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Comparing the Effect of *Psyllium* Seed on Gastroesophageal Reflux Disease With Oral Omeprazole in Patients With Functional Constipation

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Abstract

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal diseases. Several studies have been carried out on the treatment of symptoms associated with GERD. The present study aimed to compare the effect of *Psyllium* seed and oral omeprazole on GERD in patients with functional constipation. In this trial, 132 patients were divided into 2 groups. The impact of omeprazole and *Psyllium* seed on the treatment and recurrence of GERD was studied. Among the patients, the rate of response to treatment was 89.2% (n = 58) in the *Psyllium* seed group, while in omeprazole group, it was 94% (n = 63; $P = .31$). The recurrence rates of *Psyllium* seed and omeprazole groups were 24.1% (n =14) and 69.8% (n = 44), respectively ($P < .001$). The results showed that treatment of functional constipation by *Psyllium* seed in patients with GERD leads to improvement of GERD and its recurrences in comparison with omeprazole.

Keywords

gastroesophageal reflux disease, GERD, functional constipation, psyllium seed, omeprazole

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Gastroesophageal reflux disease (GERD) is the most common and important digestive disorder in medical sciences.[1] According to epidemiological studies on GERD, its prevalence is about 5% in Asian countries and 10% to 20% in Western countries.[2] Several studies have also reported about 40% prevalence of the disease in Western countries.[3] Based on statistics, 40% of Americans experience heartburn once in a month, whereas 7% to 10% of them have this experience once a day.[4] However, epidemiological studies in Iran have also reported the high prevalence of the disease, and according to some studies, the prevalence of GERD in Iran seems higher than many parts of Asia.[5-7] The common and primary symptoms of GERD are burning in the epigastric region and feeling regurgitation.[8,9] Additionally, other nonspecific symptoms that are noticeable in some patients are angina pain and respiratory symptoms.[10] In some studies, GERD has been proposed as a risk factor of lung problems.[11,12]

Aging is one of the major risk factors in increasing GERD symptoms.[13,14] Although in most studies, it was shown that gender has no effect on the development of GERD,[15-17] female gender also has been considered as a risk factor of this disease.[18] The effect of smoking on the development of reflux symptoms is yet to be well documented in numerous studies; hence, some studies considered smoking as an independent agent that results in reflux,[19,20] whereas other studies rejected any connection between smoking and GERD.[14,21,22]

Furthermore, GERD accompanied with bowel movement disorders, including functional dyspepsia, irritable bowel syndrome, and chronic constipation, is considered as a systemic disorder.[23,24] Functional dyspepsia is associated with GERD in 22% to 50% of cases and with chronic constipation in 29% of cases.[25] Dickman et al[26] in their study pointed out the association between GERD and lower abdominal symptoms and showed the overlapping of GERD with constipation in 32.9% of cases. The abdominal symptoms of patients improved after

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the treatment of GERD. Simultaneous treatment of GERD and lower digestive tract diseases is recommended in patients that are resistant to proton pumps inhibitors (PPIs). Jiang et al[27] studied the prevalence of various diseases of digestive system among patients with GERD in China. In their research, 7.5% of patients with GERD suffered from functional constipation. Therefore, for effective treatment of GERD, the accompaniment of GERD and chronic constipation should also be considered due to the common physiopathology mechanisms of the diseases. More than one seventh of the world's adult population suffers from chronic constipation.[28-30] Female population experiences constipation more than males; thus, its frequency has been reported to be 2 to 3 times more than men.[31] Generally, chronic constipation is developed by insufficient consumption of fibers and fluids in diet, resulting in impaired colonic transit or anorectal problems.[32-34] Usually, constipation is eliminated by water therapy, physical activity, and provision of dietary fiber requirement (15 g per day). In the present study, GERD is discussed as a motility disorder of digestive system with various symptoms. It was found that, in patients suffering from GERD with constipation, the symptoms of GERD do not only increase but also patients do not respond properly to antireflux treatments. Therefore, it is expected that treatment of constipation can lead to treatment of refractory GERD.

