Diploma	9 (36.0%)	7 (28.0%)
Higher	15 (60.0%)	14 (56%)
COVID-19 diagnostic method, n (%)		
RT-PCR	19 (76.0%)	13 (52%)
A combination of clinical symptoms with a chest CT scan	6 (24.0%)	11 (44.0%)
Duration of hospitalization (days), mean (SD)	8.96 (2.95)	8.92 (2.69)
Days elapsed since the initiation of symptoms, mean (SD)	29.00 (4.76)	28.52 (3.93)
Days elapsed since the last day of symptoms, mean (SD)	15.36 (3.83)	17.04 (4.04)
Oxygen therapy during hospitalization, n (%)		
Non-invasive	23 (92.0%)	23 (92.0%)
Invasive	2 (8.0%)	2 (8.0%)
Treatment received during hospitalization, n (%)		
Dexamethasone	5 (20.0%)	3 (12.0%)
Remdesivir + Dexamethasone	20 (80.0%)	22 (88.0%)
Associated comorbidities, n (%)		
Hypertension	4 (16.0%)	1 (4.0%)
Cardiovascular disease	0	1 (4.0%)
History of malignancy	0	4 (16.0%)
Type 2 diabetes mellitus	2 (8.0%)	0
Obesity (BMI $\geq$ 25)	4 (16.0%)	7 (28.0%)

Abbreviations: RT-PCR: Reverse transcriptase-polymerase chain reaction, BMI: body mass index, CT-scan: computed tomography scan

Table 2
Comparison of MMSE, MoCA, HAM-D and HAM-A scores and score changes between the two study groups.

Clinical scores	Famotidine group (N = 25), mean (SD)	Placebo group (N = 25), mean (SD)	Mean difference (95% CI)	t-value	*p-value*
MMSE score at baseline	20.48 (2.18)	20.32 (1.77)	0.16 (−0.97 to 1.29)	0.285	0.777
MMSE score at week 6	23.04 (2.03)	21.76 (1.45)	1.28 (0.28 to 2.28)	2.564	**0.014**
MMSE score at week 12	25.44 (2)	23 (1.32)	2.44 (1.47 to 3.41)	5.085	**<0.001**
Changes in MMSE score from baseline to week 6	2.56 (2.18)	1.44 (1.16)	1.12 (0.13 to 2.11)	2.268	**0.028**
Changes in MMSE score from baseline to week 12	4.96 (2.34)	2.68 (1.52)	2.28 (1.16 to 3.4)	4.091	**<0.001**
MoCA score at baseline	20.08 (1.58)	20.36 (1.6)	−0.28 (−1.19 to 0.63)	−0.622	0.537
MoCA score at week 6	23.48 (1.98)	21.68 (1.41)	1.8 (0.82 to 2.78)	3.704	**0.001**
MoCA score at week 12	25.84 (1.55)	23.28 (1.51)	2.56 (1.69 to 3.43)	5.915	**<0.001**
Changes in MoCA score from baseline to week 6	3.4 (2.06)	1.32 (1.25)	2.08 (1.11 to 3.05)	4.315	**<0.001**
Changes in MoCA score from baseline to week 12	5.76 (1.74)	2.92 (1.44)	2.84 (1.93 to 3.75)	6.288	**<0.001**
Ham-D score at baseline	12.2 (2.04)	11.6 (2.08)	0.6 (−0.57 to 1.77)	1.029	0.309
Ham-D score at week 6	10.6 (1.29)	10.76 (1.69)	−0.16 (−1.02 to 0.7)	−0.376	0.708
Ham-D score at week 12	10.04 (1.21)	10.36 (1.38)	−0.32 (−1.06 to 0.42)	−0.872	0.387
Changes in HAM-D score from baseline to week 6	−1.6 (1.19)	−0.84 (0.69)	−0.76 (−1.32 to −0.2)	−2.764	**0.009**
Changes in HAM-D score from baseline to week 12	−2.16 (1.46)	−1.24 (1.23)	−0.92 (−1.69 to −0.15)	−2.403	**0.020**
Ham-A score at baseline	10.2 (1.15)	10.3 (1.18)	−0.12 (−0.78 to 0.54)	−0.363	0.718
Ham-A score at week 6	9.8 (0.97)	10.2 (1.13)	−0.40 (−1.00 to 0.2)	−1.337	0.187
Ham-A score at week 12	9.4 (1.04)	10.1 (1.05)	−0.72 (−1.13 to −0.12)	−2.431	**0.019**
Changes in HAM-A score from	−0.32 (0.62)	−0.04 (0.2)	−0.28 (−0.54 to −0.01)	−2.127	**0.042**

