Research Article

The Effect of *Myrtus communis* L. Syrup in Reducing the Recurrence of Gastroesophageal Reflux Disease: A Double-Blind Randomized Controlled Trial

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Abstract

Background: Gastroesophageal reflux disease (GERD) is one of the most prevalent digestive diseases. Long-term treatment and recurrence of symptoms after discontinuation of medication are amongst its problems.

Objectives: The aim of this study is to investigate the impact of myrtle fruit syrup on the recurrence of symptoms in reflux patients after the discontinuance of using a PPI.

Methods: This research is a double-blind, randomized clinical study. With regard to withdrawal rate, 45 patients were selected for each group. The trial was conducted at the traditional medicine clinic at tehran university of Medical Sciences, Tehran- Iran, between November 2014 and March 2016. Diagnosis was conducted on the basis of the Mayo clinic standardized questionnaire. Every individual with heartburn or regurgitation symptoms with frequency of at least once a week was diagnosed as suffering from reflux. Omeprazole 20 mg with fasting as well as myrtle or placebo syrup 5 mL after meal were prescribed. Treatment duration was 6 weeks, after which the medicine was discontinued and patients were evaluated for 2 weeks. The cases in which recurrence of symptoms up to 14 days did not occur were considered as being non-recurrence.

Results: Eighty nine people with symptoms of reflux were studied. The recurrence of symptoms was 22 people in treatment group and 27 people in control group with no significant difference (P value = 0.179). Time delay in the onset of symptoms was 9.57 days in treatment group and 6.27 days in control group which had significant difference (P value = 0.027).

Conclusions: Although the recurrence of symptoms was lower in the treatment group than in the control group, there was no significant difference. However, treatment significantly delayed the onset of symptoms in quantitative terms. The findings show that further research should be implemented.

Keywords: Gastroesophageal Reflux, *Myrtus communis*, Recurrence

1. Background

GERD is a condition, which develops when the reflux of stomach contents causes troublesome symptoms and/or complications (1). GERD is one of the most common outpatient digestive diseases in America (2) and its prevalence in western countries is reported to be approximately 10% - 20% (3-5). This rate is about 5% in Asia and it is still increasing (6). Recent studies show that the prevalence of GERD has increased up to 2 to 6 times in the last two decades (5). Research has shown that the prevalence of this disease in Iran is about 15%, which is higher than the average amount in Asia (7-9). Typical GERD symptoms include an uncomfortable sensation of heartburn under the sternum or regurgitation of gastric contents (1, 10). Other signs include digestive symptoms (dyspepsia, dysphagia), chest pain, respiratory problems, ear, nose and throat symptoms as well as sleeping problems (10).

The treatment nowadays includes lifestyle changes and drug treatment in severe cases with the golden standard being proton pump inhibitors (PPIs) (11). Uncontrolled acid regurgitation could lead to serious and dangerous complications such as esophagitis, bleeding, esophageal stricture, Barrett's esophagus and eventually esophageal adenocarcinoma (12, 13). The long-term treatment is one of the difficulties of this illness. The discontinuance of PPIs in many cases causes the patients to be affected by increased acid secretion and recurrence of symptoms (14, 15).

The long-term use of PPIs includes potential complications such as an increased risk for developing Clostridium difficile infections (16), diarrhea, intestinal infections (17),

hip fractures ([18]), reduced absorption of nutrients such as calcium and magnesium ([19]), kidney problems ([20]), and dementia ([21]). Therefore, if we could reduce the reversibility and duration of PPI treatment, we hope to successfully treat reflux.

Today, traditional medicine and medicinal plants, especially in diseases related to the gastrointestinal tract, have been taken into more consideration ([22]). *Myrtus communis* (Myrtle) is one of the plants which is highly regarded in traditional medicine and has long been used for gastrointestinal problems ([23], [24]). Some studies in animal models have proven that myrtle fruit is more effective in the treatment of peptic ulcer than omeprazole and leads to the increase in mucus wall and improvement of histopathology symptoms ([25]).

