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Effects of Famotidine on COVID-19 Patients in Intensive Care Unit: A Retrospective Clinical Trial

Yoğun Bakım COVID-19 Hastalarında Famotidin Kullanımının Klinik Etkileri, Retrospektif Klinik Çalışma

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ABSTRACT

Objectives: Because developing a new drug is a lengthy process, the drugs used safely were tried to be repurposed for COVID-19 treatment. In this retrospective study, it was aimed to investigate the effects of famotidine on the mortality, need for invasive mechanical ventilation, and the severity of the disease in patients diagnosed with COVID-19 in the intensive care unit (ICU) by regarding laboratory results.

Methods: Data of patients treated in the ICU due to COVID-19 were retrospectively analyzed. The patients using famotidine were named Group F (n=30), and the patients not using it were named Group C (n=29). Invasive mechanical ventilation needs, 30-day mortality, intubation time, lymphocyte, ferritin, C-reactive protein (CRP), D-dimer, fibrinogen, and procalcitonin values were compared between groups. Mann–Whitney U-test and repeated measures ANOVA tests were used as statistical methods.

Results: There was no statistical difference between the groups in terms of the need for invasive mechanical ventilation, 30-day mortality, length of stay in the ICU, and intubation time. In the laboratory, lymphocyte count, ferritin and D-dimer values were similar between the groups, while CRP was higher in Group F until the 14th day. Fibrinogen and procalcitonin values were lower in Group F.

Conclusion: Famotidine treatment did not have a positive effect on the need for invasive mechanical ventilation and 30-day mortality in COVID-19 patients followed in the ICU. However, we think that it may have positive effects on coagulation, against the inflammation process and secondary infections.

Keywords: COVID-19; famotidine; intensive care unit; severe acute respiratory syndrome coronavirus 2.

ÖZET

Amaç: Yeni ilaç geliştirme çalışmaları uzun bir süreç olduğu için güvenle kullanılan ilaçlar koronavirüs hastalığı (COVID-19) tedavisi için yeniden kullanılmaya çalışıldı. Bu retrospektif çalışmada, famotidin kullanılan ve kullanılmayan COVID-19 tanısı almış hastalarda, fomatidinin yoğun bakımda mortalite, invaziv mekanik ventilasyon ihtiyacı ve hastalığın ciddiyeti üzerine etkilerinin laboratuvar sonuçları da dikkate alınarak araştırılması amaçlandı.

Yöntem: COVID-19 nedeniyle yoğun bakım ünitesinde tedavi gören hastaların laboratuvar ve klinik verileri geriye dönük olarak analiz edildi. Famotidin kullanan hastalar Grup F (n=30), kullanmayan hastalar Grup C (n=29) olarak adlandırıldı. İnvaziv mekanik ventilasyon ihtiyacı, 30 günlük mortalite, entübasyon süresi, lenfosit sayısı, ferritin, C-reaktif protein, D-dimer, fibrinojen ve prokalsitonin değerleri karşılaştırıldı. İstatistiksel yöntem olarak Mann-Whitney U testi ve Repeated Measures ANOVA testleri kullanıldı.

Bulgular: Gruplar arasında klinik verilerden invaziv mekanik ventilasyon ihtiyacı, 30 günlük mortalite, yoğun bakımda kalış süresi ve entübasyon süresi açısından istatistiksel fark yoktu. Laboratuvar olarak ise lenfosit sayısı, ferritin ve D-dimer değerleri gruplar arasında benzerlik gösterirken C-reaktif protein, Grup F'de 14. güne kadar istatistiksel olarak anlamlı derecede yüksekti. Grup F'de fibrinojen ve prokalsitonin değerleri daha düşüktü.

Sonuç: Famotidin tedavisinin yoğun bakımda takip edilen COVID-19 hastalarında invaziv mekanik ventilasyon ihtiyacı ve 30 günlük mortalite üzerine olumlu etkisi olmadı. Bununla birlikte pıhtılaşma üzerine, inflamasyon sürecine ve sekonder enfeksiyonlara karşı olumlu etkilerinin olabileceğini düşünüyoruz.

Anahtar sözcükler: COVID-19; famotidin; yoğun bakım ünitesi; SARS-CoV-2.

