Journal of Integrative Medicine 16 (2018) 126–131

Contents lists available at ScienceDirect

Journal of Integrative Medicine

journal homepage: www.jcimjournal.com/jim
www.journals.elsevier.com/journal-of-integrative-medicine

Original Research Article

Efficacy and safety of Amla (*Phyllanthus emblica* L.) in non-erosive reflux disease: a double-blind, randomized, placebo-controlled clinical trial

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ARTICLE INFO

Article history:
Received 29 October 2017
Accepted 6 January 2018
Available online 13 February 2018

Keywords:
Gastroesophageal reflux
Non-erosive reflux disease
Amla
Phyllanthus emblica
Phytotherapy
Randomized clinical trials

ABSTRACT

Background: Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal complaints. GERD, caused by the reflux of stomach contents into the esophagus, leads to troublesome symptoms such as heartburn and regurgitation. It is classified into two types: erosive esophagitis, characterized by visible esophageal mucosa erosion in endoscopy, and non-erosive reflux disease (NERD). GERD is a chronic and recurrent disease that impairs the quality of life and imposes socioeconomic and therapeutic burdens to both patients and society.

Objective: Due to the failure of the conventional treatments for GERD and to the traditional use of Amla (*Phyllanthus emblica* L.), in addition to beneficial effects shown in recent studies, we evaluated the safety and efficacy of Amla tablet for improvement of symptoms of patients with NERD.

Design, setting, participants and interventions: We designed a double-arm, randomized, double-blind, placebo-controlled clinical trial. Sixty-eight patients who had classic symptoms of GERD (heartburn, regurgitation and epigastralgia) for at least three months before the start of the trial were randomized in two parallel groups. Patients in the Amla group received two 500 mg Amla tablets twice a day, after meals, for 4 weeks. In the control group, patients received placebo tablets similar to the Amla prescription.

Main outcome measures: The patients were visited at baseline, and at the end of the 2nd and 4th weeks of intervention; their symptoms were measured on a frequency and severity scale for the symptoms of NERD, according to the quality of life in reflux-associated disease questionnaire.

Results: Frequencies of heartburn and regurgitation in both groups of the study were significantly reduced after intervention ($P < 0.001$). Repeated measures logistic regression analysis showed that, in the Amla group, there was a more significant reduction in regurgitation frequency, heartburn frequency, regurgitation severity and heartburn severity during the study period, compared with the placebo group ($P < 0.001$).

Conclusion: This randomized double-blind, placebo-controlled clinical trial demonstrated that Amla could reduce frequencies of heartburn and regurgitation and improve heartburn and regurgitation severity in patients with NERD.

Trial registration: Iranian Registry of Clinical Trials IRCT2016061428469N1.

Please cite this article as: Karkon Varnosfaderani S, Hashem-Dabaghian F, Amin G, Bozorgi M, Heydarirad G, Nazem E, Nasiri Toosi M, Mosavat SH. Efficacy and safety of Amla (*Phyllanthus emblica* L.) in non-erosive reflux disease: a double-blind, randomized, placebo-controlled clinical trial. *J Integr Med.* 2018; 16(2): 126–131.

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https://doi.org/10.1016/j.joim.2018.02.008
2095-4964/

1. Introduction

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal complaints [1]. GERD, caused by the reflux of stomach contents into the esophagus, leads to troublesome symptoms such as heartburn and regurgitation [2]. Based on the esophageal mucosa appearance in upper endoscopy, the disease is classified into two types: (1) erosive esophagitis, characterized by visible esophageal mucosa erosion in endoscopy; (2) non-erosive reflux disease (NERD), characterized by the presence of GERD symptoms without visible esophageal mucosal erosions [3].

Approximately 30% of the population in Western countries and nearby 20% of Iranian people suffers from this disease [4]. GERD is a chronic and recurrent disease that impairs the quality of life and imposes socioeconomic and therapeutic burdens to both patients and society [5].

Different therapeutic strategies are used to relieve the symptoms of these patients, such as lifestyle and dietary modification and acid suppression [6]. However, using acid suppressive drugs, such as histamine 2 receptor antagonists (H2 blocker) and proton pump inhibitors (PPIs), has not been able to completely eliminate symptoms. Previous studies reported that about two-thirds of patients with NERD, and nearly all patients with erosive esophagitis, relapse when acid suppression is discontinued [7]. Moreover, long-term consumption of gastric acid suppressants causes complications such as gastric atrophy, impaired vitamin B and iron absorption, enteric infections, osteoporosis, myopathy, acute interstitial nephritis, colon or gastric malignancies and acute coronary syndromes [8,9].