The aim of this study is to investigate the impact of myrtle fruit syrup on the recurrence of symptoms in reflux patients after the discontinuance of PPIs.

2. Methods

2.1. Study Design

The present research is an outpatient, double-blind, randomized, parallel treatment groups study which has added the myrtle fruit syrup to the main treatment as an adjuvant therapy which is the use of omeprazole. The age of the patients ranged between 20 and 60 years. The trial was conducted at the traditional medicine clinic at Tehran University of Medical Sciences, Tehran-Iran, between November 2014 and March 2016. This clinic is a governmental clinic and is part of Tehran University of Medical Sciences. All patients were visited by a gastroenterologist and included in the study if they met the inclusion criteria.

2.2. Randomization and Blinding

The patients included in the study were divided into parallel groups after completion of the consent letter. The randomization list was prepared by random allocation software for parallel group randomized trials. Simple randomization was carried out. The prescribers, including the gastroenterologist and the traditional medicine specialist, were blinded to the allocation of the medicines between the groups. The patients were also blinded to the medicines. The myrtle and placebo syrup were identical in the same physical form, packaging and labeling and divided between groups 1 and 2. The physician prescribed the syrups to the patients according to the label numbers.

2.3. Drug Preparation

Omeprazole 20 mg capsules used in this study, manufactured by Dr. Abidi pharmaceutical Co (Tehran-Iran).

The herbal medicine used in this study was myrtle fruit syrup.

Preparation of Myrtle fruit Syrup and placebo: Myrtle fruit syrup was prepared according to the traditional Iranian recipe (Ghayeni, Qarabadin-e-Salehi, 1765 AD; Aghili, Qarabadin-e-Kabir, 1781 AD) ([26], [27]).

A total of 400 g of myrtle berries were coarsely ground and macerated in an appropriate amount of water for 24 hours, then boiled for 1-hour and filtered (extraction yield = 28.9%). An amount of 650 g of sucrose and 500 g of sorbitol were added to the extract in order to prepare the syrup. The medication was supplied in bottles of 250 mL, containing either drug or placebo. The placebo was prepared based on pharmacopoeia simple syrup formula including approved color additives and had the same appearance as the myrtle syrup.

Myrtle syrup is standardized based on total phenols (Folin-Ciocalteau method) and gallic acid (Rhodanine assay) content. Each 5 mL of syrup contains 0.05 ± 0.03 g dry residue and 41 mg total phenols as gallic acid equivalents ([28]).

2.4. Ethical Considerations

The study was licensed by the ethics committee of Tehran University of Medical Sciences under NO. 126388-9021309003 based on guidelines of the Declaration of Helsinki (Hong Kong revision, 1983) and good clinical practice. All patients participating in the study read and signed the consent letter.

A recommendation for reporting the randomization clinical trial was conducted based on the definition made by the statement of consolidated standards of reporting randomized clinical trials (CONSORT). The study was registered under NO. IRCT2014102719705N1 at the Iran trial clinical registry center.