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected millions of people worldwide and caused the Coronavirus-19 (COVID-19) pandemic.[1] The mortality among COVID-19 patients hospitalized in the intensive care unit (ICU) was 48.7%.[2]

Because developing a new treatment takes a very long time, drugs with established safety profiles have been considered in the search for urgent solutions to COVID-19.[3] Famotidine is one of the alternatives being tested for treatment, because an early anecdotal report from Wuhan, China, suggested that famotidine reduced mortality in COVID-19 patients.[4]

Famotidine has been mentioned in terms of its potential role in the regulation of responses in the innate and adaptive immune system. Therefore, it was repurposed for COVID-19 treatment.[5] Famotidine has an inhibitory effect on protease enzymes essential for the survival and replication of SARS-CoV-2.[6] It was demonstrated that SARS-CoV-2 infections can cause histamine release through mast cell activation, systemic inflammation, and cytokine release. It is expected that famotidine may be useful for reducing systemic inflammation and cytokine release.[7] Due to these mechanisms of action, famotidine may have positive effects on the prognosis of intensive care patients. In the present retrospective study, it was aimed to investigate the effects of famotidine treatment in intensive care on mortality, invasive mechanical ventilation needs, and the severity of the disease by considering laboratory results.

Methods

This study was performed in compliance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Istanbul Medeniyet University Goztepe Research Hospital (Date January 13, 2021/ No. 2021/0024) and an application was submitted to ClinicalTrials.gov (NCT05122208). The laboratory and clinical data of patients treated in our ICU due to COVID-19 lung involvement between September 2020 and February 2021 were analyzed retrospectively. The patients who were not diagnosed with immunosuppression, end-stage liver disease, end-stage renal disease, psoriasis, or porphyria and were not pregnant were included in the study. Patients who had no allergic reactions to famotidine or similar drugs had received famotidine 160 mg 4 times daily PO or nasogastrically and were called Group F and patients not administered famotidine were called Group C.[8]

All patients were treated according to the standard treatment scheme of our clinic, after being diagnosed with COVID-19. However, the treatment scheme was updated after the published literature. For this reason, some patients were given Famotidine, some patients did not. Patients received favipiravir (Favicovir 200 mg Film Tablet, Atabay Kimya San. ve Tic. AS, Türkiye) 1600 mg/day PO on day 1 and 600 mg/day PO for the following 4 days as antiviral therapy. The antibiotherapy applied to the patients was based on the culture results. Fluid therapy was calculated and adjusted with appropriate crystalloid fluids, and inotropic therapy was started for patients in whom fluid therapy was insufficient.

Since SARS-CoV-2 increased the coagulation status of the patients, salicylic acid (Aspirin, Bayer Pharma, Zentiva, Kırklareli, Türkiye) 100 mg/day PO and enoxaparin sodium (Clexane®; Sanofi-Aventis Ltd, Istanbul, Türkiye) 6000 anti-Xa/day SC were administered to the patients and the treatment was revised daily according to activated partial thromboplastin time, international normalized ratio values, and prothrombin time.[9]

Prednisolone (Prednisolon, Actavis Medical; İstanbul, Türkiye) 80 mg/day i.v. was given to the patients as the efficacy of steroid therapy was demonstrated in COVID-19 patients with lung damage involvement[10] and the patient with progressive lesions shown by X-ray and increased respiratory insufficiency received prednisolone 250 mg/day for 3 days.[11] Patients also received pantoprazole sodium 40 mg/day PO for gastrointestinal system protection.

Continuous venovenous hemodiafiltration was started in patients who developed renal failure. When the respiratory needs of the patients were increased, O_2 therapy with a mask and high-flow O_2 therapy were applied consecutively. With the progression of respiratory insufficiency, mechanical ventilation support was applied according to the respiratory efforts and blood gas results.

Table 1. General characteristics between groups

	Group F		Group C		p
			Med±SD		
Age, mean±SD	64.17±11.27		66.41±17.57		0.563
GCS IQR (min-max)	3 (9–19)		5 (3–15)		0.071
APACHEII, mean±SD	16.44±6.2		18.7±10.39		0.337
length of stay IQR (min-max)	7.3 (5–37)		9.8 (4–21)		0.599
Intubation time IQR (min-max)	12 (0–37)		9 (2–19)		0.275
	n	%	n	%	
Sex					
Male	21	70	20	69	1.000
Female	9	30	9	31	
Intubation					
No	7	30.4	7	24.1	0.476
Yes	23	60.6	22	75.9	
Exitus					
No	16	53.3	10	36.7	0.341
Yes	14	46.7	19	63.3	
Diseases					
DM	11	36.7	9	30	0.784
HT	15	50	14	46.7	1.000
CAD	4	13.3	4	13.3	0.647
COPD	5	16.7	3	10	0.353
Asthma	5	16.7	0	0	0.026*
CVA	3	10	1	3.3	0.306
Other Diseases	12	40	11	36.7	1.000