Due to the failure of the conventional treatments for chronic diseases, an increasing interest in the use of herbal medicine has arisen [10–16]. Therefore, an evidence-based approach for the scientific evaluation of herbal medicines is needed [17–19]. Amla, or Indian gooseberry (*Phyllanthus emblica* L.), is one of the most widely used medicinal plants in Eastern countries, especially in Iran and India. In traditional Persian medicine and Ayurvedic medicine, this herb is used to treat many diseases, including reflux and regurgitation [20–22]. For example, Rhazes (865–925 CE) [23], Haly Abbas (949–982 CE) [14], and Avicenna (980–1037 CE) [24] discussed its different medicinal uses, including treating gastrointestinal diseases [25,26]. Amla contains high concentrations of ascorbic acid, phenols and tannins, such as gallic acid and flavonoids. An animal experimental study reported that Amla extract possesses antisecretory, antiulcer, and cytoprotective components [27]. Additionally, histopathological studies confirmed the beneficial roles of Amla against ethanol-induced liver injury in rats [28].

Due to Amla's traditional uses, in addition to beneficial effects demonstrated in recent studies, we designed a double-armed, randomized, controlled clinical trial to evaluate the safety and efficacy of Amla tablets for improvement of symptoms of patients with NERD.

2. Materials and methods

2.1. Trial design

In this double-arm, randomized, double-blind, placebo-controlled clinical trial, we evaluated the effect of Amla (*P. emblica* L.) tablet on the frequency and severity of the symptoms of NERD. No changes occurred to methods after trial commencement.

2.2. Participants

Study participants were men and women aged 16 to 80 years, who had classic symptoms of GERD (heartburn, regurgitation and epigastralgia) for at least three months before the start of the trial. Diagnosis was carried out by a gastroenterologist, based on clinical symptoms and endoscopic findings [29]. This study was conducted in Imam Khomeini Hospital and Khark Traditional Medicine Clinic, affiliated to the School of Traditional Medicine, Tehran University of Medical Sciences, Tehran, Iran, from July 2016 to April 2017. All patients provided informed consent prior to participation.

Exclusion criteria were erosive esophagitis in endoscopy, positive occult blood test, smoking, ongoing alcohol user, pregnancy, lactation, any digestive disorder which required new treatment protocols, significant surgical or medical disorders, or history of using PPIs within 10 days of the initiation of the trial or using H2 blockers within 2 weeks of the initiation of the trial.

2.3. Intervention

After diagnosis of NERD by a gastroenterologist via endoscopic assessment, all patients were asked to follow a life style modification for two weeks. Then, patients who experienced improvement of symptoms in response to the lifestyle changes were not included in the study. The remaining eligible patients who had signed the informed consent form were divided into two groups. Patients were randomly assigned to receive either Amla tablets as the intervention group, or placebo tablets as the control group. Patients in the Amla group received two 500 mg Amla tablets twice a day, after meals, for 4 weeks. The selected dose for the Amla tablet was adjusted to 2 g/day based on the previous experimental study [30]. In the control group, patients received placebo tablets similar to the Amla prescription. Participants who took less than 70% of prescribed tablets during the trial were considered to have drug intolerance. The patients were visited at baseline, and after 2 and 4 weeks of the study period; their symptoms were measured in terms of frequency and severity on a scale for the symptoms of NERD, according to the quality of life in reflux-associated disease (QOLRAD) questionnaire [31].

2.4. Preparation of drugs

The dry fruits of Amla (without stone) were purchased from the herbal market in Tehran, Iran. They were authenticated by a botanist, and a voucher specimen (Voucher number: PMP-1611) was stored at the Herbarium of the Faculty of Pharmacy, Tehran University of Medicinal Sciences, Tehran, Iran. The fruits were completely ground. The resulting powder was disinfected by microwave in three one-minute steps, and was then passed through the 60 mesh (250 μm) sieve. Tablets weighing 500 mg were prepared using a tablet press machine with the sieve powder. Fruit powder was analyzed for gallic acid content, one of the plant's main constituents. According to the Folin–Ciocalteu method, 68.75 mg of total phenol per gallic acid was contained in each tablet [32]. The toxicity of Amla was not determined independently for this study. We relied on available data [33]. Corn starch powder was used to make placebo tablets in the same size, weight, shape and color as the Amla tablet. It should be noted that the size, label and shape of the placebo bottles were also similar to bottles used for Amla tablets and were made in Faculty of Pharmacy, Tehran University of Medical Sciences by a pharmacist (Pharm D).

