Famotidine in the treatment of functional dyspepsia: a randomized double-blind, placebo-controlled trial

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Aim

In the present study, we aimed to investigate patients with a documented diagnosis of functional dyspepsia (FD) who had been admitted to our outpatient Gastroenterology Clinic and provided consent to participate in this randomized, double-blind, placebo-controlled trial of the therapeutic impact of famotidine on the symptoms and quality of life of FD patients.

Participants and Methods

A total of 160 patients attending our outpatient clinic with a diagnosis of FD according to Rome III criteria were enrolled in this double-blind study. They were randomized into case (famotidine treatment) and placebo groups; patients were asked to refill the Honk Kong dyspepsia index (a self global assessment tool) before the start of the study as well as after 3 months of treatment.

Results

Both famotidine and placebo led to significant improvements in dyspepsia symptoms, except for vomiting in both groups and loss of appetite in the placebo control group. However, the extent of these improvements was not different between the two study groups for most of the study parameters, whereas belching, feeling of acid regurgitation, heartburn, and the total score for the Hong Kong dyspepsia index were significantly more responsive to famotidine than placebo. No significant effectiveness of famotidine therapy was found regarding quality of life.

Conclusion and recommendations

This study showed a significant improvement in the total dyspepsia scores of FD, with a marked effect on belching, heartburn, and the feeling of acid regurgitation. These findings suggest that famotidine may be administered in certain FD patients who have significantly more symptoms of belching, heartburn, and acid regurgitation.

Keywords:
double-blind controlled trial, famotidine, functional dyspepsia, placebo

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Introduction

Dyspepsia is a highly prevalent condition. It has been proposed that patients with dyspepsia can be classified into different subgroups representing different pathophysiological entities. Functional dyspepsia (FD) is a clinical syndrome defined by chronic or recurrent upper abdominal symptoms without an identifiable cause by conventional diagnostic means [1]. The symptoms are often related to feeding and in the absence of any organic disease that may produce epigastric symptoms. FD symptoms include epigastric pain and discomfort, bloating, early satiety, fullness, nausea, vomiting, abdominal distension, and anorexia, which definitely fulfill Rome II criteria established in 1999, and excluded gastroesophageal reflux disease (GERD) from this entity and also removed symptoms involving heartburn from FD diagnosis [2]. These symptoms, whether recurrent or persistent, should be present for 12 weeks, with onset at least 6 months before the diagnosis.

As it is difficult to identify the exact pathogenesis of the disease in each FD individual, treatment strategies include the use of a wide spectrum of agents including antisecretory drugs, gastroprokinetics, antidepressants, and anti-helicobacter pylori agents [3]. H_2 blockers including cimetidine, ranitidine, and famotidine have been examined for the management of symptoms in patients with FD, and they have been demonstrated to be effective. However, due to the multifactorial nature of FD and the role of psychiatric factors in the symptoms of the patients, studies with more complex methodologies are required to identify agents that independently improve FD symptoms. For example, it has also been found that FD patients respond well to placebos. Thus, to determine whether these drugs can or cannot affect the disease course, we must blindly compare their effects with those of placebos.

In the present study, we enrolled patients with an established diagnosis of FD who had been admitted in

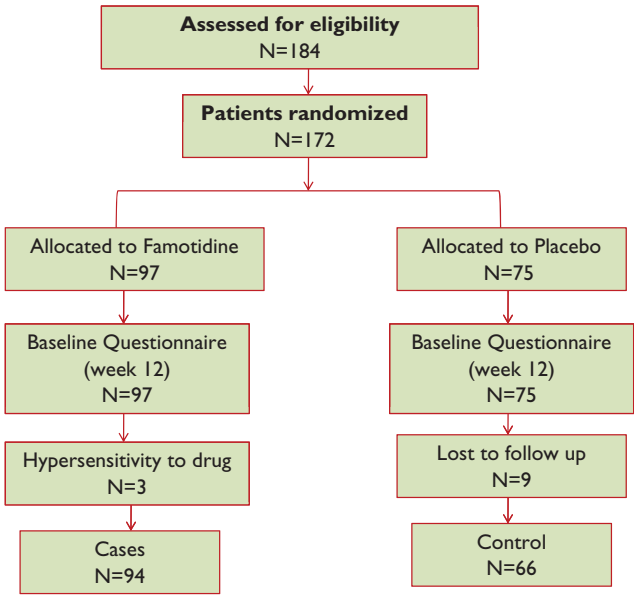
our outpatient Gastroenterology Clinic and provided consent to participate in this double-blind, placebo-controlled trial on the therapeutic impact of famotidine on the symptoms and quality of life (QoL) of FD patients.