*p<0.05 between groups. SD: Standard deviation; GCS: Glasgow coma scale; IQR: Interquartile range; APACHE II: Acute physiology and chronic health evaluation; DM: Diabetes mellitus; HT: Hypertension; CAD: Coranary artery disease; COPD: Chronic obstructive pulmonary disease; CVA: Cerebrovascular accident.

Age, sex, comorbidities, acute physiology and chronic health evaluation (APACHE II), and Glasgow coma scale (GCS) scores were obtained from patient data. Intubation time was defined as the time from 1st day in the ICU to intubation and was recorded. The length of the stay was defined as the time spent in the ICU and was recorded. Daily values of platelet count, leukocyte count, lymphocyte count, neutrophil count, ferritin, C-reactive protein (CRP), D-dimer, fibrinogen, procalcitonin, creatinine, aspartate aminotransferase (AST), lactic dehydrogenase (LDH), alanine aminotransferase (ALT), and PaO_2/FiO_2 (P/F) ratio were evaluated to plan the appropriate treatment. Data of patients were evaluated until death or discharge from the ICU.

The primary outcomes were the need for invasive mechanical ventilation and 30-day mortality. The secondary outcomes were serum markers indicating the severity of the disease (D-dimer, fibrinogen, procalcitonin, ferritin, CRP, and lymphocyte count).

Statistical Analysis

As a result of the Power analysis using the G*Power program, when the effect size d (effect size): 1.409 and the standard deviation (SD) value were taken as 158 for the LDH parameter, the sample number determined for Power: 0.80 and α:0.05 were determined as minimum n=30 people.[12] IBM SPSS Statistics 22 (IBM SPSS, Türkiye) was used for statistical analysis to evaluate the findings obtained. The conformity of the parameters to the normal distribution was evaluated with the Shapiro–Wilk test. In addition to descriptive statistical methods (mean, SD, frequency), Student's t-test was used for the comparison of normally distributed parameters between the two groups, and the Mann-Whitney U-test was used for comparisons of parameters that did not show a normal distribution. For comparisons of intragroup normally distributed quantitative data repeated measures ANOVA (post hoc Bonferroni test); for comparisons of non-normally distributed parameters Friedman test (post hoc Wilcoxon signed-rank

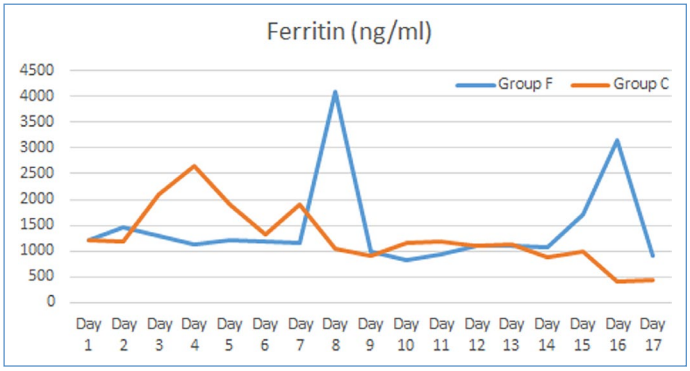

Figure 1. Ferritin values of groups.

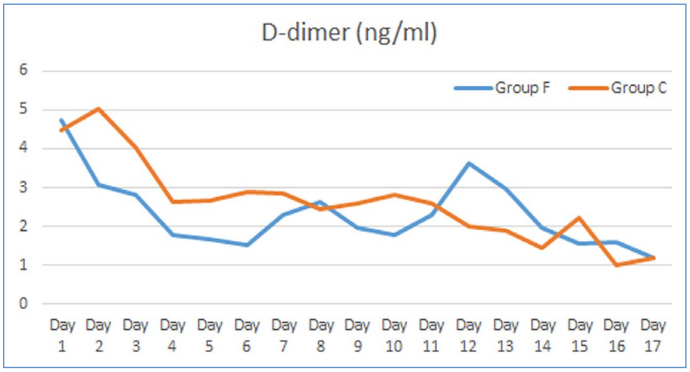

Figure 2. D-dimer values of groups.

test) was used. For comparing the qualitative data, Fisher's exact test and continuity (Yates) correction were used. Statistical significance was evaluated at the $p<0.05$ level.