2.5. Outcome measures

The primary outcome measures in this trial were changes in the frequency and severity of symptoms of NERD according to a scale based on the Persian version of the QOLRAD questionnaire [31]. The Persian version of QOLRAD is a useful questionnaire for assessing of the therapeutic response of GERD objectively. Reliability and validity of this questionnaire have been confirmed previously [31].

This questionnaire includes 24 questions which evaluate severity and frequency of GERD symptoms, such as heartburn, regurgitation into throat, chest rubbing and burning sensation in throat. At the beginning of the study and at the end of the 2nd and 4th weeks of intervention, the questionnaire was completed by patients. Any observed adverse event was also considered as a secondary outcome. No changes were made to trial outcomes after the trial commenced.

2.6. Sample size

Considering the expected difference in frequency of NERD symptoms, as the primary outcome measure between the two groups of study (standard deviation = 4), and providing for a two-sided significance level of 0.05, power of 80% and 20% dropout rate in each group, the sample size was calculated to be 34 patients in each group with a total 68 patients in all [34].

2.7. Safety assessment

In order to detect adverse outcomes and other complaints, all patients had follow-up visits with a physician every two weeks. All patients were asked to report any drug side effects, especially abdominal pain, constipation, nausea and vomiting.

2.8. Randomization

Sixty-eight eligible volunteers were randomized into two parallel arms. A statistician generated a randomized list using the NCSS Statistical Software package (Version 2007; NCSS Statistical Software, Kaysville, UT) with a simple block randomization method. Blocks of 4 were determined using a random number table, and randomization within the blocks was also determined using a random number table. Then, the eligible participants were assigned to a group by one of the investigators using the randomized list. All participants and investigators were blind to the allocation of the patients. Because placebo tablets were similar to Amla tablets in size, weight, shape and color and pill bottles were also similar between groups, patients, physicians, drug deliverers and data analysts were blinded to the type of medicine any participant received. Only the pharmacists had access to the group membership data.

2.9. Ethical considerations

The trial was in compliance with the *Declaration of Helsinki*, and was also reviewed, approved and monitored by the Ethics Committee of Tehran University of Medical Sciences with the following ethic code: IR.TUMS.REC.1394.365. Furthermore, the trial was registered by the Iranian Registry of Clinical Trials with the following code: IRCT2016061428469N1. All of the participants signed an informed consent form prior to enrollment in the study.

2.10. Statistical methods

Data are summarized as mean ± standard deviation or as a percentage. Chi-square test was used for statistical comparisons of qualitative baseline characteristics such as sex and marital status. Independent *t*-tests were used to make statistical comparisons among quantitative baseline characteristics such as age and body mass index. To assess statistical differences in heartburn and regurgitation between the two experimental groups, the Chi-square test was used. To test the difference in severity between symptoms of heartburn and regurgitation, Cramer's V statistical test was used. To estimate the significance of differences within-group variance Friedman's test was used. In order to estimate the difference between two groups in terms of the frequency and severity of heartburn and regurgitation Mann–Whitney's *U* test was used. Tests with *P* values less than 0.05 were considered significant. The intention-to-treat method was used for data analysis, this meant that all patients who began the study were analyzed in the results, even if they dropped out or violated intervention protocol. All data were analyzed using the Statistical Package for the Social Sciences (SPSS software Version: 15; IBM, NY, USA).

3. Results

3.1. Patients enrollment

From 11-07-2016 to 05-12-2016, 293 patients were assessed for eligibility. All of these patients received life style modification. One hundred and sixty-four experienced improvement of their symptoms with life style modification and were excluded from the study. Sixty-eight patients who met the inclusion criteria and consented to participate in the study were divided into two groups. Thirty-two patients were assigned to the Amla group and 36 patients to the placebo group. Fig. 1 is the flowchart of the groups' recruitment, distribution, intervention, follow-up, and analysis. Rate of loss to follow-up was 0, because all patients were asked to attend follow-up visits even if they had not complied with the study protocol. In the placebo group, five patients stated personal reasons for abandoning the study protocol before week two, and in the Amla group one patient discontinued the intervention due to worsening of heartburn after one week of treatment. However, data from all patients were analyzed because of the intention-to-treat analysis protocol employed in the study.

