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RESEARCH ARTICLE

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Efficacy of *Sagi* (a Persian Medicine-Based Mouthwash) in Recurrent Aphthous Stomatitis: A Double-Blind Randomized Placebo-Controlled Clinical Trial

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ABSTRACT

Background: Recurrent aphthous stomatitis (RAS) is a common oral disease. *Sagi* is one of the natural remedies of traditional Persian medicine that has been used as an antiseptic mouthwash. We designed a randomized, placebo controlled clinical trial to evaluate the efficacy of *Sagi* in management of RAS.

Material and Methods: In this randomized, double arm, double blind, placebo-controlled clinical trial, 26 patients received *Sagi* mouthwash as intervention group and 26 patients received placebo as the control group for four consecutive days. Primary outcome measure the pain severity of lesions assessed by visual analogue scale (VAS). The size of the aphthous lesions as another outcome was also measured via millimeter paper.

Results: Regarding within-group changes, a significant decrease was observed in the scores of pain in both group of the study ($p<0.05$). Moreover, a significant decrease was observed in the size of lesions in *Sagi* group ($p=0.003$). However, no such change was seen in the placebo group ($p=0.075$) (Table 2). According to independent sample t test, there was a significant difference in the mean change of pain score over the study period in the *Sagi* group compared with the placebo group ($p=0.004$).

Conclusion: According to the results of this study, it seems that *Sagi* mouthwash could improve the symptoms of RAS compared to placebo.

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KEYWORDS

Sagi (a Persian medicine-based mouthwash), Recurrent aphthous stomatitis, Clinical trial.

INTRODUCTION

Recurring aphthous stomatitis (RAS) is a chronic oral disease with persistent development of one or more different, painful, typically curable ulcers within one or two weeks (1). Some patients may experience such frequent episodes per year. They have almost continuous ulcer activity which can be very annoying (2).

RAS is seen all over the world, with the highest prevalence in the Middle East, South Asia and Mediterranean region. In North America, it is seen approximately in one out of five persons and is the most common cause of acute recurrent oral ulcers (3). The pathogenesis of RAS is unknown. Immune dysregulation, genetic predisposition, vitamin and mineral deficiencies, emotional stress, infectious etiologies and Several medications have been reported to play a role in aphthous ulcers growth (4). The goals of treatment of this disease are pain relief, accelerate the ulcers' healing, and decrease the severity and frequency of episodes. However, there is no definite therapy for RAS, and systemic or topical agents such as corticosteroids have been used with variable response (5). Therefore, researches to find more effective remedy are ongoing.

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Traditional and complementary medicine remedies, particularly herbal medicine, are among the suggested options for diseases with no definite therapy (6-9). There are several herbal therapies for the aphthous stomatitis which should be surveyed by scientific methods. *Sagi* is one of the natural remedies of traditional Persian medicine that has been used as an antiseptic mouthwash (10). The oak galls (*Quercus infectoria* G. Olivier), pomegranate peel (*Punica granatum* L.), gum arabic (*Acacia Arabica*), and alum are the components of Sagi. Previous studies have shown antimicrobial activity of these components. For example, alum can significantly decrease the size of aphthous lesions, severity of pain and accelerate the recovery of patients with RAS (11). Nevertheless, the efficacy of this compound herbal remedy has not been evaluated in RAS. Therefore, we also devised a randomized clinical trial managed by placebo to test Sagi's effectiveness in RAS management.

MATERIALS AND METHODS

Trial design

This study was a double-arm, double-blind, placebo-controlled randomized clinical trial. In this research, we investigated the effectiveness of Sagi mouthwash supplementation in the treatment of RAS patients. There were no improvements in the procedures since the start of the experiment.

Participants

The research was done in the Department of Oral Diseases at the Yazd University of Medical Sciences, Iran.

The participants' eligibility criteria covered male and female aged 14 to 50 years with a verified clinical diagnosis of RAS (according to a dentist clinical diagnosis). In fact, researchers could not use any other therapy until the study for their aphthous lesions. Both patients have signed the informed study consent form. The exclusion criterion included concomitant treatment with the procedure, non-compliance with the test plan, serious side effects and lack of fallow up.

Sagi preparation

The oak galls (*Quercus infectoria* G. Olivier), pomegranate peel (*Punica granatum* L.), gum arabic (*Acacia Arabica*), and alum were purchased from a local herbal market in Yazd, Iran. Samples were authenticated at the Herbarium of Faculty of Pharmacy, Yazd University of Medical Sciences, where the voucher specimens were deposited under No. Ssu0046, Ssu0045, and Ssu005 for *Quercus infectoria* G. Olivier, *Punica granatum* L., *Acacia Arabica* respectively. We powdered all three plants and mixed them together, then added water to the powder to change the consistency of the mouthwash.