Commonly used drugs for the treatment of GERD usually reduce or neutralize stomach acid. Histamine H2 receptor antagonists are used for the treatment of GERD in mild to moderate stages. In severe cases or patients suffering from GERD along with erosive esophagitis or ulcers in the esophagus, PPIs, such as omeprazole, are used. The aforementioned drugs are more effective than H2 antagonists, but mainly, about one third of patients with GERD would not respond to PPIs. Also, the recurrence of GERD is common after treatment with PPI. Proton pumps inhibitors can also lead to infection, excessive growth of bacteria in the small intestine, malnutrition, reduced bone materials, and reduction in the absorption of some other drugs such as clopidogrel in the long-term usage.[12,24]

Psyllium seed is one of the medicinal plants that has been used for the treatment of constipation in traditional Persian medicine. Plantago plant belongs to the family of Plantaginaceae with about 250 species. It has been group into 2 genus: *P ovata* and *P psyllium*.[35] Mucilage of this plant results in an increase in peristaltic movements of the bowel and increases the fecal moisture that finally affects the frequency and volume of defecation. However, *Psyllium* should be consumed with plenty of water in order to have a better impact and for easy swallowing. Medicinal forms including granules or the powder form of *Psyllium* seeds should be mixed with 240 mL of water or a tasty drink, such as orange juice, before consumption.[36] Given that treatment of gastrointestinal disorders associated with GERD, such as functional constipation, is a more effective and sustainable treatment method in the elimination of this disease, the goal of this study is comparing the effect of *Psyllium* seed on recurrence rate, time of recurrence, and response rate in GERD with oral omeprazole in patients who also suffer from functional constipation.

Materials and Methods

Study Design

This randomized clinical trial was carried out on patients from March to September 2015 at the Gastroenterology Department of Ghaem Teaching and Referral Hospital, Mashhad University of Medical Sciences, Iran. The sample size was based on the detection of changes in the primary endpoint; it was powered to detect a 20% decrease in the recurrence of GERD in patients being treated with *Psyllium*. For 80% power with a 2-sided 5% significance level, a total of 60 participants per study group are required. To account for the potential inadequacies in this study's assumptions and the follow-up of some losses, the sample size was increased by 10%. Therefore, a total sample size of 132 participants was recruited by convenience sampling. The study protocol was fully approved by the Ethics Committee of Mashhad University of Medical Sciences. This study was registered in the Iranian Registry of Clinical Trial (IRCT Number: IRCT2015040315122N2). Furthermore, the hypothesis of this study was published.[37]

Patients

Patients accepted their enrollment in the study by signing an informed consent form prior to the study. The patients included were aged 18 to 70 years and had history of at least 3 years of refractory GERD (clinical signs such as heartburn and regurgitation getting worse by bending forward) accompanied by functional constipation approved by Rome 3 criteria. Esophagitis was confirmed by upper endoscopy. Upper endoscopy was performed under midazolam sedation and by an experienced gastroenterologist from the hospital who collaborated in a prospective study.

The patients with history of digestive cancer and hernia hiatal, irritable bowel disease, endocrine diseases (eg, hypothyroidism), constipation caused by drugs, psychological diseases, cardiovascular disease, liver and kidney diseases, opioids abuse, and history of smoking were excluded from the study.

Of 180 patients referred to the Gastroenterology Clinic (Ghaem Hospital, Mashhad, Iran(, 132 patients with refractory GERD associated with constipation were confirmed by a gastroenterologist based on the inclusion criteria. None of patients took drugs for a month before the intervention.

Intervention

Patients were randomly allocated into 2 groups by simple randomization based on computer-generated random numbers (Figure 1). Allocation of patients was random and allocation was blinded. Patients were oriented toward the general goals of the study. However they did not have any information regarding the specific goals (ie, they were not aware of what was performed routinely for treatment or what was done based on the study requirements).