Results

The study was conducted with a total of 59 patients, 41 (69.5%) men and 18 (30.5%) women, between July 2020 and February 2021 in Istanbul Goztepe Prof. Dr. Suleyman Yalcın City Hospital. The patients' mean age was 65.27±14.62. There were 2 groups in the study: Group F (n=30) and Group C (n=29). Data of patients were evaluated until death or discharge from the ICU. However, statistical evaluation was made on the first 17-day values, where the data were the most intense.

The groups did not significantly differ in terms of age (p=0.563), GCS score (p=0.071), APACHE-II score (p=0.337), length of intensive care stay (p=0.599), or intubation time (p=0.275). The difference between the groups in terms of invasive mechanical ventilation need (p=1.000) or 30-day mortality (p=0.299) was not statistically significant. While the incidence of asthma in the famotidine group was significantly higher than that in the control group (p=0.026), there was no difference in other comorbidities (p>0.05) (Table 1).

There was no significant difference between the groups in terms of leukocyte, lymphocyte, neutrophil, or thrombocyte counts (p>0.05). There was also no significant difference in terms of ferritin (Fig. 1) or D-dimer (Fig. 2) values between the groups (p>0.05). CRP was significantly higher in Group F on days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, and 13 (p=0.000, p=0.000, p=0.000, p=0.000, p=0.000, p=0.000, p=0.000, p=0.002, p=0.009, p=0.056, p=0.024, and p=0.019, respectively) (Fig. 3, Tables 2 and 3). Fibrinogen on days 10, 11, and 12 was significantly lower in Group F compared to Group C (p=0.007, p=0.000, and p=0.015, respectively) (Fig. 4, Tables 2 and 3). Procalcitonin values on days 2, 3, and 5

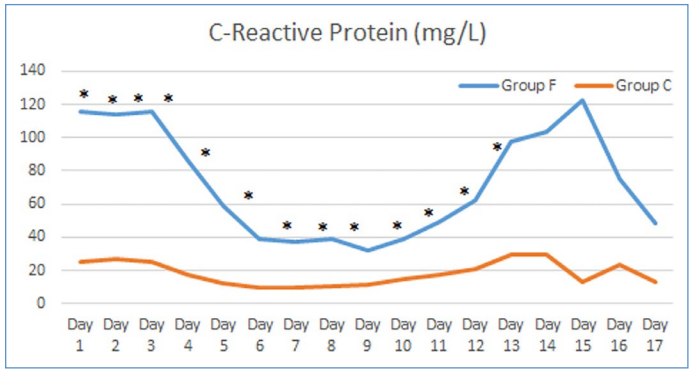

Figure 3. C-reactive protein values of groups.

*: p<0.05.

were significantly lower in Group F (p=0.034, p=0.049, and p=0.028, respectively) (Fig. 5).

There was no statistically significant difference in LDH, creatinine, or ALT between the groups (p>0.05).

AST values on day 1 were significantly low (p=0,019), while day 14 values were high in Group F (p=0.007). Except for the lower P/F ratio in Group F on day 3 (p=0.029), no significant difference was found between the groups for this parameter (p>0.05).

Discussion

In this retrospective study we conducted on COVID-19 patients treated in intensive care, showed that giving 160 mg/day of famotidine to patients did not affect the need for invasive mechanical ventilation or 30-day mortality. In addition, laboratory findings suggest that famotidine may have minimal effects on coagulation, inflammation, and secondary infections.

Since there is no accepted treatment protocol for COVID-19 all over the world, clinics have created their own treatment protocols. After the studies on the benefits of famotidine in COVID-19 patients were published, Famotidine was included in the protocol of our clinic.