(*continued on next page*)

Table 2 (*continued*)

Clinical scores	Famotidine group (N = 25), mean (SD)	Placebo group (N = 25), mean (SD)	Mean difference (95% CI)	t-value	*p-value*
baseline to week 6					
Changes in HAM-A score from baseline to week 12	−0.8 (1.19)	−0.2 (0.5)	−0.60 (−1.12 to −0.07)	−2.324	**0.027**

p-value of <0.05 was considered statistically significant. (Shown in bold).
Abbreviations: MMSE: Mini-Mental State Examination, MoCA: Montreal Cognitive Assessment, HAM—D: Hamilton Depression Rating Scale, HAM-A: Hamilton Anxiety Rating Scale.

3.3. Outcomes

Cognitive assessment: The MMSE score was used as the primary outcome to assess changes in cognitive functioning. Patients in the famotidine group had a significantly higher MMSE scores at week 6 (mean difference (95% CI) = 1.28 (0.28 to 2.28), *p-value* = 0.014) and week 12 (mean difference (95% CI) = 2.44 (1.47 to 3.41), *p-value* < 0.001). They also had a significantly larger increase in MMSE scores from baseline to week 6 (mean difference (95% CI) = 1.12 (0.13 to 2.11), *p-value* = 0.028) and from baseline to week 12 (mean difference (95% CI) = 2.28 (1.16 to 3.4), *p-value* < 0.001) (Table 2) (Fig. 2). The repeated measure GLM analysis showed a significant effect for treatment (F = 8.97, *p-value* = 0.004) and time × treatment (F = 11.00, *p-value* < 0.001) (Table 3).

MoCA was also used as a secondary outcome to assess changes in cognitive functioning. Patients in the famotidine group had a significantly higher score on the MoCA scale at week 6 (mean difference (95% CI) = 1.8 (0.82 to 2.78), *p-value* = 0.001) and week 12 (mean difference (95% CI) = 2.56 (1.69 to 3.43), *p-value* < 0.001) (Fig. 3). Increases in MoCA scores compared to the baseline were larger in the famotidine group compared to the placebo group at week 6 (2.08 (1.11 to 3.05), *p-value* < 0.001) and week 12 (2.84 (1.93 to 3.75), *p-value* < 0.001). The repeated measure GLM analysis showed a significant effect for treatment (F = 13.36, *p-value* = 0.001) and time × treatment (F = 20.5, *p-value* < 0.001) on changes in MoCA scores (Table 3).

Depression symptoms: Scores on the HAM-D scale were comparable in both groups at week 6 and week 12. The famotidine group experienced a statistically significant larger reduction in the HAM-D score at week 6 (mean difference (95% CI) = −0.76 (−1.32 to −0.2), *p-value* = 0.009) and week 12 (mean difference (95% CI) = −0.92 (−1.69 to −0.15), *p-value* = 0.02) (Fig. 4). However, this minor reduction might not be considered clinically significant. Moreover, the repeated measure GLM analysis showed a significant effect for time (F = 65.28, *p-value* < 0.001) and time × treatment (F = 5.13, *p-value* = 0.014) but not for treatment on changes of HAM-D scores.