The first group was treated with omeprazole capsules for 2 months twice in a day (20 mg half an hour before breakfast and dinner). For the second group, as prescribed, about 5 g of *Psyllium* seeds were dissolved in warm water, an hour before breakfast and dinner. The purpose of *Psyllium* seed prescription was to induce soft bowel movements, at least twice in a day, with a sense of complete defecation. The

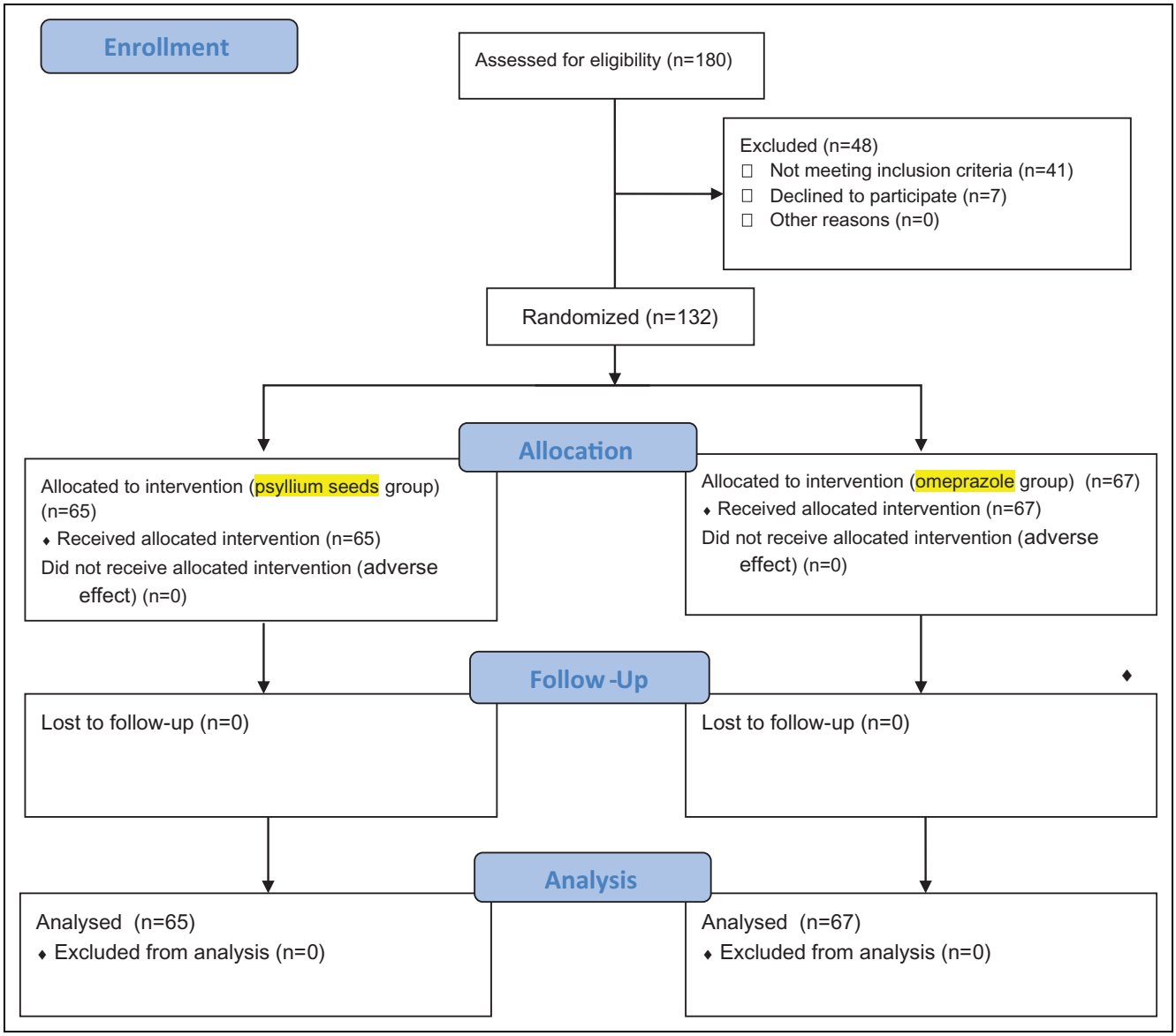

Figure 1. Study flow diagram.