2.5. Sample Size and Statistical Analysis

The initial analysis was based on an intent-to-treat population method. The sample size was implemented based on the one-sided significance level of 0.05 with a power of 0.80. With regard to the withdrawal rate, 45 patients were selected for each group. To study the changes in baseline variables compared to the treatment group, the Chi-square test was used for qualitative variables and T-test for quantitative variables. The significance criteria for the P value was 0.05. The SPSS XIII was applied for statistical analysis (SPSS Inc., Chicago, IL, USA).
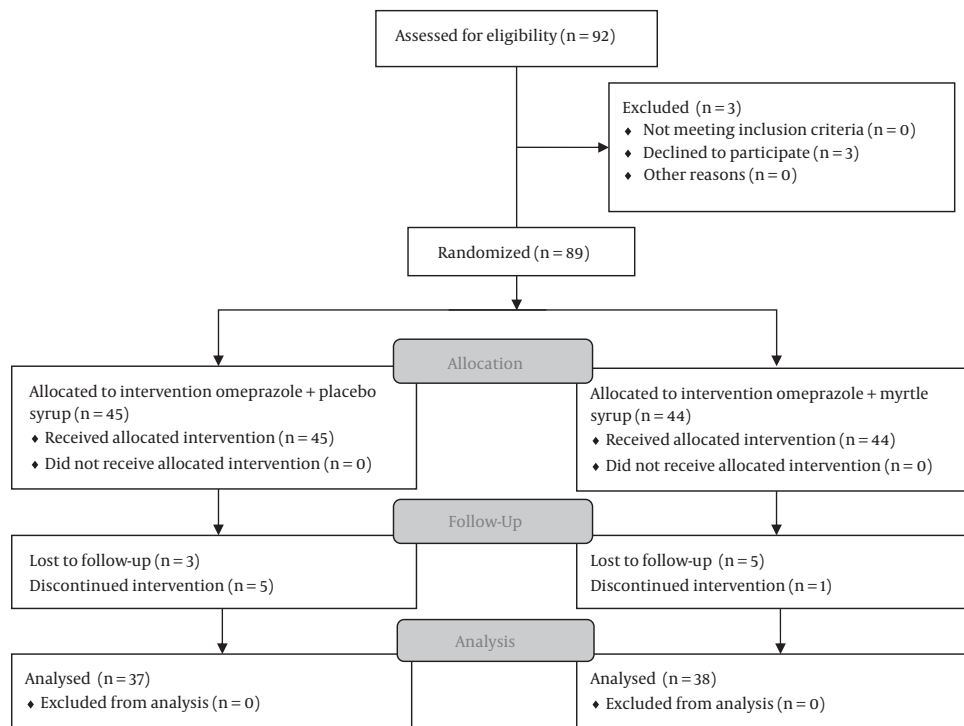
Figure 1. CONSORT (Consolidated Standards of Reporting Trials) Flow Diagram

2.6. Inclusion Criteria

Patients between 20 and 60 years old with one of the regurgitation or heartburn symptoms with a frequency of at least once a week were included in the study (10).

2.7. Exclusion Criteria

The exclusion criteria include the following cases: 1- gastrointestinal surgery 2- liver failure 3- history of cancer 4- melena or gastrointestinal bleeding 5- inflammatory disease of the gastrointestinal tract 6- significant weight loss in the past three months 7 - $40 \leq$ BMI 8- severe chest pain 9- pregnancy 10- using PPI during the last month 11- regular use of nonsteroidal anti-inflammatory drug (NSAIDs) 12- warning signs 13- lack of tendency to participate in study 14- drug allergy and 15- emergence of severe complications according to CTC table.

2.8. Intervention

The participants were divided into two groups: omeprazole 20 mg with fasting and 5 mL of myrtle syrup 20 minutes after every meal (breakfast-lunch-dinner) for the treatment group. The control group also took omeprazole 20 mg with fasting and 5 mL of placebo syrup 20 minutes after every meal. The intervention period

was 6 weeks. The patients were visited prior to intervention, 6 weeks later and 2 weeks after discontinuance of the medicine. The medication was interrupted after 6 weeks and the patients were followed up for 2 weeks. The cases with no recurrence of symptoms up to 14 days were considered as non-recurrence. In case of recurrence of symptoms, the time and intensity were recorded and the patients were advised to continue the treatment.

2.9. Patients' Assessment

The Mayo clinic standardized questionnaire was used for assessment for GERD. The Persian translation of the standardized questionnaire was prepared and the validity and reliability have also been measured in a previous study (29).