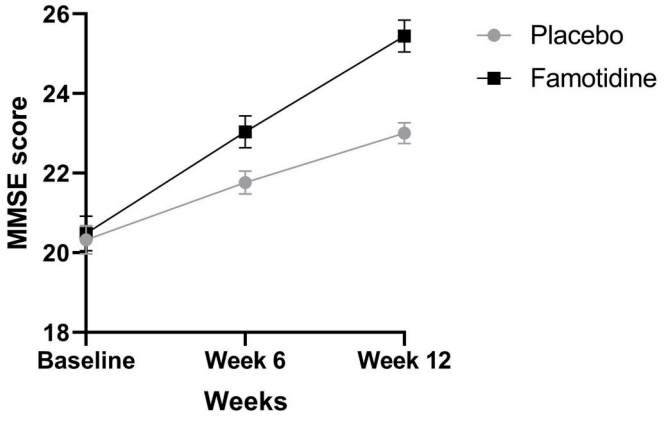

Fig. 2. Comparison of MMSE scores [mean (standard error)] between the study groups.

Table 3
Results of the general linear model repeated-measures analysis.

Source	Type III Sum of Squares	df	Mean Square	F	*p-value*
Mini-Mental State Examination (MMSE)					
Tests of Within-Subjects Effects					
week	365.08	1.744	209.392	123.62	**<0.001**
week * treatment	32.49	1.744	18.637	11.00	**<0.001**
Error (week)	141.76	83.689	1.694		
Tests of Between-Subjects Effects					
Intercept	74,861.34	1	74,861.340	10,707.22	**<0.001**
treatment	62.73	1	62.727	8.97	**0.004**
Error	335.60	48	6.992		
Montreal Cognitive Assessment (MoCA)					
Tests of Within-Subjects Effects					
week	472.09	2	236.047	179.09	**<0.001**
week * treatment	54.04	2	27.02	20.5	**<0.001**
Error (week)	126.53	96	1.318		
Tests of Between-Subjects Effects					
Intercept	75,622.83	1	75,622.827	14,569.31	**<0.001**
treatment	69.36	1	69.360	13.36	**0.001**
Error	249.15	48	5.191		
Hamilton Depression Rating Scale (HAM-D)					
Tests of Within-Subjects Effects					
week	76.81	1.517	50.647	65.28	**<0.001**
week * treatment	6	1.517	3.983	5.13	**0.014**
Error (week)	56.48	72.798	0.776		
Tests of Between-Subjects Effects					
Intercept	17,908.81	1	17,908.807	2552.32	**<0.001**
treatment	0.06	1	0.060	0.01	0.927
Error	336.80	48	7.017		
Hamilton Anxiety Rating Scale (HAM-A)					
Tests of Within-Subjects Effects					
week	6.413	1.374	4.666	12.152	**<0.001**
week * treatment	2.253	1.374	1.640	4.269	**0.031**
Error (week)	25.333	65.971	0.384		
Tests of Between-Subjects Effects					
Intercept	15,100.17	1	15,100.17	4949.973	**<0.001**
treatment	6.407	1	6.407	2.100	0.154
Error	146.427	48	3.051		

p-value of <0.05 was considered statistically significant. (Shown in bold).

Anxiety symptoms: The scores on HAM-A scale in both groups at week 6 and week 12 were compared. At week 6 and week 12, the famotidine group revealed a statistically significant decrease in the HAM-A scores with (mean difference (95% CI) = −0.28 (−0.54 to −0.01), *p-value* = 0.042) and (mean difference (95% CI) = −0.60 (−1.12 to −0.07), *p-value* = 0.027), respectively (Fig. 5). This slight decrease, however, might not be deemed clinically significant. In addition, the

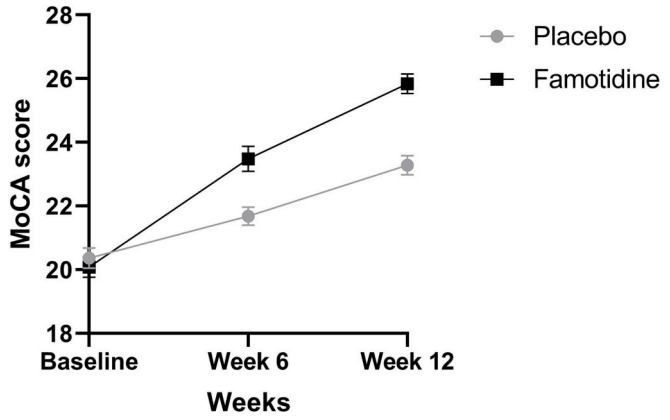

Fig. 3. Comparison of MoCA scores [mean (standard error)] between the study groups.