patients were visited each day in the first week and then every week in order to evaluate their clinical signs and responses to treatment for 2 months. After 2 months, the oral omeprazole and psyllium seeds were discontinued. Patients (of the 2 groups) whose clinical symptoms of GERD were completely eliminated at the end of second month were followed for another 3 months with the same intervals in order to evaluate the disease recurrence intervals. (It is worth mentioning that people whose symptoms did not improved at this stage were considered as intractable and were excluded.) The follow-up of patients was continued every week for 3 months and the severity of returned symptoms (heart burn and regurgitation) were scored based on visual scale (this scale was done by the patients). Patients with the score of 0 were considered as "complete responders," while those who had scores of 1 to 4 were classified as "partial responder," and eventually those with more than or equal to score 5 were classified as "nonresponders" and they were excluded from the research.

Data Analysis and Statistical Analysis

The data were analyzed using SPSS version 16 software. Chi-square test or Fisher's exact test was used for analyzing the qualitative groups. *T* test or Mann-Whitney *U* test was carried out to compare the quantitative variables of the 2 groups. The significance level in all tests was considered as $P < .05$.

Results

A total of 180 patients referred to the gastroenterology clinic were examined, among which 132 (73.3%) patients were selected for study after being found to meet the criteria for GERD with functional constipation. The omeprazole group included 67 patients, 33 males (49.3%) and 34 females (50.7%), while 65 patients participated in *Psyllium* group (32 males [49.2%], 33 females [50.8%]). The difference was not

Table 1. Comparison of Both Groups in Response and Recurrence Rates.

	Response Rate		Recurrence Rate		Day of GERD
Group	Response, n (%)	No Response, n (%)	Recurrence, n (%)	No Recurrence, n (%)	Recurrence
Psyllium	58 (89.2%)	7 (10.8%)	14 (24.2%)	44 (75.8%)	69.8 ± 25.2
Omeprazole	63 (94%)	4 (6%)	44 (69.8%)	19 (30.2%)	16.1 ± 15.8
P value	.3		<.001		<.001

Abbreviation: GERD, gastroesophageal reflux disease.

significant ($P = .99$). The average age of the *Psyllium* seed group was 41.6 ± 11.6 years, whereas it was 41.0 ± 12.6 years in the omeprazole group ($P = .79$). The duration of GERD in *Psyllium* seed and omeprazole groups were 5.8 ± 3.1 and 5.9 ± 3 days, respectively ($P = .67$).

Response to Treatment

In the evaluation of the first 2 months of treatment, in the *Psyllium* seed group, 58 patients (89.2%) responded to treatment and 7 individuals (10.8%) did not. However, in the omeprazole group, 63 patients (94%) responded to treatment, while 4 patients (6%) did not. Thus, the difference was statistically not significant ($P = .3$).

The time required to respond to treatment was 6.66 ± 2.2 days in the *Psyllium* seed group and 3.03 ± 2.3 days in the omeprazole group ($P < .001$). In fact, the *Psyllium* seed group responded later to treatment (Table 1).

Recurrence of Symptoms

After discontinuation of the 2-month treatment period, the number of patients who experienced the recurrences were 14 (24.2%) in the *Psyllium* seed group and 44 (69.8%) in the omeprazole group ($P < .001$).

The recurrence average day of the *Psyllium* seed group was 69.6 ± 25.2 days, whereas in the omeprazole group, it was 16.1 ± 15.8 days. In this case, both differences were statistically significant ($P < .001$; Table 1).