Table 2. Biochemical values in group F

	Ferritine ng/ml	CRP mg/L ng/ml	D Dimer ng/mL	Fibrinogen ng/mL	Procalcitonin	LDH U/L
1st day	1940.8±4045.1	19.8±23.2	4.6±6.1	583.2±150.4	28.4±116	481.3±255
2nd day	1786.4±3337.7	42.7±76.7	5.2±7.9	568.7±160.1	28.8±109.1	466.6±213.3
3th day	2669.1±5837.4	25.4±56.9	4.2±5.4	567±144.9	49.7±152.4	500.6±184.8
4th day	3273.4±5344	17.6±36.5	2.7±2.3	515.2±146.6	37.7±145.2	421.3±117.7
5th day	2490.5±4291.5	13±25.5	2.7±2.7	502.9±157.5	5.1±17.1	531.8±310.5
6th day	1960.9±3675.3	9.8±17.3	3±3.6	485.2±140.7	3.9±11.6	1363.8±3470.9
7th day	1984.3±3025.5	10.3±20.9	2.9±3.8	443.1±134.6	49.6±154.7	527.9±401.9
8th day	1045.4±1252.3	10.6±19.5	7.4±24	440.6±140	0.6±0.5	445.1±157.7
9th day	905.2±698.5	11.8±18.8	2.6±2.7	448.7±141.5	0.3±0.2	465.8±199.3
10th day	1151.9±749.5	14.8±25.5	2.8±2.7	524.2±159.8	0.3±0.1	25875.5±96971.1
11th day	1172.3±960.7	17.6±28.4	2.6±2.4	551.7±153.2	0.3±0.2	478.4±269.5
12th day	1112.6±914.3	20.6±31.2	2±1.7	550.8±130.4	0.7±0.6	480.2±275.4
13th day	1116.9±1056.5	29.2±44.2	1.9±1.3	529.5±133.9	13.6±22.8	373.3±114.9
14th day	872.8±709.6	29.8±42.3	1.5±1	510.9±136.6	0.6	406.2±100.7
15th day	991.8±799.5	13.2±14	2.2±2	426.6±102.4		440.3±200.6
16th day	412.6±237.4	23.1±38.4	1±0.5	389.6±112.8	0.9	360.8±61.3
17th day	438.2±158.7	13±21.8	1.2±0.9	372.5±86	1.5	456.7±180.9

CRP: C-reactive protein; LDH: Lactic dehydrogenase; U/L: Unit per liter.

Table 3. Biochemical values in group C

	Ferritine ng/mL	CRP mg/mL	D Dimer ng/mL	Fibrinogen ng/mL	Procalcitonin ng/mL	LDH U/L
1st day	1217.9±1338.6	216.4±500.2	4.7±6.4	680.9±242.7	11.1±3.3	457.9±135.5
2nd day	1451.8±1884.8	114±67.2	3.1±3.8	656.9±203.6	1.9±5	476.7±164.1
3th day	1285.8±1879.3	115.6±98.8	2.8±2.8	26277.4±13588	1.4±2.8	497.4±197.3
4th day	1126.4±1234.9	86.2±89.4	1.8±1.3	525.4±180.7	1±1.3	444.3±149.2
5th day	1199±1693.5	59.1±69.7	1.7±1.5	485.6±176.3	0.6±0.7	439.4±163
6th day	1184.9±1761.4	39.2±39.6	1.5±1.1	447.3±156.5	0.5±0.6	443.8±196.7
7th day	1164.81434 .2±	37.3±40.1	2.3±2.1	416.8±110.4	0.5±0.8	415.8±130.2
8th day	3981.2±15146.4	42.6±44.7	2.5±3.5	406.7±131	0.3±0.3	409.4±128.5
9th day	983.3±886.3	32.8±26.3	2±1.7	402.9±119.6	4.7±20.8	397.2±105.1
10th day	825.3±616.4	37.7±37.7	1.8±1.1	3395.8±90.9	0.5±0.6	426.9±125.3
11th day	932.1±738	49.4±50.5	2.3±2.8	364.1±105	0.5±0.8	418.8±156.3
12th day	1094.4±775.9	61.8±55.9	3.6±4.1	403.6±156	7.4±25.6	438.1±159.6
13th day	1099.7±853.8	97.4±82.1	2.7±2.6	417.9±185.9	8.5±26.4	406.8±164.9
14th day	1075.2±836	103.7±110.4	2±1.4	297.7±239.8	1±1.4	475.5±90.1
15th day	1708.3±2590	122.2±130.9	1.5±0.8	375.4±159.6	11±27.7	491±133.3
16th day	3143.9±6700	75.4±73.7	1.6±1.1	330.1±175.3	8.7±20.5	520±241.8
17th day	905.2±359.2	48.6±58.8	1.2±0.6	291.8±147.2	5.8±11.9	551.8±184.9

CRP: C-reactive protein; LDH: Lactic dehydrogenase; U/L: Unit per liter.

