Original Article

Evaluating the Effect of Oral Gabapentin on the Improvement of Gastrointestinal Symptoms in Patients with Functional Dyspepsia Resistant to Conventional Treatments

Abstract

Background: Dyspepsia is one of the most common gastrointestinal (GI) problems and is more prevalent in adults. Environmental hypersensitivity and anxiety and depression are among the factors that can cause this disease. In this regard, gabapentin as a gamma-aminobutyric acid (GABA) analog used in the treatment of neuropathic pain and may be effective in controlling the symptoms of GI disorders. Therefore, the present study aimed to evaluate the effect of oral gabapentin on the improvement of GI symptoms in patients with functional dyspepsia (FD) resistant to conventional treatments. **Materials and Methods:** In a double-blind clinical trial, 126 patients with FD resistant to conventional treatments, referred to gastroenterology clinic of Hajar Hospital of Shahrekord in 2017–2018, were randomly assigned to two groups; patients in the control group received omeprazole alone, and the case group received omeprazole plus gabapentin. The severity of GI symptoms was recorded and evaluated by the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire before and after treatment (4 weeks). **Results:** GSRS total score in the group who received gabapentin (16.89 ± 6.89) was significantly lower than controls (20.00 ± 9.31) (P = 0.036). It also found that gabapentin, as an adjunctive drug, plus omeprazole could play a significant role in GI symptom improvement, such as pain, reflux, and indigestion. **Conclusion:** Gabapentin as an adjunctive drug could be more effective in reducing the severity of GI symptoms in patients with dyspepsia, especially neurological symptoms (such as pain, reflux, and indigestion).

Keywords: *Functional dyspepsia, gabapentin, gastrointestinal disorders*

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Introduction

Dyspepsia, also known as indigestion, is a common symptom with an extensive differential diagnosis and a heterogeneous pathophysiology. It affects approximately 25% of the world's population each year; however, most patients do not require drug therapy.[1] Currently, existing treatment options for dyspepsia include *Helicobacter pylori* eradication, the use of proton-pump inhibitors (PPIs), and prokinetics. Although treatment of functional dyspepsia (FD) is still under discussion, the use of treatments mentioned above can improve symptoms in a small number of patients.[2] It is hypothesized that analgesic drugs by affecting the central process of pain can reduce the environmental sensitivity causing the FD. Carbamazepine, tramadol, pregabalin, and gabapentin are medications that can be used to reduce the environmental sensitivity.[3]

Gabapentin is a gamma-aminobutyric acid (GABA) analog that is initially developed for treating epilepsy but is currently used for various cases, including pain relief, and in particular neuropathic pain (such as headache and back pain).[4] Gabapentin has a structure similar to gamma-butyric acid but is not converted into GABA or a GABA agonist in the body. It does not eliminate or inhibit gamma-butyric acid reuptake. Moreover, a mechanism which helps gabapentin has the analgesic and anticonvulsant effects in humans and has not yet been fully determined.[4] Currently, some doctors are prescribing the gabapentin to prevent migraine headaches, treat nystagmus, and reduce neuropathic pain.[5-7] However, there are few studies on analgesic effects of gabapentin and other effects of it.

On the other hand, many studies have indicated that there is a direct significant

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relation between the gastrointestinal (GI) symptoms, depression, and anxiety disorder. Therefore, it can be mentioned that most of the GI disorders occurring in people such as indigestion, reflux, and abdominal pain have a neurological origin.[8-10] In this regard, some previous studies have suggested the effect of the effects of gabapentin and pregabalin on decreasing rectal sensitivity and reducing neurotransmitter release in the GI tract in patients with irritable bowel syndrome (IBS).[11,12] Therefore, given that gabapentin is used in the treatment of neuropathic pain and environmental hypersensitivity, it seems to be useful to control and reduce the symptoms of neurological diseases, such as IBS and dyspepsia. Therefore, this study aims to evaluate the effect of gabapentin on the treatment of patients with FD, which also includes the large population of patients with GI problems.