Discussion

GERD is one of the usual disorders associated with different societies. In Tehran, its prevalence in males and females is 6.6% and 11.1%, respectively. In Gonbad Kavous city, 12.7% of the patients experienced reflux once or twice in a week and 46.2% once in a month.[6] Due to the serious complications of GERD such as erosive esophagitis and esophageal cancer, which are associated with high morbidity and mortality, its follow-up and treatment seem very important.[38] Various studies have reported the accompaniment of GERD with other bowel movement disorders especially with irritable bowel syndrome,[23,39-42] and thus treatment of associated disease that result in treatment of GERD is recommended.[27,43-45] Perveen et al[25] reported the accompaniment of GERD with dyspepsia to be in the range of 22% to 25%, about 29% with constipation and about 40% with irritable bowel syndrome, but the relationship between constipation and GERD is yet to be investigated by researchers. In a research conducted by Baran et al, 38 patients suffered from constipation, which result in slow gastric emptying.[46] The association of GERD with constipation and the treatment of constipation have been investigated in order to improve GERD.[47] In our study, the occurrence of functional constipation in patients with GERD was significant. This fact is suggestive of GERD as a digestive system dismotility disorder that can justify its resistance to treatment and recurrence of GERD symptoms. PPIs have been mentioned as the initial treatment of GERD in various studies. However, the side effects of these medicines, as well as the likelihood of disease recurrence, is high.[43-45] In a study carried out by Barrat et al in Pakistan, omeprazole was introduced as the first drug of choice for the treatment of GERD.[48] In a study conducted by Kinoshita and Ishihara,[49] the rate of response to PPI treatment after 4 weeks in patients with GERD with erosive esophagitis was about 56% and 37% in patients with nonerosive type. PPI success was increased to 90% and 75%, respectively, after 6 months of treatments. In our study's clinical trial, the effects of *Psyllium* seed on GERD was investigated and compared with omeprazole capsules. *Psyllium* seed was used to cure constipation due to its efficiency and low side effects as an affordable method of treatment. In this study, at first, the rate of response to omeprazole was obtained as 94%, while that of *Psyllium* seed was obtained as 89.2%. This indicates that initially, the response to omeprazole in reducing GERD symptoms was much faster than *Psyllium* seed. It means that reduction of stomach acid in the early stages improves reflux symptoms faster compared to the treatment of constipation. But in patients administered with *Psyllium* seed for the treatment of constipation, a significant reduction of GERD symptoms was observed. Although the number of days needed for response to treatment in the *Psyllium* seed group were more than in the omeprazole group, ultimately the patients had more feeling of well-being without GERD symptoms. The mechanism of *Psyllium* seed in the treatment of GERD is attributed to its potency in improvement of functional constipation. Therefore, due to the side effects of chemical medicines, such as omeprazole, *Psyllium* seed can be used as a desirable alternative therapy in the treatment of GERD. The most important point in the treatment of GERD is that it relapses after the termination of treatment. The study of Moraes-Filho et al[45] revealed that the rate of relapse in patients cured with PPIs was 72%. In a study conducted by

Perry et al,[50] PPIs' administration in GERD failed in 40% to 30% of cases. In the present clinical trial, the average number of days between the recurrence of GERD in *Psyllium* seed and omeprazole groups showed significant difference between both groups. This means that the disease recurrences were lower in the *Psyllium* seed group, and in patients who had experience of recurrences in this group, the numbers of days with which GERD symptoms begin were more than the omeprazole group. This reflects the fact that the prescription of *Psyllium* seed in the prevention of GERD recurrence is much more effective and stable than omeprazole. The results demonstrated that constipation with GERD occurs very regularly. The relief of symptoms and decrease in GERD recurrences are achieved by treatment of constipation. *Psyllium* seed is suggested as an effective, inexpensive, and low complication treatment. This plant has not only similar efficiency with PPIs in the treatment of GERD symptoms but also it is considered as an effective treatment in the prevention of the disease recurrences in comparison with PPIs. *Psyllium* seed has been mentioned as a drug of choice in the treatment of GERD in patients accompanied by functional constipation.

Conclusion

The use of *Psyllium* seed in the treatment of functional constipation in patients with GERD is very safe, effective, cheap, and easily available, and this treatment also minimizes the chance of recurrence of GERD compared to omeprazole.

Authors' Note

This study is part of a student dissertation.

Author Contributions

All authors contributed to the following in this study: idea generation, writing of proposal, gathering data, and writing the manuscript, revising, and submission.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This research was approved by the Mashhad University of Medical Sciences Research Council (Approval No. 930965).

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