In a retrospective study involving 878 patients in Wuhan, 83 patients were found to be given Famotidine, and they found that patients given Famotidine had less intubation, lower CRP and Ferritin levels, and lower in-hospital mortality.[4] Famotidine treatment especially regulates innate and adaptive immune responses.[5] Famotidine treatment espe-

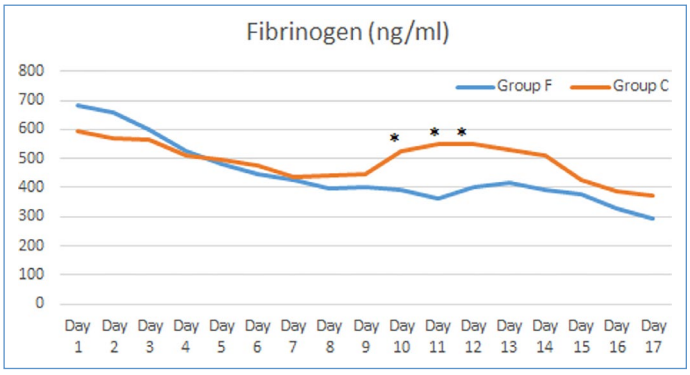

Figure 4. Fibrinogen values of groups.

*: p<0.05.

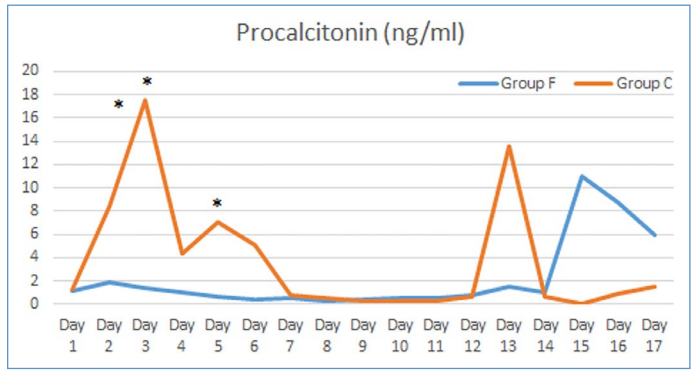

Figure 5. Procalcitonin values of groups.

*: p<0.05 .

cially regulates innate and adaptive immune responses. It modulates B cells based antibody generation, T helper cell cytokine release, differentiation and proliferation of T cell, mast cell, and dendritic cell response degranulation. Therefore it was repurposed for COVID-19 treatment Famotidine has an inhibitory effect on protease enzymes essential for the survival and replication of SARS-CoV-2.[6]

Famotidine is safely used with no interactions with other medications in 20 mg/day PO single dose to 160 mg/day PO divided into four as a histamine-2 receptor antagonist. It was shown that famotidine had the predicted steady-state concentration at different doses.[13] The use of higher-than-standard doses may result in beneficial effects from famotidine. Hogan et al.[14] administered famotidine 20 mg IV/PO and cetirizine 10 mg IV/PO as the first dose of therapy, and famotidine 40 mg/day PO and cetirizine 20 mg/day PO subsequently. Balouch et al.[15] reported that 20–40 mg/day PO famotidine did not increase the risk of infection. Janowitz et al.[16] administered famotidine in a high dose, 240 mg/day, for 11 days to non-hospitalized patients with COVID-19 and they did not experience any serious side effects. Moreover, no patient needed hospitalization for COVID-19 symptoms. Singh et al.[17] stated that the amount of calcium in the famotidine preparation might affect the prognosis of the disease because calcium supplementation decreases lipotoxicity. Lipotoxicity is important because it may increase the severity of the disease and result in organ failure. They explain that different results can be found due to different doses and different applications. In the present study, COVID-19 patients received famotidine at 160 mg/day in addition to the treatment.