Materials and methods

Participants

All patients attending our outpatient gastroenterology clinic and diagnosed with FD and meeting the following criteria were subsequently included in this study: (a) having symptoms of dyspepsia including epigastric pain and discomfort, early satiety, nausea, vomiting, abdominal distension, and anorexia for 3 months or longer within the preceding 1 year; (b) the possibility of an organic disease was ruled out after evaluations by endoscopy; and (c) no associations between severity of symptoms and defecation, or other changes in stools. A total of 178 patients were included, exceeding the calculated sample size. To calculate sample size, we used STATA software (version 9.1, STATA Corporation, TX, USA). After conducting a pilot study of 10 patients in the case and 10 patients in the control groups, and considering acid regurgitation as one of the main study factors, we obtained a mean ± SD score of -0.75 ± 1 for the case group and -0.25 ± 0.9 for the controls. These data, with a power of 85% and an α of 0.05, were entered into the software, which yielded a sample size of 66 patients per group. We also predicted a 10% dropout rate (Fig. 1); and thus we attempted to increase the sample size as much as possible to compensate for this loss. The trial was initiated with 97 patients in the case group and 75 patients in the placebo group. The gap was due to the lack of provision of placebo by the supporting companies. Only patients who had been admitted to undergo endoscopy and full laboratorial evaluations were included in the study. Patients were excluded from the study if any of the following conditions or criteria existed: a past history of gastrectomy; organic brain damage; documented neurologic disorder; considerable psychological disorders, serious cardiopulmonary and/or hepatorenal disorders; neoplasm, severe chronic obstructive pulmonary disorder or congestive heart failure, addiction to opium or alcohol, continuous use of the following drugs: cardiologic, antihypertensives, psychological agents, corticosteroids, iron, and calcium; history of usage of anti-helicobacter drugs during the past 3 months, a past history of major surgical interventions on the gastrointestinal tract, a past history of developing hypersensitivity to the study drug or any of its components; and/or pregnancy or potential pregnancy. During the study, the administered agents or did not use them regularly were excluded from the study. According to the mentioned criteria, 12 patients were excluded from the study: two did not agree to enrollment; one had Alzheimer's disease; four had severe chronic obstructive pulmonary disorder and/or heart failure; three were under treatment with cardiologic/psychiatric drugs; one had a history of hypersensitivity to the drug; and one was pregnant. After entering the study (97 cases and 75 controls), 12 patients did not complete the study: nine did not attend the clinic for follow-up and three reported hypersensitivity to the drug and opted out of the study (Fig. 1).

Figure 1.



Flow chart of the trial.

Study design

This study was designed as a randomized, double-blind, placebo-controlled trial. Randomization was computer-generated, with allocation concealment by opaque sequentially numbered sealed envelopes. Participants were randomized into two groups, and received either famotidine or placebo for a period of 12 weeks. Famotidine was obtained from Tehran Darou (Tehran Darou Company, Tehran, Iran) and the placebo was starch manufactured by Dr Abidi Pharmaceutics (Dr Abidi Pharmaceutics, Tehran, Iran). Both famotidine and placebo were filled into capsules with exactly the same features; each of them contained 40 mg. All the patients underwent treatment with 40 mg of famotidine or placebo twice daily, after breakfast and dinner. Concomitant use of other drugs was not allowed. After this time period, patients received one capsule daily for the remaining 8 weeks. The study was approved by our local Ethics Committee, and all patients provided written informed consent. For patients 16 years of age or younger, consent was given by at least one of the parents.