Materials and Methods

This was a double-blind clinical trial that has been registered in www.irct.ir with the code of IRCT20120709010222N19. The population of the present study consisted of all the patients with FD, referred to gastroenterology clinic of Hajar Hospital of Shahrekord in 2017–2018. Of these patients, based on the formula comparing between two groups at a 95% confidence level and statistical power of the test of 80%, and considering standard the deviation equivalent to 2 from previous study,[3] 126 patients (36 patients in each group) were randomly selected by convenience sampling. The study inclusion criteria were people aged 40–60 years who were diagnosed with FD based on the Rome IV criteria and satisfied to participate in the present study.

Noted that in the last two years these patients FD has been treated with various drugs such as omeprazole, pantoprazole and cimetidine but no response was observed, and they were referred to a gastroenterologist for further investigation on treatment and have been recognized as FD resistant to treatment.

Moreover, the patients with sensitivity to gabapentin or serious side effects resulted from gabapentin usage, and those who stopped taking gabapentin or failed to follow prescribed treatment were excluded.

After abstaining both the approval of the Ethics Committee of Shahrekord University of Medical Sciences and patients' written consent, based on the Rome IV criteria, 126 patients who had at least one of the symptoms of sensation of bloating after eating, feeling of uncomfortable early fullness, feeling pain, or burning in the epigastric region with no background cause for justifying these symptoms were identified as patients with FD and included in the study.

It should be noted that patients who had these symptoms for the last 3 months, with symptom onset at least 6 months before diagnosis, were evaluated by a gastroenterologist. Moreover, if there were any alarming signs of the organic abdominal pain (such as vomiting, weight loss, the extreme posterior sternalis burning, and feeling pain while eating) and severe disability for doing daily activities (reduced physical activity and absenteeism in the workplace, etc.); the endoscopy was performed in the patients, and finally, a diagnosis of FD for patients was defined.

Afterward, through the simple random sampling, samples were divided into two case and control groups every other one (63 patients in any group). Before the intervention, patients' information such as age, sex, and history of previous diseases, as well as the patients' clinical status, i.e., the severity of GI symptoms in patients, including pain (e.g., abdominal pain, hunger pangs, and nausea), reflux (e.g. heartburn and the return of the stomach acid), diarrhea (e.g. loose stool and urgency of the excretion), constipation (e.g. hardness of stool or a feeling of incomplete evacuation), and dyspepsia (e.g. abdominal sounds, abdominal bloating, burping, and excessive gas in the stomach) were evaluated based on the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire and recorded as a 0–7 scale, with 0= "no pain/discomfort" and 7= "severe pain/discomfort."[13] All of the information has been gathered by a resident of gastroenterology who was not aware about the research process.

It should also be noted that to blind the present study, the medicines were manufactured by a pharmaceutical company (Darou Pakhsh Co.,), matched their color and shape, and marked by the pharmacist in the labeled packages, as a and b, and the patient and the therapist/intervener had no information about treatment and a double-blind study was established.

The case group received 20 mg omeprazole once daily plus 300 mg gabapentin twice a day,[14] and the control group received 20 mg omeprazole once daily plus 300 mg placebo twice daily; the treatment process lasted for 4 weeks in both the groups.[7]

How to use/take gabapentin: one 300 mg capsule at night for 3 nights, then 300 mg twice a day for 4 weeks. In order to support a double-blind study, a placebo medication was given to the control group with the same instruction.

It should be noted that in the group who received gabapentin, 5 patients due to lack of follow-up during treatment and the discontinuation of medication and 2 patients due to sensitivity to the drug and the occurrence of sleepiness and severe nausea were excluded from the study. In addition, in the control group, 2 patients were excluded from the study due to lack of follow-up during treatment. Therefore, the patients allocated to the gabapentin group were reduced to 56 and in the control group to 61 [Figure 1].

Finally, after the intervention, GI symptoms of these patients were recorded and evaluated by the GSRS questionnaire again.