Various mechanisms were described previously for the improvement of COVID-19 by using famotidine in different studies. One of these mechanisms is the inhibition of 3-chymotrypsin-like protease, which acts on proteins important for viral replication by famotidine.[18] However, it has been shown that famotidine does not have any effect on 3-chymotrypsin-like protease and does not alleviate SARS-CoV-2 infection.[13,17] It is also claimed that famotidine resulted in vascular inflammation by the activation of G-protein-coupled receptors, which was presumed to activate immune cell mobilization.[13]

Histamine-2 receptor antagonism or inverse agonism mediated by famotidine may have beneficial effects by inhibiting pathological histamine release and preventing mast cell activation.[19] Mukherjee et al.[20] mentioned the effects of famotidine and histamine in Toll-like receptor 3 signal regulation for gene expression and mechanisms in cells infected by SARS-CoV-2. They claimed famotidine can improve the outcome of COVID-19 by alleviating histamine-induced inflammation and cytokine release. In a study they stated that famotidine had effects on the antiviral response in infected cells and alleviated cytokine production, but had no effect on viral replication.

In a retrospective study of 1620 patients, 84 patients who were given Famotidine 24 h after admission to the hospital were compared with other patients who were not. Intubation rate and mortality were found to be twofold reduction,[21] while some studies have not supported this beneficial effect of famotidine.[22-25] Janowitz et al.[16] gave high-dose oral famotidine to non-hospitalized COVID-19 patients and observed a significant improvement in disease-related symptoms. However, some studies have indicated that famotidine has no significant clinical benefits in COVID-19.[26] Balouch et al.[15] did not find any prophylactic benefit in COVID-19 with the use of famotidine in 20–40 mg/day. Furthermore, Kow et al.[27] suggested no significant reduction in the severe course of illness with famotidine treatment in COVID-19 in a meta-analysis. In addition, Li et al.[28] reported that

there was no reduced or increased risk of severe disease in COVID-19 patients with famotidine use in their meta-analysis. Ma et al.[29] mentioned that the role of famotidine remains uncertain due to the absence of reliable evidence for clinical outcomes of COVID-19. In this retrospective study, no significant difference could be detected due to the treatment of famotidine given at 160 mg/day.

In severe COVID-19 cases, it has been shown that fibrinogen, CRP, ferritin, and some cytokines are released as a result of an overreaction from the liver after acute inflammation. In this context, CRP is released from the liver as a defense mechanism against pathogens. CRP release, which is considered to be anti-infective, was also observed in the acute phase of Covid -19 patients.[30,31] Although CRP measurements in the 1st days were high in Group F, the disappearance of this difference from day 14 suggested that the use of famotidine may have a positive effect on inflammation. Famotidine has been documented to abolish the negative effect of histamine receptor 2 mediated on cytokine production (especially TNF-alpha).[32] In our study, CRP values were recorded as higher in Group F than in the other group until the 13th day.

In a retrospective study, it was determined that procalcitonin level was correlated with the severity of COVID-19 disease.[33] In the group given famotidine, a lower procalcitonin level was measured in the first 8–10 days. The reason for this may have been decreased inflammation and cytokine release due to famotidine. However, after day 10, procalcitonin measurements were similar. Since this is a period of increased secondary bacterial infections, there may be no difference between the groups. In our study, procalcitonin values measured in the 1st day were significantly higher in the control group compared to the famotidine group.

It has been determined that there are changes in plasma protein expressions as a result of pathophysiological changes after viral infections. Differentially expressed proteins is identified in the plasma during COVID-19 could help us understand the molecular pathophysiology of disease. In a study, the highest protein expression after COVID-19 infection was observed in the fibrinogen gamma chain, fibrinogen alpha chain, and fibrinogen beta chain. In addition, it has been shown that fibrinogen is effective both as an antimicrobial in immune system cells and in clot formation.[34] In a study on fibrinogen in patients with COVID-19, it was claimed that fibrinogen secreted as an acute phase reactant may be effective in protecting the patient.[35] It has been claimed that the coagulation system activated as a result of increased fibrinogen in COVID-19 patients and the predisposition to embolism may be the main reason for the fatal course of this disease.[34] Similarly, other studies have reported that fibrinogen level is correlated with the severity of the disease and is an indicator of poor prognosis.[36,37] Considering the initial values in our study, fibrinogen values were similarly high in both groups. However, it was found to be significantly lower in Group F than the control group on 10–12 days. In addition, in the following days, it was observed that the fibrinogen values in the famotidine group were lower than the control group. However, these values are not statistically significant. According to these results, we believe that the severity of the disease is milder in patients treated with famotidine, since the fibrinogen level was found to be lower in Group F.