The questionnaire consists of 79 questions including 4 main questions about the four major symptoms of reflux such as heartburn, regurgitation, chest pain, and dysphagia. In each of the main symptoms, severity, frequency, and duration of symptoms were studied. The patients with any symptoms of heartburn and regurgitation with a frequency of once a week were regarded as positive for reflux (10). The severity and frequency of symptoms after 6 weeks of treatment and then 2 weeks after discontinuation of the medicine were measured for the second time.

2.10. Safety Measurements

The safety measurements were evaluated according to an adverse events (AEs) report, CTC table, and clinical examinations. All the AEs were monitored during the study and the results were precisely recorded. It was also investigated whether these symptoms have relation with intervention. In case that the patients had these symptoms, they were questioned during the last visit to find out whether these symptoms existed before the intervention and if their severity has increased during the intervention. During the study only one person was affected by diarrhea grade 1 and others exhibited no symptoms.

3. Results

Eighty-nine people were enrolled in the study and received the medicine (45 women and 44 men, mean age = 40.56 years with a range of 25 - 60 years). Seventy-five people completed the study and 14 people could not continue the study after taking the medicine. Out of the placebo group, two people did not begin the study due to a special diet, two people were excluded due to the interference of another medicine and one person left the study one week after taking the medicine due to no observed change. Out of the intervention group, one person was excluded from the study due to experiencing trauma during the fourth week of the study.

A total of 8 people (5 people medicine and 3 people placebo) were lost to follow-up. The demographic properties of both groups had no significant difference (Table 1). Table 2 also shows the main symptoms in both groups prior to implementation of the study. Tables 1 and 2 demonstrate that both groups had no difference in demographic properties and disease symptoms.

Table 3 displays the frequency of symptoms or reflux in both groups at the beginning, 6 weeks after treatment (discontinuance of medicine) and 2 weeks after discontinuance of the medicine. After 6 weeks of treatment, both groups showed a significant decrease in reflux symptoms when compared to the beginning of the treatment. The decrease in the treatment group was higher than in the control group, although there was no significant difference between the two groups. The severity and frequency of reflux in both groups after treatment had significant decreased in comparison to prior treatment groups (Table 3).

Out of the total 75 people who completed the study, 26 people did not experience the recurrence of symptoms untill 2 weeks of discontinuance of treatment (16 people from the treatment group and 10 people from the placebo group), where no statistically significant difference was found (P value = 0.179).

Table 1. Demographic Properties of Patients in the Control and Treatment Groups

Variables	Treatment	Control
Age, Mean $\pm$ SD	9.48 $\pm$ 41.24	9.24 $\pm$ 39.88
Sex, No. (%)		
Women	18 (47.36)	18 (48.64)
Men	20 (52.64)	19 (51.36)
Smoking, No. (%)		
No	34 (89.5)	32 (86.5)
Yes	4 (10.5)	5 (13.5)
Married, No. (%)		
Married	30 (78.9)	33 (89.2)
Single	8 (21.1)	4 (10.8)
Educational degree, No. (%)		
University	18 (47.4)	17 (47.2)
No university	20 (52.6)	19 (50.1)
Missing	-	1 (2.7)
Height		
cm, Mean $\pm$ SD	68.168 $\pm$ 11.27	170.11 $\pm$ 10.10
Weight		
kg, Mean $\pm$ SD	73.97 $\pm$ 16.83	76.97 $\pm$ 15.63
BMI	25.92 $\pm$ 4.65	26.41 $\pm$ 4.19

The average time to the recurrence of symptoms after discontinuation of omeprazole was 6.27 days in placebo and 9.57 days in treatment group (P value = 0.027).