Assessments of symptoms and QoL were carried out before the study was initiated (week 0) and at the end of the study (week 12) using the Hong Kong index of dyspepsia, a validated questionnaire for assessment of symptom severity for patients with dyspepsia, Persian edition.

Ethics

The study was approved by the local ethics committee. In Iran, trial registration is not yet a prerequisite for

publishing the results of randomized controlled trial (RCT) study.

Statistical analysis

All the statistical analyses were performed using SPSS version 17.0 software (SPSS Inc., Chicago, Illinois, USA). Analyses were carried out using the χ^2-test, Student's *t*-test; Fisher's exact test, Bonferoni's test where appropriate; and nonparametric analyses using Wilcoxon's test and a nonparametric χ^2-test. *P*-values of less than 0.05 were considered as statistically significant in test results.

Results

Overall, 160 patients with a diagnosis of FD who completed the study were included in the final analysis. A total of 94 (58.8%) patients were in the case group and the remaining 66 patients (41.3%) were included in the control group. There were 95 (59.4%) women and 65 (40.6%) men. Patients' age ranged from 11 to 82 years, with a mean ± SD of 39.4 ± 15.4. In total 47 (29.4%) patients were categorized as having ulcer-like FD and 65 (40.6%) were categorized in the dysmotility group; the remaining 48 (30%) were included in the study as nonspecific FD patients. Only eight (5%) patients reported to be smokers.

Table 1 compares the baseline characteristics of patients and the disease among the study groups. Patients in the famotidine treatment group were significantly older at the time of the study, and had a shorter FD disease duration and were less likely to have a regular exercise regimen than those in the placebo group. Tables 2 and 3 show that both famotidine and placebo resulted in significant improvements in dyspepsia symptoms, except for vomiting in both groups and loss of appetite in the placebo control group. However, the extent of these improvements was not different between the two study groups for most of the study parameters, whereas belching, feeling of acid regurgitation, heartburn, and the total score for the Hong Kong dyspepsia index were significantly more responsive to famotidine than placebo. QoL parameters were been evaluated and compared for both the groups. All the QoL parameters improved significantly after the administration of both famotidine and placebo; however, there was no significant difference between the two study groups.

Table 1. Comparison of baseline characteristics of the patients and the disease among the study groups

Variables	Famotidine group	Placebo group	*P*-value
Age (mean year ± SD)	41.7 ± 16.3	36.1 ± 13.4	0.023
Male sex (%)	40 (42.6)	25 (37.9)	0.625
Dysplasia type (%)			0.631
Ulcer like	25 (26.6)	22 (33.3)	
Dysmotility	39 (41.5)	26 (39.4)	
Nonspecific	30 (31.9)	18 (27.3)	
Duration of dysplasia (over 1 year)	60 (63.8)	53 (81.5)	0.02
Reflux (%)	44 (46.8)	29 (39.7)	0.749
Regular exercise (%)	10 (10.6)	16 (24.2)	0.029
Personality and behavior (%)			0.232
Nothing	37 (39.4)	20 (30.3)	
Stress disorders	40 (42.6)	38 (57.6)	
Depression	6 (6.4)	2 (3)	
Depressive stressful	9 (9.6)	3 (4.5)	
Obsessive	2 (2.1)	3 (4.5)	
Reaction to dairy			0.572
No reaction	63 (67)	46 (69.7)	
Crumping	29 (30.9)	17 (25.8)	
Diarrhea	2 (2.1)	3 (4.5)	
Findings in endoscopy (%)			0.184
Esophagitis (%)	5 (5.5)	1 (1.5)	
Antral gastritis	59 (46.8)	37 (56.1)	
Pan gastritis	6 (6.6)	4 (6.1)	
Duodenitis	3 (3.3)	1 (1.5)	
Gastroduodentitis	9 (9.9)	7 (10.6)	
Two or more of the above mentioned	9 (9.9)	16 (24.2)	
Helicobacter pylori (%)	40 (45.5)	26 (41.9)	0.739
History of dyspepsia treatment (%)	36 (38.3)	16 (24.2)	0.086