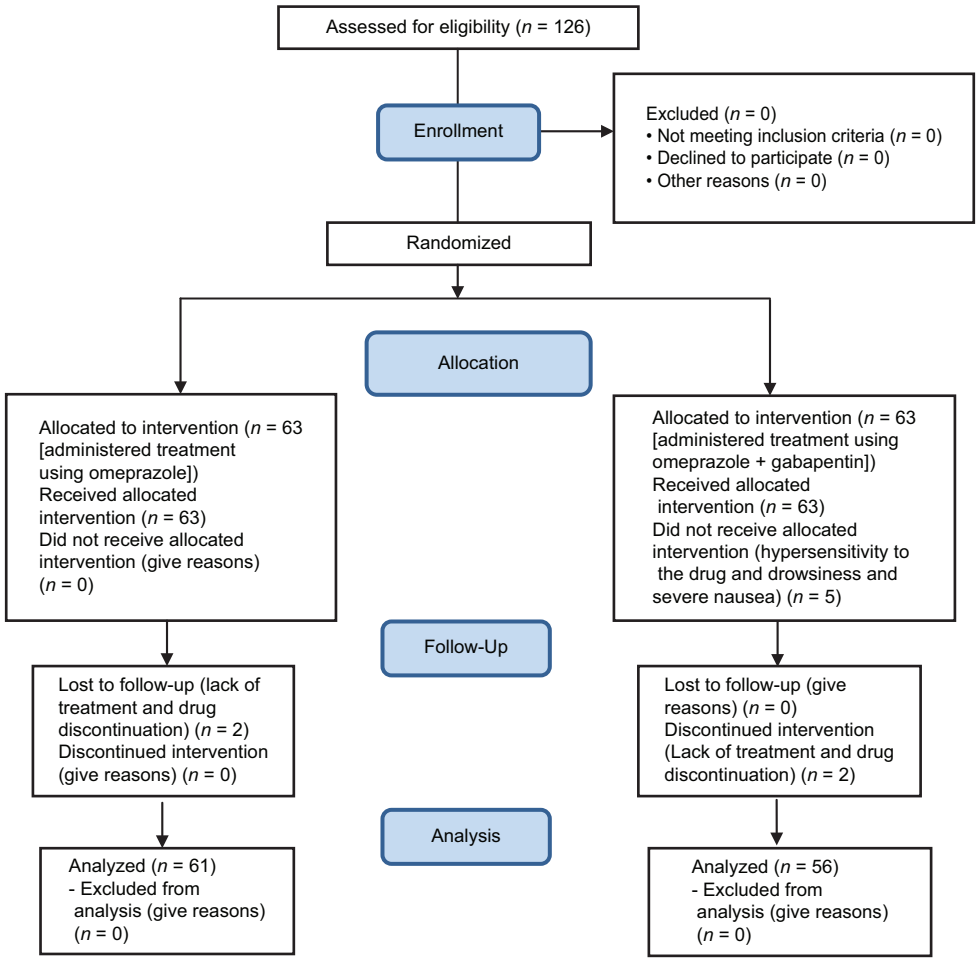

Figure 1: Consort flow diagram

After collecting the data, they were entered into SPSS (version 22; SPSS Inc., Chicago, Ill., USA), and descriptive statistics, such as the mean, standard deviation, and frequency percentage, were used. According to the results from Kolmogorov–Smirnov test based on the normality of the data, inferential statistics, such as Chi-square, independent, and paired sample *t*, were used. In all analyses, $P < 0.05$ was regarded as statistically significant.

Results

In this study, among 61 patients in the control group who received omeprazole alone, 46 (75.4%) patients were male and 15 (24.6%) were female, with a mean age of 45.84 ± 8.95 years, and among 56 patients in the case group who received omeprazole plus gabapentin, 45 (80.4%) patients were male and 11 (19.6%) were female, with a mean age of 47.13 ± 8.31 years. There was no statistically significant difference between the two groups with respect to age and sex ($P > 0.05$) [Table 1].

On the other hand, the evaluation of mean GI symptom scores obtained from GSRS questionnaire, such as diarrhea, abdominal pain, constipation, indigestion, and reflux,

Table 1: Demographic characteristics of patients in the two groups of study

Characteristics	Case (*n*=56)	Control (*n*=61)	*P*
Sex (%)			
Male	45 (80.4)	46 (75.4)	0.665
Female	11 (19.6)	15 (24.6)	
Age (year)	45.84±8.95	47.13±8.31	0.661

showed that the two groups were matched in terms of the severity of GI symptoms mentioned, and there was no significant difference between the two groups ($P > 0.05$) However, during treatment (after the treatment relative to before the treatment), the GI symptom severity was significantly reduced in both the groups ($P < 0.05$). Furthermore, after the intervention, the mean severity reduction of GI symptoms, including reflux, dyspepsia, and abdominal pain, in the case group was significantly higher than that in controls ($P < 0.05$). Furthermore, after the intervention, no significant difference in the mean symptom reduction of diarrhea and constipation was observed between the two groups ($P < 0.05$) [Table 2].