4. Discussion

Although GERD is one of the most prevalent digestive diseases and PPI is its standard therapy, the need for long-term acid suppression and recurrence of symptoms after discontinuation of therapy are the main problems in patients with GERD. The aim of this study was to evaluate the effect of myrtle fruit syrup on the recurrence of GERD symptoms after discontinuance of omeprazole. The results showed that although the recurrence of symptoms was seen in both groups, however, the number of patients who did not experience recurrence in the treatment group was more than in the control group (16 people against 10 people), without a significant statistically difference. Perhaps one reason is that the sample size was small and the study should be conducted with a larger sample size. The average of delay in the onset of symptom recurrence in the treatment group was 50% more than in the control group (9.57 days against 6.23 days). The findings indicate that the

Table 2. Properties of the Main Symptoms in Both Groups Prior to Implementation of the Study

Variables	Heartburn		Regurgitation	
	Treatment	Control	Treatment	Control
Frequency of symptoms				
Every day	20 (45.4)	19 (42.2)	14 (31.8)	13 (28.9)
One or more per week	19 (43.2)	25 (55.6)	18 (40.9)	20 (44.4)
Less than once a week or no symptoms	5 (11.4)	1 (2.2)	12 (27.3)	12 (26.7)
Severity of symptoms				
Slight	1 (2.3)	0	3 (6.8)	2 (4.4)
Medium	27 (61.4)	26 (57.8)	31 (70.4)	35 (77.8)
Severe	7 (15.9)	14 (31.1)	5 (11.4)	4 (8.9)
Very severe	7 (15.9)	4 (8.9)	1 (2.3)	1 (2.2)
No symptoms	2 (4.5)	1 (2.2)	4 (9.1)	3 (6.7)
Duration of onset of symptoms				
During the last 12 months	6 (13.6)	5 (11.1)	10 (22.7)	3 (6.7)
1 to 5 years	17 (38.7)	14 (31.1)	11 (25)	18 (40)
Almost between 5 to 10 years	11 (25)	16 (35.6)	11 (25)	11 (24.4)
More than 10 years	8 (18.2)	9 (20)	8 (18.2)	10 (22.2)
No symptoms	2 (4.5)	1 (2.2)	4 (9.1)	3 (6.7)

Table 3. The Frequency of Symptoms in Both Groups at the Beginning of the Study, 6 Weeks After Treatment (Discontinuance of Medicine) and 2 Weeks After Discontinuance of Medicine[a]

Variables	Treatment Group			Control Group		
	Beginning of study	6 weeks after treatment	2 weeks after discontinuance of medicine	Beginning of study	6 weeks after treatment	2 weeks after discontinuance of medicine
Heartburn	39 (88.6)	8 (21)	18 (47.3)	44 (97.7)	10 (27)	24 (64.8)
Regurgitation	32 (72.7)	2 (5.2)	12 (31.5)	33 (73.3)	5 (13.5)	19 (51.3)
Reflux[b]	44 (100)	9 (23.6)	22 (57.8)	45 (100)	10 (27)	27 (72.9)

[a]Values are expressed as No. (%).
[b]Reflux is defined as the existence of heartburn or regurgitation with a frequency of once a week.

myrtle syrup may be effective in delay in relapse of symptoms, and decreasing the drug need.

Nowadays about 60% - 80% of patients are obliged to have long-term use of acid reducing medication and they can not discontinue the medication (30, 31). Multiple factors are involved in the pathology of reflux, such as hypersecretion of gastric acid and pepsin, excess oxidant and inflammatory factors such as high IL-8, IL-6 and IL-1 β, rising MPO, lipid peroxidation, GSH/GSSG ratio, histamine, decreasing catalase, gastrointestinal motility and delayed gastric emptying, LES abnormalities, impaired esophageal clearance, abnormalities in esophageal mucosa, hiatal hernia, pyloric incompetence, and possibly bile reflux (32-34). Among these factors, the oxidant and inflammatory agents may play a more important role (33, 34). PPIs treat reflux through the inhibition of acid secretion, while it does not have an impact on the increment of antioxidant and inflammatory level (35); therefore, the use of anti-inflammatory and antioxidant factors with a PPI may be a better choice for control of GERD. As we know, acid inhibition alone is not a proper therapeutic modality for curing GERD on a long term basis (33, 35).

