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Research Article

Effect of *Aloe Vera* and Pantoprazole on Gastroesophageal Reflux Symptoms in Mustard Gas Victims: A Randomized Controlled Trial

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ABSTRACT

Background: Gastro-esophageal reflux disease (GERD) is a common complaint of sulphur mustard (SM)-exposed subjects. Routine treatments such as proton-pump inhibitors (PPIs), H_2-blockers and anti-acids cannot control GERD symptoms completely. *Aloe vera* is a medicinal plant that has been shown to reduce gastric acid secretion. The efficacy of pantoprazole with or without *A. Vera* juice in alleviating GERD symptoms was investigated in SM-exposed subjects.

Methods: Male patients with a history of SM exposure and diagnosed GERD were enrolled and assigned to treatment with pantoprazole (40 mg before breakfast) plus *A. vera* syrup (5 mL bid before breakfast and at bedtime) (n=44), or pantoprazole alone (40 mg before breakfast) (n=41) for a period of 6 weeks. GERD symptoms were assessed at baseline and weeks 3 and 6 of study using the Reflux Symptom Index (RSI) questionnaire.

Results: Seventy-five patients (n=38 and 37 in the *A. vera* + pantoprazloe and pantoprazole group, respectively) completed the study. No significant difference was found between the groups regarding demographic characteristics and baseline RSI score ($p>0.05$). A decreasing trend in RSI score was observed in both groups by the 3rd and 6th week of study ($p<0.001$). There was a greater reduction of RSI score in the *A. vera* + pantoprazloe versus pantoprazole group ($p<0.001$). There was no report of any side effects from *A. vera* during the course of trial.

Conclusion: Findings of the present study suggested a significant improvement in the severity of GERD symptoms in SM-exposed subjects following addition of *A. Vera* to pantoprazole.

Introduction

Sulfur mustard (SM) is a chemical warfare agent that was frequently used in the Iraq-Iran War (1980-1988) against Iranian civilians and military forces. Currently, about 34,000 Iranians suffer from the long-term side effects of SM. SM complications are mainly in the lungs, eyes and skin.[1] Another complication of SM exposure is gastro-esophageal reflux disease (GERD). It has been shown that the prevalence of esophagitis in SM-exposed subjects is about 70%.[2] GERD-related micro-aspiration is also prevalent in these patients.[3] On the other hand, some drugs that are used in these patients, such as theophylline, can cause GERD.[4] It has been suggested that GERD may contribute to the exacerbations of bronchiolitis obliterans which is one of the most common complications of SM exposure.[5]

Currently, proton pump inhibitors such as pantoprazole are among the most widely administered treatments of GERD.[6] Although these drugs are effective, a proportion of patients experience inadequate response to treatment, and experience adverse effects such as neutropenia,[7] hip fracture (in at-risk patients),[8] *Clostridium difficile* infection,[9] and interstitial nephritis in long-term use.[10] Therefore, there is a need to new and safe therapies for long-term use in SM-exposed subjects who are resistant or intolerant to proton pump inhibitors.[11]

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In the traditional Chinese medicine (TCM), Kampo (traditional Japanese medicine), Ayurveda (traditional medicine in India), Iranian traditional medicine and traditional African medicine, different herbs are used to treat heartburn, regurgitation, nausea and vomiting.[12-16] *Aloe vera* is a cactus plant that belongs to the Liliaceae family. There are more than 300 species of this family but only 2 species (*Aloe barbadensis* Miller and *Aloe aborescens*) have been studied.[17]. Some documented therapeutic effects of this plant are anti-inflammatory;[18,19] anti-bacterial;[20] anti-oxidant [21] and hypoglycemic effects.[22] In limited experimental studies, the effects of *A. vera* juice on gastrointestinal parameters such as gastric acid secretion have been shown.[23] Also, it has been reported that *A. vera* has cytoprotective effects on gastric mucosa through induction of endogenous prostaglandin production.[24] The aim of this study was to compare the efficacy of oral pantoprazole with and without *A. vera* juice in the treatment of GERD symptoms in SM-exposed subjects.