Finally, the mean severity reduction in the total GSRS score of the control group was 5.09 ± 4.54 and in the case

Table 2: Determination and comparison of the mean gastrointestinal symptom severity based on Gastrointestinal Symptom Rating Scale questionnaire in the two groups of study

GSRS	Gabapentin (*n*=56)	Control (*n*=61)	*P*
Diarrhea			
Before	1.48±2.72	1.01±2.71	0.344
After	1.05±2.04	0.62±1.96	0.232
P	0.001	0.040	
Abdominal pain			
Before	5.62±2.69	4.81±3.08	0.118
After	2.62±1.70	3.48±2.37	0.022
P	<0.001	<0.001	
Constipation			
Before	3.59±3.47	4.19±4.74	0.417
After	2.97±3.13	3.84±4.66	0.219
P	<0.001	0.014	
Indigestion			
Before	11.48±4.62	10.40±5.08	0.215
After	7.01±3.58	8.55±4.62	0.039
P	<0.001	<0.001	
Reflux			
Before	3.78±3.20	4.68±2.52	0.080
After	2.27±1.98	3.51±2.26	0.001
P	<0.001	<0.001	

GSRS: Gastrointestinal Symptom Rating Scale

group was 9.05 ± 5.89. Overall, the reduction rate of the GI symptom severity in the group who received gabapentin was significantly higher than that in the group who received omeprazole alone ($P < 0.001$) [Figure 2].

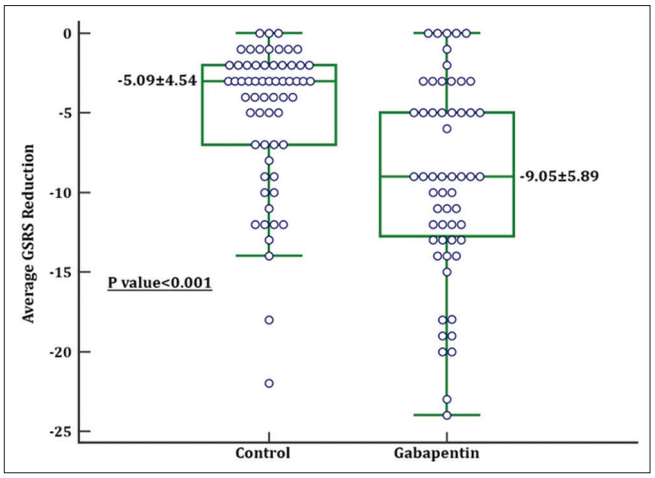

Figure 2: Box plot of the reduction of the total gastrointestinal symptom score in the two groups of study

Discussion

The results of the present study from the two groups who received omeprazole alone and omeprazole plus gabapentin (300 mg), respectively, with an mean age of over 45 years demonstrated that there was a significant improvement in GI symptoms in both the groups, based on questionnaires GSRS, but the improvement rate and the severity reduction of symptoms in the group who received gabapentin were significantly higher than those in the control group who received omeprazole. The more detailed study on each of GI disorders in the patients showed that symptoms, such as diarrhea and constipation, were significantly improved in both the groups over the treatment course, and none of the groups was preferred to the other, as well as there was no significant difference between the two groups with respect to the improvement rate and the reduction of symptoms of diarrhea and constipation ($P > 0.05$). However, other symptoms, such as pain (e.g. abdominal pain, hunger pangs, and nausea), reflux (e.g., heartburn and the return of the stomach acid), and dyspepsia (e.g. abdominal sounds, abdominal bloating, burping, and excessive gas in the stomach), were reduced in both the groups and resulted in the patients' improvement; the severity reduction of symptoms and the improvement rate in the group who received gabapentin were significantly higher than those in the control group who received omeprazole. Indeed, it might be said that in the treatment course of the patients, symptoms that had a neurological origin had been shown a better response.