In our review of the literature there have not yet been any studies on the evaluation of the effect of herbal medicines on reducing the recurrence rate and on the delay of onset of GERD symptoms. However, there are sev-

eral studies on the effects of herbal products in the treatment of reflux which indicate that these plants are effective in the treatment of GERD through antioxidant and anti-inflammatory and induce effects on the LES and mucosal layer of the esophagus. For instance, in another study showed that crucumin has been effective in the treatment of reflux through anti-oxidant and anti-inflammatory effects. In histopathological terms, it also leads to esophagus lesion recovery (36). Singh et al. also showed that *Panax quinquefolium* was effective in the treatment of reflux through increase in the ratio of GSH/GSSG (35). Ku et al. also studied the impact of the *Lonicera Japonica* plant in the treatment of reflux and found that the plant leads to the recovery of reflux through antioxidant and anti-inflammatory impacts such as increased GSH and SOD and catalase activity as well as increased mucosal thickness (37). Tsai et al. conducted an ex vivo study and proved that the *Salvia miltiorrhiza* plant was effective in the treatment of reflux. It affects the extra- and intracellular calcium and increases tonicity of the LES valve (38). Abdel-Aziz et al. found that the compounds of a medication called stw5, with anti-inflammatory and anti-oxidant effects such as affecting TNF-α, IL-1 β and TBARS, leads to the recovery of symptoms and even histopathology reflux (39). In another study showed that rikkunshito, a traditional Japanese multi-herbal medicine, caused significant improvement in PPI-refractory reflux disease. In this study has shown to have a similar effect on PPI-refractory reflux disease (36).

Myrtle possesses astringent, carminative, demulcent, analgesic, antiseptic and anti-inflammatory features (24). According to Iranian traditional Medicine references, myrtle strengthens the stomach and affects the LES. If myrtle is used after a meal, it reduces constipation (40) and constipation aggravates reflux (41).

Sumbul et al. proved that the aqueous extract of myrtle fruit reduces the ulcer index, total acidity and gastric juice volume and increases the gastric pH and gastric wall mucus and is more effective than omeprazole. Myrtle also leads to the improvement of histopathological effects on a gastric ulcer (25). The study by Zohalinezhad et al. also indicated that the myrtle fruit has impacts similar to omeprazole for the treatment of reflux and found no significant difference between myrtle fruit and omeprazole (42). The mentioned study evaluated the effects of myrtle for the treatment of GERD, whereas the present study investigated the impact of myrtle on the delay of onset of symptoms after the discontinuance of medicine.

Although the results of this study are not based on the acid reducing effects of medicine, a suggestion is that increasing the resistance of mucosal layer by anti-oxidant effects of myrtle syrup may be a novel therapeutic modality for control and treatment of GERD. Recurrence of GERD symptoms is one of the serious problems of its treatment. As no prior research in this files has been found, this is the first study describing the recurrence of GERD symptoms. It is the novelty of the study that could reveal new ideas about the treatment of GERD. Myrtle syrup can delay the onset of symptoms for about 50% during 2 weeks follow-up, which could be the other strength of our study.

Our limitations in this study were the small sample size and short duration of treatment and follow-up. It is suggested that myrtle should be prescribed for a longer duration and patients be followed-up for a longer period. The changes of drug dose and frequency may also be effective in the treatment and prevention of recurrence of symptoms, which needs further investigation. It seems that the patients should be followed-up after the discontinuance of medicine for a longer duration. If the relationship between symptoms and endoscopic findings or esophageal pH meter is considered, more precise results would be obtained.

4.1. Conclusion

Addition of myrtle fruit syrup to oral omeprazole does not have a significant effect in the recurrence of symptoms in patients affected by reflux. The interval time between discontinuation of omeprazole and recurrence of symptoms, however, was longer in the treatment group than in the control group. Therefore further studies with a larger sample size and a longer follow-up are recommended.

Footnote

Conflict of Interests: There is no conflict of interest.

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