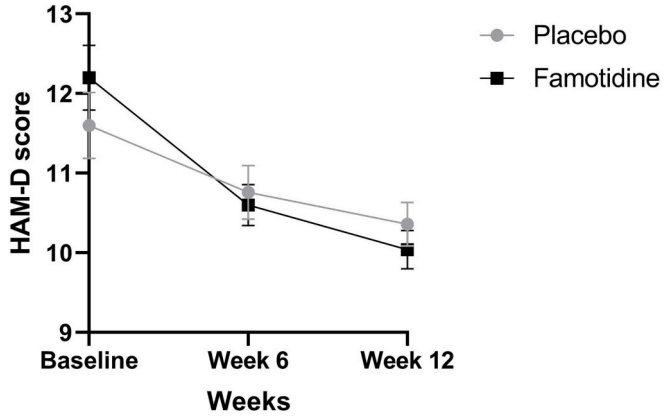

Fig. 4. Comparison of HAM-D scores [mean (standard error)] between the study groups.

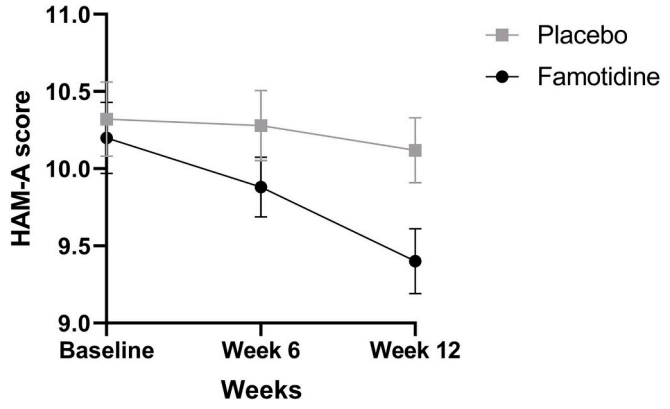

Fig. 5. Comparison of HAM-A scores [mean (standard error)] between the study groups.

repeated measure GLM analysis indicated that time (F = 12.15, *p-value* < 0.001) and time × treatment (F = 4.27, *p-value* = 0.031) had significant effects on changes of HAM-A scores.

Adverse effects: We observed the following side effects in both groups with a mild severity: nausea, dizziness, weakness, insomnia, diarrhea, fatigue, headache, and constipation. No unexpected adverse effect was discovered. There was no significant difference in the frequency of adverse effects between the two trial groups (Table 4).

Table 4
Frequency of adverse events among the trial arms.

Side effect	Famotidine group (N = 25)	Placebo group (N = 25)	*p-Value*
Nausea	6 (24.0%)	5 (20.0%)	0.733
Dizziness	7 (28.0%)	5 (20.0%)	0.508
Weakness	4 (16.0%)	2 (8.0%)	0.667
Insomnia	3 (12.0%)	5 (20.0%)	0.702
Diarrhea	6 (24.0%)	4 (16.0%)	0.480
Fatigue	4 (16.0%)	6 (24.0%)	0.480
Headache	5 (20.0%)	3 (12.0%)	0.702
Constipation	5(20.0%)	3 (12.0%)	0.702

4. Discussion

To the best of our knowledge, this is the first clinical trial targeting post-COVID-19 cognitive impairment and assessing the safety and efficacy of famotidine in improving cognitive impairment. We found significant improvement in cognitive functioning measured by MMSE and MoCA after six and twelve weeks of treatment with famotidine. Although the famotidine group experienced a statistically significant larger reduction in the HAM-D and HAM-A, this minor reduction might not be considered clinically significant. Cognitive functioning depressive and anxiety symptoms improved with time in both groups.