Discussion

FD is a very common disease, with about 30–50% of all patients attending primary care clinics having FD symptoms, which include a wide spectrum of episodic or persistent symptoms of the upper gastrointestinal tract [4]. The pathology of FD is highly complex including psychological and physical problems whose mechanisms have not been clearly defined. The reported causes of FD in the literature are motility disorders, acid hypersensitivity, perception disorders, psychological factors, and *Helicobacter pylori* infection, but none of them have been shown to independently cause the disease. In the present study, FD patients were enrolled through a selection process according to the Rome III criteria [5], and esophagogastroduodenoscopy was performed for all of them to rule out other diagnoses and confirm the subtypes of FD. According to the Rome criteria, FD or non-ulcer dyspepsia was classified into four subcategories including ulcer-like, dysmotility-like, reflux-like, and unspecified in 1991, whereas in 1999, the Rome II classification included the reflux-like subgroup in another disease category defined as GERD, which led to only three subcategories for FD disease [2]. In the current study, we did not detect any beneficial effect of famotidine treatment on the QoL of patients with FD when compared with that in the placebo group. This finding is in contrast to the results of another double-blind, placebo-controlled trial on Japanese FD patients [6], in which the authors reported a beneficial effect of famotidine therapy on the QoL of FD patients, although there are some methodological differences between the two studies. Our study included 160 patients, which is about eight times larger than that in the study by Kato *et al.* [6]; however, Kato and colleagues. used a crossover approach in their study, which can empower their findings. The parameters used for the evaluation of QoL were also different in the two studies. Moreover, a meta-analysis of 22 randomized, double-blind, placebo-controlled studies showed that patients in 15 (68%) of the included studies showed a better response to H_2 blocker agents than placebo [7].

Table 2. Self-scored severity of functional dyspepsia symptoms among the study groups (range: 0–5 for each parameter)

	Administration of famotidine			Administration of placebo			Change in scores after treatment		
Symptoms scores (mean ± SD)	Before	After	*P*-value	Before	After	*P*-value	Famotidine	Placebo	*P*-value
Obvious stomach pain	2.4 ± 1.3	1.5 ± 0.7	<0.001	2.6 ± 1.2	1.6 ± 0.9	<0.001	−0.9 ± 1.1	−0.9 ± 1.2	0.994
Bloating	3 ± 1.3	1.9 ± 1.1	<0.001	3 ± 1.4	1.9 ± 0.9	<0.001	−1.1 ± 1.2	−1.1 ± 1.2	0.749
Dull stomach pain or sense of pressure	2.6 ± 1.1	1.6 ± 0.8	<0.001	2.6 ± 1.1	1.7 ± 0.8	<0.001	−1 ± 0.9	−0.8 ± 1.1	0.351
Starving-associated stomach pain	2.3 ± 1.4	1.6 ± 0.8	<0.001	2.4 ± 1.3	1.8 ± 1	0.003	−0.8 ± 1	−0.6 ± 1.2	0.408
Stress-associated stomach pain	2.4 ± 1.2	1.5 ± 0.7	<0.001	2.6 ± 1.3	1.9 ± 1.1	0.002	−0.9 ± 1.1	−0.7 ± 1.1	0.262
Vomiting	1.2 ± 0.6	1.1 ± 0.4	0.259	1.2 ± 0.5	1.1 ± 0.3	0.224	−0.1 ± 0.5	−0.1 ± 0.6	0.946
Nausea	1.8 ± 1.2	1.3 ± 0.6	<0.001	1.6 ± 1.1	1.2 ± 0.6	0.028	−0.6 ± 0.9	−0.3 ± 0.9	0.148
Belching	2.7 ± 1.3	1.6 ± 1	<0.001	2.6 ± 1.3	1.8 ± 1	<0.001	−1.1 ± 1.1	−0.7 ± 1.1	0.050
Acid regurgitation	2.3 ± 1.4	1.6 ± 0.8	<0.001	1.9 ± 0.9	1.6 ± 0.8	0.028	−0.8 ± 1.1	−0.3 ± 0.9	0.009
Heartburn	2.4 ± 1.2	1.5 ± 0.7	<0.001	2 ± 1.1	1.6 ± 0.8	0.004	−0.9 ± 1.1	−0.5 ± 1	0.007
Feeling of acidity in stomach	2.2 ± 1.2	1.5 ± 0.8	<0.001	2.3 ± 1.2	1.7 ± 1	0.007	−0.6 ± 1	−0.5 ± 1.2	0.501
Appetite loss	1.8 ± 1.1	1.3 ± 0.8	<0.001	1.7 ± 1.1	1.4 ± 0.9	0.095	−0.5 ± 1	−0.3 ± 1	0.152
Total score	27.2 ± 8.6	18.1 ± 5.6	<0.001	26.4 ± 6.9	19.4 ± 5.4	<0.001	−9.1 ± 6.2	−7 ± 6.6	0.050