Methods

This study was designed as a randomized open-label trial in male SM-exposed veterans who referred to the Lung Clinic of the Baqiyatallah Hospital (Tehran, Iran) during 2011-2012.

Inclusion criteria were evidence of exposure to SM and presence of GERD signs and symptoms confirmed by physician, age > 40 years. Exclusion criteria were presence of hematemesis, odynophagia, other gastrointestinal disorders (e.g. peptic ulcer, irritable bowel syndrome and obstructive diseases), hepatic diseases, malnutrition syndrome or hematologic diseases, use of muscle relaxant drugs (e.g. anticholinergic agents or calcium channel blockers), history of hypersensitivity to pantoprazole or *A. vera* preparations, lack of concurrent participation in another study, and not taking the study medications for more than one week.

Eligible subjects were all male and divided into two groups: the first group received pantoprazole tablet (Chemidaru Pharmaceutical Co., Tehran, Iran; 40 mg in the morning; n= 44) and *A. vera* syrup (Barij essence Pharmaceutical Co., Kashan, Iran; 5 mL bid in the morning and at bedtime; n=41). The second group only received pantoprazole tablet at a dose similar to the first group. All subjects underwent the treatment protocol for 6 weeks and their clinical symptoms were assessed by Reflux Symptom Index (RSI) questionnaire at baseline and weeks 3 and 6 of the study.

RSI questionnaire included 9 questions with 5 answers for each question, yielding a score range of 0 to 45. Higher scores indicated a more severe disease. A score below 10 is usually considered as being treatment-responsive or symptom-free.[25] During the period of treatment, patients were evaluated for the incidence of adverse events. The study protocol was approved by the institutional Ethics Committee and written informed consent was obtained from participants.

Statistical analyses were performed using SPSS software version 20. Normality of data was checked using the Kolmogorov-Smirnov test. Group comparisons were made using paired *t*-test and Repeated Measures ANOVA. A two-sided *p*-value < 0.05 were considered as statistically significant.

Results

Seventy-five patients completed the study (38 in the *A. vera* group and 37 in the control group). Mean baseline RSI in all patients was 28.35±8.67. Demographic characteristics of patients in each group are listed in Table 1. There was no significant difference between the study groups in terms of age, BMI, and history of smoking and using anti-reflux medications at baseline. Those subjects with the history of anti-reflux treatment before inclusion to the trial were still symptomatic and their disease was not controlled in spite of treatment.

Table 1. Demographic characteristics of patients in the study groups.

	***Aloe vera* + pantoprazole**	**Pantoprazole**	***p*-Value**
Age (Mean ± SD)	49 ± 5.93	48.02 ± 4.29	0.30
BMI (Mean ± SD)	26.92 ± 3.96	27.49 ± 3.47	0.10
Smoking history	13.6%	9.8%	0.07
Anti-reflux drug history	61.4 %	51.2 %	0.10
RSI score	29.09 ± 8.11	27.55 ± 9.29	

Values are expressed as mean ± SD.

Table 2. RSI scores at baseline, and weeks 3 and 6 of the study.

	RSI baseline	**RSI week 3**	**RSI week 6**
***Aloe vera* + pantoprazole**	29.09 ±8.11	12.28±7.21	5.17±3.64
Pantoprazole	27.55±9.29	14.28±9.79	11.89±9.99

Values are expressed as mean ± SD. P<0.001 according to repeated-measures ANOVA.