Intervention

Two different classes were assigned to the participants. Sagi mouthwash was randomly distributed to the intervention group, or they got placebo mouthwash as the control group. For both classes, patients were instructed to rinse their mouths with 15 cc of the medications (e.g. Sagi or placebo) every six hours and keep the solution for their mouths for 30, 4 consecutive days. The drugs were packed with the same shape, size and weight in the bottles. More than 70 percent of the bottles in the study were considered as patients' non-adherence. Both patients in both classes have used Persica mouthwash because of ethical concerns. Persica (a marketable herbal mouthwash) is used as a regular stomatitis treatment in Iran (12, 13).

Outcome measures

The primary finding of this clinical research was the magnitude of pain in visual analog scale (VAS) lesions. The lesions were also weighed by a millimeter of paper as a further test. The secondary result was the side effects of the operation. Both patients were asked to report side effects such as allergic reactions.

Randomization and blinding

Convenient sampling was performed from all qualifying RAS patients who referred to the Yazd University of Medical Sciences dentistry school clinic. Fifty-two qualifying patients were randomized by researchers using a random number table in two parallel groups. The allocation of the intervention was blinded to dentists, patients and data analysts.

STATISTICAL METHODS

Data analysis was done using Statistical Package for the Social Sciences software, version 21 (SPSS Inc., Chicago, IL, USA). The means and standard deviations of the dependent outcomes were described distinctly for each group. The paired *t*-test was used for comparison of means before and after the intervention in each group. Independent sample *t*-test was used to determine the means changes in outcomes between the two groups of the study. P values less than 0.05 was considered significant.

Ethical issues

The study was performed in compliance with the Helsinki Declaration (2008 revised) and the Ethics Committee of the Yazd University of Medical Sciences (IR.SSU.REC.1396.182). In fact, the trial was registered with the following code by the Iranian

Registry of Clinical Trials: IRCT20190408043200N1. Before inclusion in the study, all patients signed the informed consent form.

RESULTS

Participants recruitment and flow

From July 2019 to February 2020, 56 patients were evaluated for eligibility. Fifty-two of them had the inclusion criteria. Twenty-six patients were assigned to the Sagi group and 26 to the placebo group. Figure 1 is a flow chart demonstrating the patients' screening, enrollment, allocation, follow-up, and analysis.

