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CLINICAL STUDY

Efficacy and safety of Aloe vera syrup for the treatment of gastro-esophageal reflux disease: a pilot randomized positive-controlled trial

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Abstract

OBJECTIVE: To investigate the use of Aloe vera (A. vera) for the treatment of gastroesophageal reflux disease (GERD) symptoms and compare its effects with those of omeprazole and ranitidine.

METHODS: In this pilot, randomized controlled trial, 79 subjects were allocated to A. vera syrup (standardized to 5.0 mg polysaccharide per mL of syrup) at a dose of 10 mL/d, omeprazole capsule (20 g/d) or ranitidine tablet (150 mg in a fasted state in the morning and 150 mg 30 min before sleep at night) for a period of 4 weeks. The frequencies of eight main symptoms of GERD (heartburn, food regurgitation, flatulence, belching, dysphagia, nausea, vomiting and acid regurgitation) were assessed at weeks 2 and 4 of the trial.

RESULTS: A. vera was safe and well tolerated and reduced the frequencies of all the assessed GERD symptoms, with no adverse events requiring withdrawal.

CONCLUSION: A. vera may provide a safe and effective treatment for reducing the symptoms of GERD.

Key words: Aloe vera; Gastroesophageal reflux disease; Complementary therapies; Treatment outcome; Randomized controlled trial

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic, recurrent and progressive disease associated with a wide range of esophageal (e.g. esophageal ulcer, esophageal cancer, Barrett's disease) as well as non-esophageal (e.g. respiratory problems, chest pain, angina) complications. Mucosal damage caused by gastric refluxate means that GERD occasionally shows similar symptoms to functional dyspepsia and irritable bowel syndrome.[1]

Official statistics suggest that 44% of the population of the United States experience GERD symptoms at least once a month, and 20% at least once a week.[2,3] The overall prevalence of GERD in the Western world has been reported to be about 10%-20%, making it one of the most common gastrointestinal diseases.[4] However,

despite the high prevalence of GERD, its definitive diagnosis and clinical differentiation from other morbidities is difficult, at least partly because of the presence of atypical manifestations such as laryngopharngeal reflux, chronic cough, asthma and dental erosions.[1] Notably, GERD symptoms have been reported to adversely affect patients' daily activities and quality of life, and impose a substantial cost on healthcare systems.[5,6]

Regarding the recurrent nature of GERD, most patients require continuous and long-term medication. Proton pump inhibitors and H_2 receptor blockers are the most commonly prescribed drug classes for GERD. However, despite their proven effect and widespread use, adverse events such as hypochlorhydria, cardiac events and increased risk of hip fractures have led to concerns over the safety of these drugs,[7,8] resulting in a surge of interest in identifying natural remedies that can effectively control GERD symptoms and prevent its complications.

Aloe vera (A. vera) is a medicinal plant with wide applications in the pharmaceutical industry for both systemic[9,10] and dermatologic disorders.[11-14] A. vera gel has been demonstrated to possess several pharmacological actions including antioxidant, anti-inflammatory, analgesic, anti-proliferative, and anti-diabetic properties.[15] Furthermore, A. vera has also shown anti-ulcer,[16,17] wound-healing,[18] and antimicrobial[19] effects, all of which may be relevant to the treatment of GERD and its comorbidities. However, despite these promising mechanisms of action and positive findings in preclinical models of GERD and peptic ulcers,[16,17] clinical evaluations of A. vera gel as a treatment for GERD have been scarce. The present trial aimed to explore the clinical efficacy of A. vera syrup compared with the standard medications omeprazole and ranitidine in patients suffering from GERD symptoms.

METHODS

Subjects

This randomized, open-label, positive-controlled clinical trial enrolled patients aged 18-65 years who were diagnosed with GERD and referred to the endoscopy ward at the Baqiyatallah Hospital (Tehran, Iran). The study protocol was approved by the institutional Ethics Committee and written informed consent was obtained from all participants. Exclusion criteria were pregnancy, breastfeeding, and presence of hematemesis, odynophagia, treatment-resistant GERD, other gastrointestinal disorders (e.g. peptic ulcer, irritable bowel syndrome, obstructive diseases), hepatic diseases, malnutrition syndrome, hematologic diseases, use of muscle relaxant drugs (e.g. anticholinergic agents, calcium channel blockers), or history of hypersensitivity to A. vera preparations.

Treatments

Seventy-nine eligible subjects were randomly allocated to A. vera syrup (10 mL once a day), omeprazole capsule (20 mg once a day) or ranitidine tablet (150 mg in a fasted state in the morning and 150 mg 30 min before sleep at night) for a period of 4 weeks. Randomization was performed using a random-number table controlled by the pharmacy. A. vera syrup was formulated by the Barij Essence Pharmaceutical Co., (Mashade Ardehal, Kashan, Iran), and was standardized to 5.0 mg polysaccharide per mL of syrup.