STATA software was used to calculate sample size (mean ± SD). $\alpha = 0.05$, power = 80%.

Table 3. Self-scored quality-of-life parameters among the study groups (range: 0–5; for each parameter)

	Administration of famotidine			Administration of placebo			Change in scores after treatment		
Have your stomach symptoms made the following:	Before	After	*P*-value	Before	After	*P*-value	Famotidine	Placebo	*P*-value
General emotional health feeling	2.4 ± 1.3	1.6 ± 0.9	<0.001	2.4 ± 1.4	1.7 ± 1.1	<0.001	0.9 ± 1.1	0.7 ± 1.1	0.205
Irritable, tense and frustrated	2.4 ± 1.3	1.5 ± 0.9	<0.001	2.3 ± 1.3	1.6 ± 1	0.002	0.9 ± 1.1	0.7 ± 1	0.249
Disturbed ability to participate in fun activities	2.4 ± 4.4	1.4 ± 0.7	0.026	1.9 ± 1.1	1.5 ± 0.9	<0.03	0.9 ± 4.2	0.4 ± 0.9	0.258
Disturbed enjoyment from participating in fun activities	1.9 ± 1.1	1.4 ± 0.7	<0.001	1.8 ± 1	1.4 ± 0.7	<0.003	0.5 ± 0.8	0.4 ± 0.8	0.710
Disturbed ability to eat and drink	2.2 ± 1.3	1.5 ± 0.9	<0.001	2 ± 1	1.5 ± 0.8	<0.022	0.7 ± 1.1	0.5 ± 1.1	0.289
Disturbed enjoyment from eating and drinking	2.2 ± 1.2	1.4 ± 0.8	<0.001	2.2 ± 1.2	1.6 ± 0.8	0.001	0.7 ± 1	0.6 ± 1.3	0.473
Feeling that you will have dyspeptic problem life-long	2.6 ± 1.3	1.4 ± 0.8	<0.001	2.5 ± 1.5	1.6 ± 1	<0.001	1.2 ± 1.3	1 ± 1.4	0.229
Feeling that your dyspeptic symptoms are due to a serious disease (cancer, cardiac disease, etc.)	2.2 ± 1.4	1.3 ± 0.7	<0.001	2.2 ± 1.3	1.3 ± 0.7	<0.001	0.9 ± 1.3	0.8 ± 1.2	0.665
Disturbed your job or educational activities	1.9 ± 1.3	1.3 ± 0.7	<0.001	1.9 ± 1.1	1.3 ± 0.7	<0.001	0.6 ± 1	0.6 ± 1	0.742
Disturbed enjoying your educational or occupational activities	1.9 ± 1.2	1.3 ± 0.7	<0.001	1.9 ± 1.1	1.4 ± 0.7	<0.001	0.6 ± 0.9	0.5 ± 0.9	0.413
Total score	21.6 ± 9.3	14.1 ± 6.2	<0.001	21.2 ± 8.8	15 ± 6.4	<0.001	7.5 ± 6.9	6.2 ± 7.6	0.270