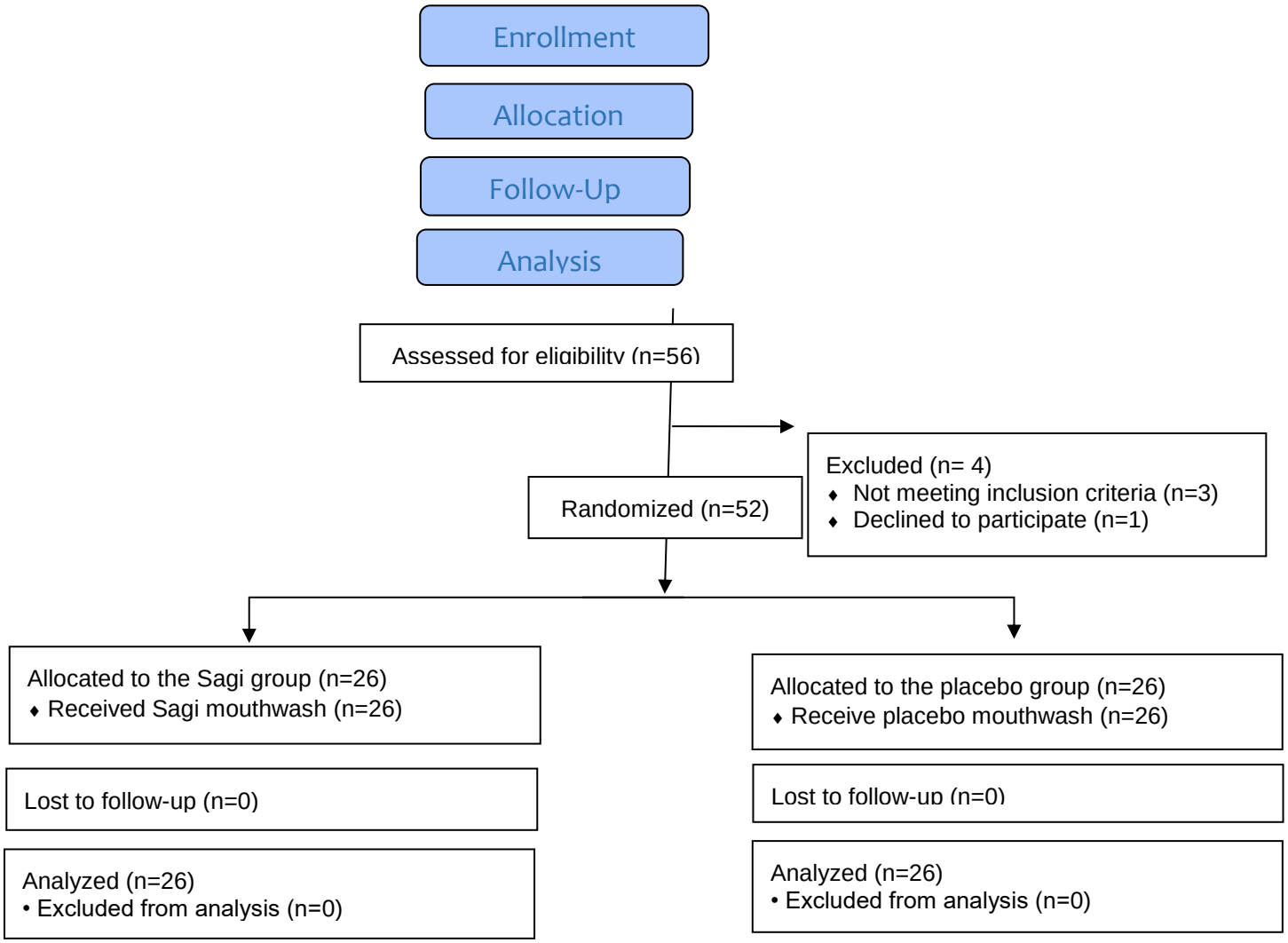

Figure 1. Flow diagram of the patients' enrolment, groups' allocation, follow up, and final analysis

Baseline data

The mean age of the patients was 29.36±8.15 and 29.64±6.65 years in the Sagi and placebo groups, respectively that did not show significant difference between groups (p value=0.895). Other baseline demographic data are shown in Table 1. According to Table 1, there was no significant difference in baseline characteristics between the two groups of the study (p>0.05).

Table 1. Baseline demographic data and clinical features of the trial participants

Baseline Characteristics	Sagi group (N=26)	Placebo group (N=26)	P- value
Age (Year), Mean (±SD)	29.36±8.15	29.64±6.65	0.895
Sex (Male/Female) (N)	12/14	10/16	0.779
The mean number of lesions	1.82±1.16	1.84±1.31	0.940
The mean number of recurrence per year	3.42±2.53	3.26±2.82	0.837

Clinical response

Regarding within-group changes, a significant decrease was observed in the scores of pain in both group of the study (p<0.05). Moreover, a significant decrease was observed in the size of lesions in Sagi group (p=0.003). However, no such change was seen in the placebo group (p=0.075) (Table 2). According to independent sample t test, there was a significant difference in the mean change of pain score over the study period in the Sagi group compared with the placebo group (p=0.004).

Table 2: Result of Pain score and Lesion size before and after intervention

		Groups		
		Sagi	**Placebo**	**P value$^{\mu}$**
Pain score	Before	5.26±1.99	3.84±1.84	0.010
	After	3.00±1.67	3.15±1.99	0.764
	P value*	0.000	0.017	
Lesion size (mm)	Before	5.48±1.98	4.71±1.66	0.193
	After	3.92±2.51	4.07±1.85	0.800
	P value*	0.003	0.075	

μ: p value resulted from independent sample *t*-test

*: p value resulted from paired sample *t*-test

DISCUSSION

In this study, the effectiveness of the Sagi in treating RAS patients was tested in a randomized, double-blind, placebo-controlled clinical trial. Sagi may increase RAS pain in comparison with placebo.

Medicinal plants have typically been used to cure aphthous ulcers in Persian medicine, such as Carthamus tinctorius, Arnebia euchroma, Portulaca oleracea, Punica granatum, and morus alba (14). Some of these herbal remedies is Sagi, which is mixed with oak galls and pomegranate peel (Punica granatum L.), gum arabic (Acacia Arabica), and alum.

While no research on the efficacy of Sagi on RAS has been performed so far, studies have investigated the impact of Sagi components separately. Rafieian et al. tested the impact of topical alum treatment on aphthous ulcers in a two-blind, randomized, placebo-controlled clinical trial (11). Fifty females received random mucosal adhesive patches in two groups, packaged in five days in two simple formats and in aluminum-containing patches. Recovery time, pain frequency and lesion size changes were reported. The estimated cumulative recovery time was 7.52 days in an alum group and 12.2 days in a placebo group. By contrast with placebo, lesions were slightly lower by size and pain frequency after aluminum therapy. The findings of our research correspond to your sample. The only exception was that we did not test the full rehabilitation time in our analysis. In another study, Gavanji et al tested the efficacy of P. granatum extracts on small RAS as a natural therapy using the double-blind experimental approach (15). We found that P. granatum alcoholic and water extracts had a major therapeutic effect on mild RAS.

CONCLUSION

According to the findings of this study, Sagi mouthwash seems to be able to boost RAS symptoms over placebo. Nonetheless, further clinical tests with greater samples and longer research length are needed for a clearer evaluation of their effectiveness and health.

STUDY LIMITATIONS

A significant drawback of this analysis was the low sample size. We also propose that subsequent experiments of a greater sample size be undertaken. Another disadvantage is the lack of understanding of the full healing of lesions in the report. The effectiveness of the therapy drug can be seen best by faster wound healing. Apart from the aforementioned

drawbacks of the research, the use of a placebo group in this experiment is a positive idea, and the restriction of open-label clinical studies with potential prejudice did not threaten this experiment.

CONFLICT OF INTEREST

None of the authors has a conflict of interest to declare.

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