Efficacy measures

Assessment of treatment efficacy was symptom-based.[20,21] Improvements in common GERD symptoms were measured according to a modified Reflux Disease Questionnaire,[22] which is a validated, self-administered scale that is widely used for the assessment of anti-reflux treatment effects.[23] The frequencies of eight main symptoms of GERD, namely heartburn, food regurgitation, flatulence, belching, dysphagia, nausea, vomiting and acid regurgitation, were assessed at weeks 2 and 4 of the trial and were compared between the different treatment arms.

Statistical analysis

Statistical analyses were performed using SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA). Within-group comparisons of the frequencies of GERD symptoms were carried out using the binomial sign test. Between-group comparisons were made using Pearson's χ^2 or Fisher's exact test. Quantitative data are expressed as the mean ± standard deviation ($\bar{x} \pm s$). In all analyses, a two-sided P value < 0.05 was considered to be statistically significant.

RESULTS

The demographic characteristics of the study groups including age, sex, body mass index, educational level and smoking habit are shown in Table 1. There were no significant differences in any of these parameters between the groups.

The severities of GERD symptoms were assessed after 2 and 4 weeks of treatment. The baseline frequencies of all the evaluated GERD symptoms were similar in the A. vera, ranitidine and omeprazole groups (P > 0.05). The frequencies of all GERD symptoms were reduced at both 2 and 4 weeks of treatment in the A. vera group compared with baseline, with a trend towards further improvement in the frequencies of heartburn, flatulence and belching from weeks 2-4 of the trial (Table 2).

In the omeprazole group, the frequencies of all assessed symptoms were significantly reduced compared with baseline at both time points (weeks 2 and 4) and the frequencies of heartburn, flatulence, belching and acid regurgitation showed further reductions at week 4 compared with week 2 (Table 2).

In the ranitidine group, the frequencies of heartburn,

flatulence, belching, nausea, vomiting and acid regurgitation were significantly reduced at week 2 compared with baseline. The frequencies of all assessed symptoms except flatulence were significantly reduced at week 4 compared with both baseline and week 2, while flatulence was reduced at week 4 compared with week 2 (Table 2).

A. vera had less effect on reducing the frequencies of heartburn at weeks 2 and 4 compared with omeprazole, and at week 4 compared with ranitidine, and less effect on flatulence at week 4 compared with omeprazole, and at weeks 2 and 4 compared with ranitidine. Patients in the A. vera group also had a higher frequency of belching at week 4 compared with patients in the omeprazole group. Frequencies of other symptoms were comparable between the study groups.

There were two reports of adverse reactions in the A. vera group (one vertigo and one stomachache), three in the omeprazole group (one headache, one constipation and one heartburn), and three in the ranitidine group (one of constipation, two heartburn, and two diarrhea) (Table 3). These adverse events were responsible for two drop-outs in the ranitidine group and two in the omeprazole group, but none in the A. vera group.

DISCUSSION

The results of the present randomized controlled trial provide evidence for the efficacy of A. vera gel syrup in reducing the common symptoms of GERD. This efficacy of A. vera was comparable to those of the standard drugs ranitidine and omeprazole in relation to most symptoms. An epidemiological study in Poland reported that A. vera was routinely used to treat gastric hyperacidity, as well as gastric and duodenal ulcers in cigarette smokers.[24] In an experimental study, intravenous administration of aloctin A, a glycoprotein present in Aloe species, was shown to reduce the secretion of gas-

Table 1 Demographic characteristics of study subjects ($\bar{x} \pm s$)

Parameter		Aloe vera	Omeprazole	Ranitidine
N		28	27	24
Female (*n*)		15	19	11
Age (years)		46±17	48±17	47±14
BMI (kg/m^2)		52±4	26±5	25±4
Smoking (*n*)		3	3	2
Educational level (*n*)	Illiterate	3	3	3
	Under diploma	11	11	11
	Diploma	4	8	4
	University	10	5	15

Note: BMI: body mass index.

Table 2 Frequency of GERD symptoms in the study groups at baseline, and at weeks 2 and 4 of the trial [*n* (%)]