Famotidine is a selective H2 receptor antagonist used for gastric acid suppression, which can cross the blood-brain barrier [35]. Controversial findings have been reported on the effects of famotidine on cognitive functioning, with most studies investigating its potential neuropsychiatric effects on schizophrenia. Several studies reported that famotidine adjunct to standard treatment improved symptom severity in patients with schizophrenia [20–23]. However, a meta-analysis showed that adjunctive therapy with H2 receptor antagonists did not improve overall symptoms in these patients [36]. Nevertheless, the results of this meta-analysis should be interpreted cautiously as psychopathological evaluation scales were different between the included studies, and they were unable to assess positive and negative symptoms separately and the long-term effects of H2 receptor antagonists.

There is still ongoing research to determine the exact mechanism of action of famotidine in treating COVID-19. Despite the fact that famotidine is a H2 receptor antagonist, some studies have suggested that its therapeutic effects may be due to off-target effects, such as inhibition of viral replication or immune modulation. Furthermore, the scavenging of reactive oxygen radicals, notably the hydroxyl ion, is an additional off-target mechanism of famotidine that may be clinically significant in reducing inflammation and damage [37]. In one study, famotidine was found to reduce the levels of certain proteins associated with interferon pathway, NF-B pathway, and TLR signaling in SARS-CoV-2-infected cells when compared to cells treated with histamine alone [38]. The use of Metascape software to analyze the proteomic data revealed that famotidine treatment caused significant changes in pathways related to interferon response, cytokine production, viral infection, and NF-KB signaling [38]. Additionally, certain proteins were found to be upregulated in cells treated with famotidine, but the gene ontology analysis indicated that these proteins were not linked to viral infection. These findings suggest that while famotidine may not have an impact on viral replication, it could potentially influence the antiviral response in infected cells and the production of cytokines.

Some cross-sectional studies reported an association between H2 receptor antagonist use and reduced risk of Alzheimer's disease [24,25], while others had contradictory results [39]. However, longitudinal studies did not confirm such an association [40–42] or even suggested a potentially increased risk for Alzheimer's disease, at least in a subgroup of participants using H2 receptor antagonists [43,44]. Notably, most of these studies only included elderly participants. An in-vitro study suggested a neuroprotective effect for famotidine via inhibiting glycogen synthase kinase 3 beta (GSK-3β) signaling [45], which was found to improve cognition in animal models [46]. Accordingly, a recent animal

model study showed that famotidine improved recognition memory in an acute ketamine model of schizophrenia [47].

In 2020, a single case study reported that 20 mg twice daily oral famotidine improved neuropsychiatric symptoms developed post-COVID-19 in a young patient [19]. Interestingly, they stated that the patient reported a marked improvement after just four days on famotidine. Given the role of neuroinflammation in mediating neurological consequences of COVID-19 [48], another potential mechanism for famotidine in ameliorating long-term post-COVID-19 neuropsychiatric symptoms might be activation of the vagus nerve inflammatory reflex leading to an anti-inflammatory response [49].

During the pandemic, several studies, but not all [12–15], supported the beneficial effect of famotidine in COVID-19. Famotidine has been identified as a possible candidate that may block viral enzyme 3chymotrypsin-like protease (3CLpro) which is essential for replication of SARS-CoV-2 [50]. Notably, Toll-like receptor 3 (TLR3)-dependent signaling is a crucial innate immune mechanism of action when a corona viral infection occurs [38]. Famotidine therapy, in particular, reduces histamine-induced TLR3 expression in SARS-CoV-2 infected cells and may diminish TLR3-dependent signaling cascades that result in activation of IRF3 and the NF-κB pathway, hence limiting antiviral and inflammatory responses [38]. Interestingly, famotidine treatment of SARS-CoV-2 infected cells results in downregulation of the inflammatory markers CCL-2 and IL-6, which are responsible for the cytokine release syndrome that predicts a poor prognosis in COVID-19 patients [51]. Several subsequent trials [12–16,52] have demonstrated the protective effect of famotidine in decreasing the risk of developing severe disease or mortality in individuals with COVID-19 [16,52]. However, several meta-analyses showed that famotidine did not reduce the risk of poor outcomes in hospitalized patients with COVID-19 [53–55].