An interesting finding of the current study is that both famotidine and placebo had a highly significant effect on all of the QoL parameters evaluated in this study, although no difference was detected between them. This finding is consistent with several previous reports that have observed significant improvements using placebo therapy, although there are studies that have shown no marked therapeutic effect of placebo in reducing FD symptoms[8]. Kato *et al.* [6] reported that placebo treatment was associated with no improvement in either symptoms or QoL. They rationalized their controversial finding with their methodology; they used a crossover approach, which may have been advantageous for identifying true drug responders and nonresponders [9]. As patients were administered both the active and the nonactive drug in the crossover study, the placebo effect was considerably reduced. But this does not explain why a placebo can affect FD symptoms overall. This shows the major impact of psychological factors including the patient–physician relationship and receiving attention and being followed on the treatment of these patients.

We also found only a minimal therapeutic effect of famotidine compared with placebo on the symptoms of FD. As it can be seen in Table 2, among the symptoms studied, belching, feeling of acid regurgitation, heartburn, and the total score of the Honk Kong dyspepsia index were significantly improved at higher rates in the famotidine group. Similar to the QoL, all dyspepsia symptoms were highly responsive in both famotidine-administered and placebo-administered groups, except for vomiting in both the groups and loss of appetite in the placebo group.

Some studies including meta-analyses have shown the effectiveness of H_2 blockers in the treatment of FD [4,7,9]. However, the majority of these studies have examined reflux-like FD, which has been excluded from the FD disease classification and was put under a different disease category thus, the findings of these studies cannot be compared with those of the novel classification. Because reflux-like FD (as was defined in the early version of FD classification) represents endoscopy-negative GERD and has a tendency to show a better response to antisecretory pharmacologic agents, one may presume that H_2 blockers might be less effective with the new FD criteria. Even in the current study, the symptoms with highest response to famotidine were heartburn and acid regurgitation, which are similar to

symptoms of GERD. However, very few studies have been conducted on the basis of the Rome II criteria or later clarifications. In the present study, comparing the beneficial effects of famotidine with that of placebo, we found that FD patients responded more favorably to famotidine, with a significantly lower total dyspepsia symptoms score. In a previous study, Kato *et al.* [6] also reported that famotidine can induce improvements in symptoms in FD patients, although there is a controversy on the symptoms responding to the drug between the two studies. Although the current study found that belching, acid regurgitation, and heartburn were significantly reduced by famotidine, Kato *et al.* [6] reported a positive effect of famotidine on abdominal pain, indigestion, and reflux syndrome in the gastrointestinal symptom rating scale questionnaire scores, with abdominal pain showing the highest improvement. In the present study, we did not find any beneficial impact in reducing abdominal pain with the use of famotidine. Another study by Seno *et al.* [10] also showed that famotidine had significantly improved symptoms of dyspepsia in FD patients, although the symptoms were not evaluated separately. Kinoshita *et al.* [11] found that famotidine not only had a beneficial impact on the symptoms of FD patients, but also it had advantages over some other agents, whereas Otaka *et al.* [12] did not detect any priority for use of famotidine over other agents in the FD treatment as it was effective but not superior to other agents.

Conclusion and recommendations

This study showed a significant improvement in the total dyspepsia scores of FD, with a marked effect on belching, heartburn, and feeling of acid regurgitation, but we did not find any beneficial effect with the use of famotidine compared with placebo in QoL. These findings suggest that famotidine may be administered in certain FD patients who have belching, heartburn, and acid regurgitation as the major symptoms. More studies are required to confirm or modify our study results.

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Conflicts of interest

There are no conflicts of interest.

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