Item	Aloe vera			Omeprazole			Ranitidine		
	Baseline	Week 2	Week 4	Baseline	Week 2	Week 4	Baseline	Week 2	Week 4
Heartburn	17 (100.0)	4[a] (23.5)	5[a] (29.4)	24 (100.0)	13[ab] (54.2)	15[ab] (62.5)	25 (100.0)	9[a] (36.0)	13[ab] (52.0)
Food regurgitation	10 (100.0)	1[a] (10.0)	1[a] (10.0)	11 (100.0)	2[a] (18.2)	2[a] (18.2)	16 (100.0)	1 (6.3)	2[a] (12.5)
Dysphagia	12 (100.0)	4[a] (33.3)	4[a] (33.3)	12 (100.0)	1[a] (8.3)	1[a] (8.3)	9 (100.0)	0 (0.0)	2 (12.5)
Flatulence	17 (100.0)	1[a] (5.9)	2[a] (11.8)	21 (100.0)	5[a] (23.8)	9[ac] (42.9)	23 (100.0)	12[ac] (52.1)	7[ac] (30.4)
Belching	15 (100.0)	2[a] (13.3)	3[a] (20.0)	19 (100.0)	7[a] (36.8)	10[ab] (52.6)	21 (100.0)	3[a] (14.3)	7[a] (30.4)
Nausea	5 (100.0)	1[a] (20.0)	1[a] (20.0)	12 (100.0)	4[a] (33.3)	4[a] (33.3)	15 (100.0)	8[a] (53.3)	10[a] (66.7)
Vomiting	1 (100.0)	1 (100.0)	1 (100.0)	3 (100.0)	2[a] (66.7)	2[a] (66.7)	6 (100.0)	2[a] (33.3)	4[a] (66.7)
Acid regurgitation	20 (100.0)	10[a] (50.0)	10[a] (50.0)	20 (100.0)	12[a] (60.0)	13[a] (65.0)	24 (100.0)	10[a] (41.7)	16[a] (66.7)

Notes: GERD: gastroesophageal reflux disease. [a]$P < 0.05$: within group comparison with respect to baseline value; [b]borderline significant difference versus A. vera group at the respective time point; [c]between-group comparison at respective time point (week 2 or 4) in the A. vera group.

Table 3 Reported adverse events in the study groups [*n* (%)]

Item	Aloe vera	Omeprazole	Ranitidine
Headache	0 (0.0)	1 (4.0)	0 (0.0)
Constipation	0 (0.0)	1 (4.0)	1 (4.5)
Heartburn	0 (0.0)	1 (4.0)	2 (9.1)
Vertigo	1 (3.8)	0 (0.0)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	2 (9.1)
Stomachache	1 (3.8)	0 (0.0)	0 (0.0)
Tenesmus	0 (0.0)	0 (0.0)	0 (0.0)
None	24 (92.3)	23 (88.0)	19 (86.4)

tric juice, acid and pepsin, and inhibit acute gastric lesions in rats.[25] Another study in rats with gastric ulcers showed that treatment with A. vera reduced leukocyte adherence to postcapillary venules, elevated serum concentrations of interleukin-10, and reduced serum tumor necrosis factor-α (TNF-α). In addition, histopathological examination revealed reduced gastric inflammation and ulcer size, and enhanced epithelial cell proliferation and gastric gland growth following A. vera treatment. These protective effects of A. vera were comparable to those of the standard drug sucralfate.[17]

Oxidative stress and inflammation have been implicated as key factors in the pathophysiology of GERD.[26] The efficacy of A. vera gel in reducing the symptoms of GERD might thus be partly attributable to its antioxidant and anti-inflammatory ingredients.[27] A. vera possesses antioxidant capacity and was shown to reduce oxidative damage in several experimental models, including CCL_4-induced hepatotoxicity and chronic liver fibrosis.[28] There are several mechanisms responsible for the antioxidant actions of A. vera, including scavenging of free radicals, reduction of lipid peroxidation and up-regulation of antioxidant enzymes.[27,29,30] In addition, leukocyte infiltration and circulating concentrations of TNF-α were significantly reduced following administration of A. vera to Helicobacter pylori-infected mice.[31] Of relevance to its role in gastrointestinal disorders, A. vera has shown strong antimicrobial effects against H. pylori,[19] as well as having a reducing effect on gastric acid secretion.[32] This effect has been proposed to be associated with the action of lectins present in A. vera, which inhibit aminopyrin uptake by parietal cells, thereby reducing acid secretion.[33]

The results of the present study indicated that consumption of A. vera was safe and well tolerated, and unlike the comparator treatments, its use was not associated with treatment withdrawal. This plant has been classified as Generally Recognized As Safe based on clinical evidence and a long ethnobotanical history supporting its safety. Furthermore, A. vera preparations are relatively inexpensive and widely available, and have been shown to possess therapeutic activities against several other disorders that commonly accompany GERD, such as peptic ulcers,[16,17] irritable bowel syndrome,[34] ulcerative colitis,[35] type 2 diabetes[9,10] and dyslipidemia.[9,10]

To conclude, the results of this pilot, randomized controlled trial indicate that A. vera syrup provides a safe and effective treatment for reducing the frequency of GERD symptoms. A. vera should therefore be suggested as an effective supplement in patients suffering from GERD. Further studies are needed to investigate the impact of treatment with higher doses of A. vera, and also to explore the efficacy of A. vera treatment in reducing long-term complications of GERD such as Barrett's esophagus, esophageal strictures, erosive esophagitis and esophageal carcinoma.

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