Regarding omeprazole and its therapeutic effect, it can be said that omeprazole is PPI and can inhibit gastric acid secretion by inhibiting H^+/K^+ ATPase enzyme system at secretory surface of gastric parietal cells. Despite the significant effect of omeprazole on the levels of gastric acid and reflux, it due to its extensive side effects, and many interactions with other drugs (e.g., diazepam, phenytoin, and warfarin) increase the plasma levels of these drugs, which have attracted attention of researchers to other types of drugs.[15]

On the other hand, gabapentin is one of these drugs that it is an analog of GABA and its effects exert through reducing the neurotransmitter glutamate and attaching to the α2δ1 subunits of voltage-gated calcium channels but not through GABA receptors.[16,17] A study conducted in 2007 showed that gabapentin monotherapy could be led to an improvement in pain and improvement of the quality of life in the patients.[18] Another study found that gabapentin as one of the most important drugs could be used in neuropathic pain syndromes.[19] Gabapentin is prescribed to treat neuropathic pain, but recently, it has been used for other cases.

In animal studies, gabapentin and its subgroups, such as pregabalin, have been used to prevent central nervous system disorders and functional GI disorders, and their significant effects on reducing the release of neurotransmitters at the spinal and supraspinal levels by the α2δ1 subunit ligands have been shown.[11]

In line with the present study, Stein *et al*. investigated the effect of pregabalin on GI symptoms in patients with generalized anxiety disorder (GAD) and showed in a

subgroup of patients with GAD and high GI disorder that pregabalin, as one of the subgroups of gabapentin, at doses of 300–600 mg/day was more effective in the severity reduction of GI symptoms (due to reducing anxiety rate in these patients) compared to the placebo.[3]

In this regard, Houghton *et al*. also pointed out the importance of the ability of pregabalin to normalize rectal sensitivity in the IBS patients.[20] In addition, in a meta-analysis on the patients with anxiety disorders and severe GI or IBS symptoms who received pregabalin in comparison with benzodiazepine, receivers were more resistant and less likely to be excluded from the study.[21,22] In fact, resistance is an important dimension to be taken into account in medical decisions, and this is one of the advantages of pregabalin.

Moreover, the results of a study conducted by Gale and Houghton indicated that the major cause of IBS was environmental hyperneurosensitivity that the δ2 receptors of calcium channels should be involved in it.[12] Indeed, considering the role of these receptors as well as the effects of gabapentin and pregabalin on these receptors, as well as reviewing the previous studies, it can be said that gabapentin and pregabalin can be used to treat the IBS patients.

In addition, it should be noted that, in line with the current study, the use of gabapentin as a pain relief, especially in neuropathic pain, has been evaluated and approved in many studies, medical procedures, and various diseases, so that in various studies, gabapentin is used 100 mg 2 times a day, and the majority of studies suggested daily 300 mg dose of gabapentin.[23,24] It has been shown to be effective and useful in controlling and reducing the different types of pain, including back pain,[25] sciatica, and spinal canal stenosis.[18,26] In this regard, in their study, Liu *et al*. also found that due to the analgesic effects of the GABAB receptor agonist, baclofen significantly decreased the pain in mice with FD.[27] Therefore, it can be said that ion channels may play an effective role in pain control mechanisms in the GI tract, and sensitivity of the pain pathway in the GI tract is the major cause of the functional pain in the GI tract; the cause of this sensitivity can be an environmental stimuli or even without a particular cause in the details of the ion channels in the nervous system.[28] Therefore, it seems that gabapentin with binding to the calcium channel subunits leads to reduce pain sensitivity and blocks the central pain syndrome; therefore it can prescribe as an effective medication with indirect impacts on GI symptoms improvement.

Conclusion

According to the results of this study, both treatments in the case group (omeprazole plus gabapentin) and controls (omeprazole alone) were effective in reducing the severity of GI symptoms. However, gabapentin, as an adjunctive drug plus omeprazole, could play a significant role in the improvement of GI symptoms, such as pain, reflux, and dyspepsia, while improving the symptoms of diarrhea and constipation had a similar effect to prescribing omeprazole alone and could not be different in terms of the therapeutic effect.

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Conflicts of interest

There are no conflicts of interest.

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