3.2. Baseline clinical characteristics

The mean age of participants in the Amla and placebo groups was (42.28 ± 12.04) and (42.79 ± 11.57) years, respectively. The ages of participants were not different between two groups ($P = 0.117$). Other demographic data of the participants (sex, marital status, body mass index and duration of the disease) are shown in Table 1. There were no significant differences in baseline clinical characteristics between the two groups (Table 1; $P > 0.05$).

3.3. Clinical response

Within-group changes in the frequency of heartburn and regurgitation in both groups were significantly reduced after intervention ($P < 0.001$). Severity of heartburn and regurgitation both were significantly reduced in the Amla group compared to the placebo group (Table 2).

Repeated measures logistic regression analysis showed that over the course of the study, the Amla group had a more significant reduction in regurgitation frequency, heartburn frequency, regurgitation severity and heartburn severity compared to the placebo group ($P < 0.001$).

3.4. Adverse effects

No adverse effects of the interventions (abdominal pain, constipation, nausea or vomiting) were reported by patients. Only one patient in the Amla group reported worsening of heartburn and abandoned the intervention.

4. Discussion

In this study, we evaluated safety and efficacy of Amla for improving NERD symptoms via a double-blind, randomized,

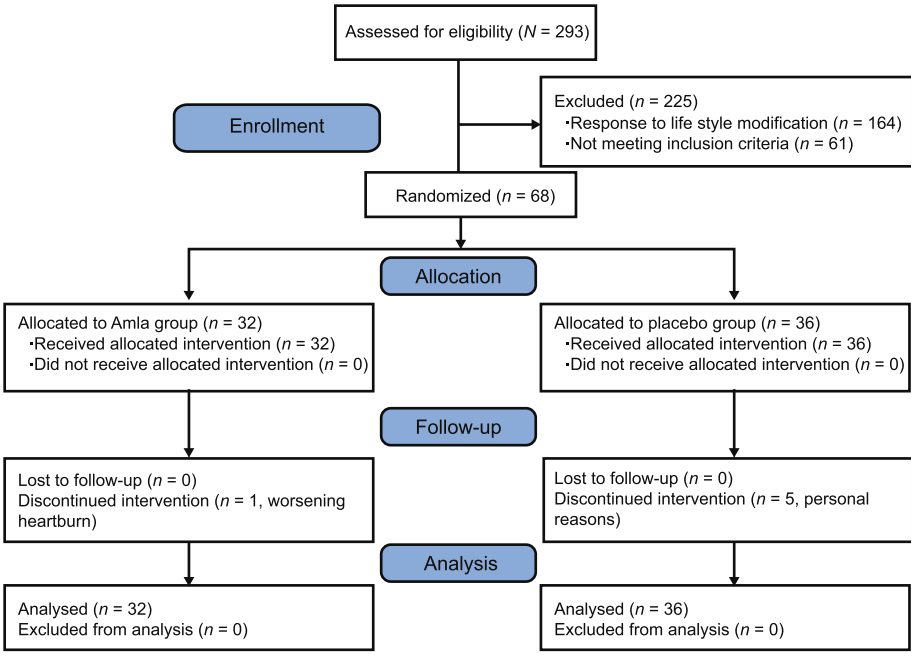

Fig. 1. Flow diagram of the study.

placebo-controlled clinical trial. Amla was shown to significantly reduce regurgitation and heartburn frequency and severity in NERD patients, compared to placebo. Given that the reduction in the symptoms in the Amla group was close to 50%, this effect is clinically significant. Given that the reduction in severity of the symptoms in the Amla group was also close to 50%, this effect was clinically significant. It should be noted that in seven placebo-controlled trials of PPI therapy, the therapeutic gain for regurgitation response averaged 17% relative to placebo; this effect was more than 20% lower than that observed for heartburn [35].

To the best of our knowledge, this study is the first clinical trial that investigates the effectiveness of Amla in patients with NERD. Although numerous animal and experimental studies have been conducted on Amla, only one study demonstrated clinical efficacy of Amla; that study explored the management of iron deficiency anemia based on Ayurvedic medicine [36]. Non-clinical studies have shown the beneficial role of Amla in cancer, diabetes, hepatic and heart diseases, ophthalmic disorders and anemia [37]. Moreover, antioxidant, antimicrobial, immunomodulatory, antipyretic, analgesic, anti-hyperlipidemic, cytoprotective, antitussive,

Table 1
Demographic data of the patients participating in the trial.