Neurological and neuropsychiatric symptoms are both prevalent three months following an acute COVID-19 infection, according to a meta-analysis of over 10,000 individuals drawn from 18 published investigations [7]. Three months after acute COVID-19 disease, over one-third of patients still had neurological/neuropsychiatric post-COVID-19 syndrome symptoms, including fatigue, cognitive dysfunction (brain fog, memory issues, concentration challenges), and sleep disturbances. Long-term symptoms (six months or more after infection) were substantially more frequent than mid-term symptoms (three to six months post infection). Post-COVID-19 syndrome is a long-term global public health concern that affects hospitalized and non-hospitalized people. Neurologic symptoms during acute COVID-19, such as anosmia, dysgeusia, and headache, were not evident throughout the post-COVID-19 syndrome, indicating they normally vanished. Long-term cognitive impairment may be an effect of these abnormal processes, which is confirmed by the Premraj et al. meta-analysis. [7].

Famotidine is widely considered as a very safe medication for everyday use, and in many countries, it is even sold without a prescription. A recent analysis, however, highlights situations in which its usage, along with other H2 receptor antagonists, has been linked to increased delirium [56]. In a variety of clinical situations, individuals with delirium benefit from having their H2 antagonist therapy discontinued [57,58]. This study did not find any significant differences in the clinical profile of the included population, but the small sample size prevented us from making a definitive conclusion about the balance of risks and benefits associated with the medication being studied. Further research with a larger sample size may be needed to provide more conclusive evidence on this matter.

While this is the first study to evaluate the efficacy and safety of famotidine on cognitive impairment, depression and anxiety symptoms in post-COVID-19 conditions, it has several limitations. First, the trial's registration failed to delineate between primary and secondary outcomes, despite all measured outcomes being reported in the registration. Second, the follow-up time of our study was only 12 weeks, limiting us from assessing the long-term effects of famotidine in treating cognitive dysfunction, depression and anxiety symptoms induced by long COVID-19. Third, the sample size was modest but adequate for statistical power. Further studies with greater sample sizes and extended follow-up periods are necessary to evaluate the potential therapeutic value of famotidine on cognitive and behavioral impairment following post-COVID-19 infection. Fourth, additional investigations must utilize a standardized definition of "cognitive dysfunction" and use quantitative neurological testing to identify particular deficiencies (memory, spatial, sensorineural) and assess efficacy and safety of famotidine therapy. Fifth, the cytokine and chemokine profiles of the patients were not measured to assess effects of famotidine therapy and investigate possible correlations to cognitive impairment and depressive symptoms post-COVID-19 infection. RCTs should evaluate alterations in cytokine and chemokine profiles after famotidine therapy in the future. Sixth, we enrolled patients with at least 20 days elapsing since the onset of symptoms and at least seven days elapsing since the last day of symptoms. However, different studies have used different follow-up periods for defining long COVID, with WHO defining long covid as "continuation or development of new symptoms three months after the initial infection" for long COVID [59,60]. Seventh, we did not assess the effect of famotidine on other signs and symptoms of post-COVID-19 infection, such as anosmia, as these outcomes were out of the study's scope. However, future investigations can assess the potentials effects of famotidine on the other features of long COVID-19. Lastly, influence of possible confounders (i.e., disease severity and duration) on therapy response may be studied in the future with larger sample sizes.

5. Conclusion

To conclude, famotidine, a selective H2 receptor antagonist, has demonstrated promising results in improving cognitive impairment, depression and anxiety symptoms in post-COVID-19 infection conditions, along with its widespread usage in relieving gastrointestinal reflux. In our 12-week double-blinded, placebo-controlled clinical trial, we assessed the potential therapeutic value of famotidine therapy in treating cognitive and behavioral dysfunction induced in post-COVID-19 infection. The current RCT reported improvements in cognitive impairment, depression and anxiety symptoms caused by post-COVID-19 infection. Ideally, additional RCTs are needed to evaluate famotidine therapy in treating psychiatric symptoms caused by long COVID-19.

Disclosure statement

The authors have no competing interests to report.

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Declaration of Competing Interest

No conflict of interest exists for any of the authors associated with the manuscript.

Data availability

Data is available on request from the authors.

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