From the point of view of organ damage, ALT, AST, creatinine, and LDH measurements showing liver, kidney, and heart functions in our patients were similar. In our study, P/F ratios, which indicate the level of lung damage, were calculated between 100 and 200 values in both groups and these results were statistically similar between the two groups. According to this result, we concluded that there was no difference between the groups in terms of lung involvement. Intubation time and mechanical ventilation time, which are the other findings of our study, were also recorded as similar in the two groups.

Recent studies reported that famotidine treatment leads to improvements in symptoms of COVID-19 and reduces the risk of intubation or death. Freedberg et al.[21] found that patients who received different intravenous and oral doses of famotidine within the first 24 h of hospitalization had a twofold reduced risk of clinical deterioration leading to intubation or death. Mathers et al.[4] studied patients receiving famotidine by either oral or intravenous routes and they found lower rates of mortality, intubation, and combined mortality/intubation in these patients. In addition, Hogan et al.[14] reported that cetirizine and famotidine treatments resulted in a reduction in intubation rates, symptom progression, and mortality, compared with published reports of COVID-19 inpatients.

Some studies reported that famotidine has not shown any beneficial effects on COVID-19 mortality. The study of Shoaibi et al.[22] found similar death and death/intensive care use between famotidine users and nonusers in COVID-19. Furthermore, Yeramaneni et al.[24] analyzed hospitalized COVID-19 patients retrospectively and found 30-day mor-

tality did not change with famotidine treatment within 24 h of hospital admission. They also reported that starting famotidine treatment in hospital without previous use had a 77% higher risk of 30-day mortality. However, Kuno et al.[23] reported a decreased risk of in-hospital mortality from COVID-19 with famotidine treatment. Similarly, Zhou et al.[25] reported that developing severe COVID-19 disease, such as need for ICU admission or intubation, or death, was higher with proton pump inhibitor or famotidine use. Sun et al.[38] examined 36635 patients in 5 studies and found that famotidine treatment did not reduce the development of serious illness, death, or intubation in COVID-19 patients.

In our study, the invasive mechanical ventilation needs and invasive mechanical ventilation duration were the same in the patients. The use of famotidine was not found to have had an effect on invasive mechanical ventilation length. In addition, intensive care stay and mortality in the ICU were similar between the patients who were treated and were not treated famotidine group despite the high levels of CRP in Group F.

Lymphocyte counts, D- dimer, and ferritin were thought to be potential prognosis predictors.[39] Lower ferritin levels among famotidine-treated patients were also reported.[4] Freedberg et al.[21] claimed that famotidine may decrease cytokine release in SARS-CoV-2 infection, taking the lower peak ferritin values in famotidine users as proof. However, Cheung et al.[26] did not find any relationship between COVID-19 severity and famotidine. Furthermore, they found leukocyte count and lactate dehydrogenase as predictive parameters used for determining COVID-19 severity.

In our study, lymphocyte counts and ferritin as prognostic serum markers were not affected by famotidine use. D-dimer values were similarly high in the two groups. Famotidine use did not apparently affect the coagulation status of patients.

In the studies conducted, it has been observed that the use of famotidine can be effective in the period of replication and cytokine release. According to the results obtained, it may have beneficial effects in the clinic when used in the early period. However, we may not have been able to detect a notable difference, since intensive care patients were included in our study.

Our study has some limitations. Besides the vaccination status of the patients and whether they had previous COVID-19 not being taken into account, it was also not known whether they had taken famotidine before. Another limitation is that other treatments and supportive care in addition to famotidine treatment are administered in the ICU; however, we could not distinguish the effects of these supportive treatments. Moreover, the number of patients investigated in the study may have been insufficient for the results to be meaningful.

The present clinical investigation showed that giving 160 mg/day of famotidine to patients who needed intensive care due to worsening respiratory functions did not affect the need for invasive mechanical ventilation or 30-day mortality. In addition, laboratory findings suggest that famotidine may have minimal effects on coagulation, inflammation, and secondary infections.

Disclosures

Ethics Committee Approval: The study was approved by İstanbul Medeniyet University Goztepe Research Hospital Ethics Committee, Date: 13.01.2021, decision number: 2021/0024.

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