Variable	Amla group (n = 32)	Placebo group (n = 36)	P value
Male/female (n)	8/24	7/29	0.547*
Duration of disease (mean ± SD, years)	1.83 ± 0.38	1.61 ± 0.49	0.112†
Single/married (n)	8/24	6/30	0.292*
Body mass index (mean ± SD, kg/m^2)	26.68 ± 3.68	26.23 ± 3.05	0.582†

SD: standard deviation.
† Independent sample t-test.
* Chi-square test.

Table 2
Severity and frequency of non-erosive reflux disease symptoms in the Amla and placebo groups before and after 2 and 4 weeks of treatment.

Item	Time	Amla group (n = 32)	Placebo group (n = 36)	P value†
Frequency of heartburn	Baseline	3.78 ± 0.78	4.10 ± 1.06	0.107
	2 weeks	1.73 ± 0.96	3.17 ± 0.86	0.001
	4 weeks	1.27 ± 0.59	3.17 ± 0.86	0.001
	P value*	0.001	0.001	
Severity of heartburn	Baseline	2.16 ± 0.64	2.00 ± 0.37	0.246
	2 weeks	1.50 ± 0.71	1.97 ± 0.32	0.001
	4 weeks	1.13 ± 0.34	1.89 ± 0.41	0.001
	P value*	0.001	0.097	
Frequency of regurgitation	Baseline	3.58 ± 0.98	3.79 ± 0.13	0.029
	2 weeks	1.52 ± 0.79	3.60 ± 0.55	0.001
	4 weeks	1.45 ± 0.82	2.86 ± 0.95	0.001
	P value*	0.001	0.001	
Severity of regurgitation	Baseline	2.04 ± 0.52	2.10 ± 0.56	0.309
	2 weeks	1.30 ± 0.59	1.97 ± 0.32	<0.001
	4 weeks	1.09 ± 0.31	1.93 ± 0.65	<0.001
	P value*	<0.001	0.156	

† Mann–Whitney's U test.
* Friedman's test.

memory enhancing, neutralizing snake venom, and gastroprotective effects of Amla have all been shown in current research [38].

According to reliable traditional Persian medicine references, such as *Canon of Medicine* written by Avicenna (980–1037 AD) [39], Amla has a cold and dry temperament. It was introduced as a potent gastrotonic and gastroprotective herb. It can be used as an anti-reflux, anti-nausea, cardiotonic and cerebrotonic agent, too. Amla is an astringent herb; hence, it has been used for stopping diarrhea and bleeding [25].

Dysfunction of peripheral factors (luminal, mucosal and sensory afferents) as well as central factors (psychological, stress and sleep) is proposed in the pathophysiology of NERD. According to this hypothesis, diffusion of refluxed gastric acid into the intercellular spaces activates chemosensitive nociceptors whose signals are transmitted via the dorsal horn of the spinal cord to the brain for symptom perception [40,41]. Possible mechanisms of action for Amla's observed effects on NERD symptoms include inhibition of the diffusion of refluxed gastric acid into the intercellular spaces, decreased intercellular space volume and suppression of brain-gut interactions. These should be evaluated in future studies [42,43].

Even with the randomized controlled trial protocol in the present study, we had some limitations which should be considered for consistent interpretation of our results. The small sample size and the short duration of the study period were the main limitations. As this was a preliminary study, we chose the short duration study time and calculated the minimum necessary sample size; this approach is consistent with previous study methods [44,45]. However, it is suggested that further studies be conducted with a longer follow-up and greater sample size.

5. Conclusion

This randomized double-blind, placebo-controlled clinical trial demonstrated that Amla (*P. emblica*) could reduce frequency and severity of heartburn and regurgitation in patients with NERD. Nevertheless, larger-scale qualified methodological trials with longer duration of the intervention are needed to replicate and expand our preliminary findings in this trial, and to make conclusions for the efficacy of this herbal treatment in managing symptoms of this chronic and recurrent disease, over larger time-scales.

Acknowledgements

This study was conducted in collaboration with Colleges of Traditional and Complementary Medicine of Tehran University of Medical Sciences, and was a part of a PhD thesis by Dr. Shahnaz Karkon that approved by the Ethics Committee (code IR.TUMS.REC.1394.365.) that are all appreciated. The authors thank research vice chancellery of Tehran University of Medical Sciences for funding supports.

Conflict of interests

The authors declare no competing interests.

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