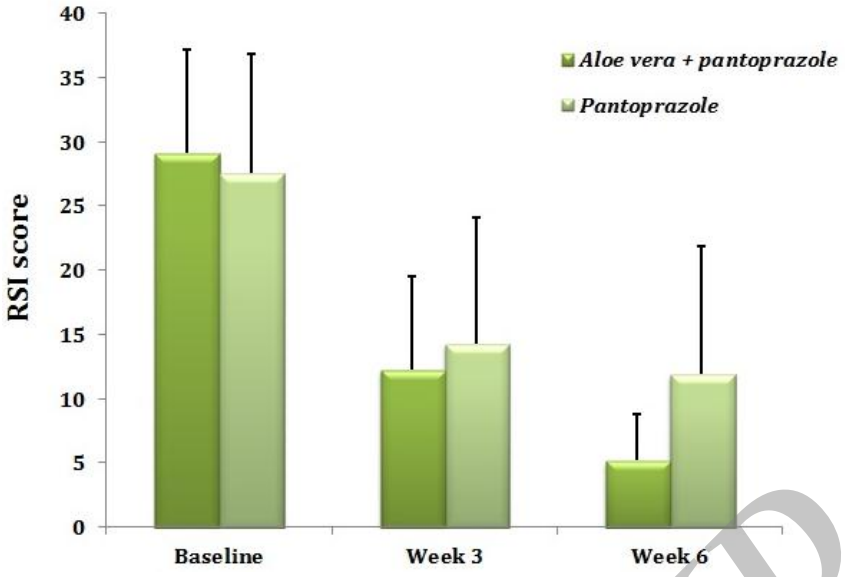

Figure 1. RSI scores at baseline, and weeks 3 and 6 of the study. Values are expressed as mean ± SD.

Likewise, baseline RSI score was not significantly different between the study groups. (p=0.420). In both groups, there was a significant decreasing trend in the RSI score from baseline to weeks 3 and 6 of the study. Repeated-measures ANOVA indicated a significantly greater reduction of RSI score in the *A. vera* compared with the control group (p<0.001) (Table 2; Figure 1). In the *A. vera* group, 71.87% of patients had RSI score < 10 at the end of trial, while in the control group 65.62% reached RSI < 10 at the end of trial. Despite the numerically greater number of patients with RSI score < 10 in the *A. vera* versus control group, this difference did not reach statistical significance (p=0.487). Patients did not report any side effects from *A. vera* during the course of study.

Discussion

In this randomized open-label clinical trial, we evaluated the efficacy of pantoprazole with or without *A. vera* in decreasing GERD symptoms in SM-exposed victims. In spite of the high prevalence of GERD, gastritis and microaspiration,[5] these complications are undertreated in SM-exposed subjects. To the authors' knowledge, although the beneficial effects of *A. vera* in improving GERD symptoms have been reported, no study has yet explored the efficacy of *A. vera* as adjunct to pantoprazole for controlling GERD symptoms, neither in mustard-exposed nor in any other type of population.

The use of complementary and alternative medicine, in particular herbal medicine, has always been an indispensible solution to increase the efficacy and reduce the adverse effects of synthetic drugs in various diseases.[11] In a previous animal study, Yusuf et al. showed that *A. vera* can inhibit gastric acid secretion. Increased mucus synthesis, bicarbonate secretion and mucus layer blood flow were suggested as potential mechanisms for the anti-acid activity of *A. vera*. It has also been shown that *A. vera* can block histamine H_2 receptors in parietal cell.[23] Aside from inhibition of acid secretion, *A. vera* can inhibit prostaglandin $F_2\alpha$ and thromboxane B_2 production, leukocyte adhesion and neutrophil migration in peptic ulcer disease. Also, *A. vera* has cytoprotective effects through increasing endogenous prostaglandins such as prostaglandin E_2, and accelerating ulcer healing via promotion of angiogenesis and reduction of vasoconstriction.[24]

In line with the present findings, a previous case-series of patients with proton pump inhibitor-resistant GERD showed that treatment with *A. vera* syrup (45 mL bid before breakfast and bedtime) for 2 weeks improves the symptoms as early as one week post-treatment, and has no side effects.[26]

Conclusion

In conclusion, findings of the present study suggested a significant improvement in the severity of GERD symptoms in SM-exposed subjects following addition of *A. vera* to pantoprazole compared with pantoprazole monotherapy. Whether higher doses of *A. vera* could cause improvements within a shorter time period remains to be investigated in future studies. In addition, future studies are required to confirm the present questionnaire-based findings using endoscopic, pH monitoring, manometric and histopathological assessments.

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Conflict of interests

The authors claim that there is no conflict of interest. The authors are thankful to the Barij essence Pharmaceutical Co. (Kashan, Iran) and Chemidaru Pharmaceutical Co. (Tehran, Iran) for providing the study medications.

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