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Efficacy of propolis mouth wash for treatment of recurrent aphthous stomatitis

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ABSTRACT

Introduction: Recurrent aphthous stomatitis (RAS) is an oral lesion in the form of round or oval, single or multiple painful inflammatory ulcers in the non-keratinized mucosa. The etiology of RAS has not yet to be clearly identified; however, inflammatory process mediated by the action of free radicals and oxidative stress is a possible mechanism. This study aimed to assess the efficacy of propolis for treatment and decrease in frequency of RAS.

Materials and Methods: This triple-blind, placebo-controlled clinical trial was conducted on 45 patients with RAS. Patients were divided into two groups of intervention (n=22, propolis) and control (n=23, placebo). Total antioxidant status (TAS) and level of superoxide dismutase (SOD) and glutathione peroxidase (GPx) of the saliva were measured at baseline and three months after the intervention. Number, size and location of ulcers, pain intensity according to a numerical scale, the healing time and salivary flow rate were assessed at three months compared to baseline. Data were analyzed using Mann Whitney and t-tests.

Results: Significant differences were noted between the two groups of propolis and placebo and also within each group at three months compared to baseline in terms of number and size of ulcers, the intensity of pain, the frequency of occurrence and the healing time (P<0.001). TAS (P=0.909), SOD (P=0.943) and GPx (P=0.094) were changed but were not significantly different before and after the intervention. The difference in salivary flow rate was not significant either (P=0.153). No complication occurred in any group.

Conclusion: Propolis mouthwash can be effective for prevention and treatment of RAS.

Key words: Antioxidants, Recurrent aphtouse Stomatitis, propolis, Saliva, treatment.

Introduction

Recurrent aphthous stomatitis, commonly known as canker sore, is among the most common oral mucosal conditions. The prevalence of this ulcerative, painful non-keratinized oral mucosal lesion varies from 5 to 66% with a mean of 20% in the general population. It has a slightly higher prevalence in females and also in higher socioeconomic classes. The onset of RAS in 80% of the cases is before the age of 30 [1-4]. It only involves the non-keratinized oral mucosa in the form of single or multiple painful ulcers with an erythematous margin with no other sign and symptom [5,6]. The exact etiology of this condition has yet to be identified but a recent theory suggests that free radicals may play a role in development of RAS by triggering oxidative stress [7].

Evidence shows that an imbalance between the level of free radicals and reactive oxygen species plays a critical role in initiation and progression of oral inflammatory lesions [8]. Considering the role of oxidative stress in inflammatory conditions and the inflammatory nature of RAS, oxidative stress appears to play a role in development of RAS as well [9].

Since no definite etiology has been identified, treatment of RAS is non-specific and symptomatic [10]. At present, the currently used standard medications for RAS include analgesics, anesthetizers, anti-inflammatory drugs, disinfectants, steroids, Sucralfate, tetracycline, silver nitrate and immunoregulatory drugs [11]. However, none of the currently used medications result in definite treatment. RAS has a good prognosis and can spontaneously heal within a couple of days. However, it causes problems in eating, speech, deglutition and tongue movement, which decrease the quality of life of patients and negatively affect the physical and mental aspects of quality of life [11]. Considering the limited efficacy of the available treatments for RAS and the side effects of chemical drugs, this study aimed to introduce a new treatment for RAS.

Propolis is a food supplement available over the counter. It contains flavonoids, which are capable of activating the immune system and have antimicrobial and anti-oxidant properties as well as free-radical scavenging ability [12-14]. Propolis has been used for treatment of inflammatory and ulcerative diseases with successful results [3,15,16]. Propolis has shown to have no or minimal side effects and only a few cases of contact dermatitis have been reported [14,17]. It has long been used for treatment of oral ulcers in traditional medicine in the Middle East. Samet et al. reported a significant reduction in the frequency of occurrence of ulcers following the use of 500mg propolis daily [18].

Considering the need for a treatment for RAS and the side effects of available chemical medications, this study aimed to assess the efficacy of propolis mouthwash for treatment of RAS. The effect of propolis mouthwash on salivary TAS, SOD and GPx and number, size and location of ulcers, pain intensity, the healing time, frequency of occurrence and salivary flow rate were also assessed at three months.

Materials and Methods

This randomized controlled clinical trial was approved in the Ethics Committee of Tehran University of Medical Sciences and registered in Ir.TUMS.REC1392.654 and all the patients signed informed consent. This study was conducted on patients between 18 to 60 years presenting to the Oral Medicine Department of School of Dentistry. Sample size was calculated to be 22 subjects in each group according to a study by Samet et al, [18] and using Minitab software considering α=0.05 and β=0.2 with a minimum significant difference in 4 lesions and standard deviation of 3.5. Forty-five patients with RAS including 18 males (40%) and 27 females (60%) with a mean age of 27.6±7.3 years (range 18 to 53) were divided into two groups of intervention (n=22) and control (n=23) using balanced block randomization method. Subjects were thoroughly informed about the study and written informed consent was signed by them. Subjects who were capable of filling out the consent form and had a history of RAS for at least three times a year or had an active aphthous ulcer (in its first to third day of occurrence in their mouth according to the diagnosis of an oral medicine specialist were included.

The exclusion criteria were any local or systemic disease such as diabetes mellitus, hepatitis, hypertension, cardiac disease, arthroplasty, rheumatic fever, mental disorders, tuberculosis, jaundice, cerebrovascular accident, renal diseases and AIDS, dyspnea, use of immunosuppressive agents or systemic steroids in the past three months or local steroid therapy in the past one month, use of folic acid containing drugs, anti-oxidants, nutritional supplements such as minerals and multivitamins in the past three months, Behcet's disease, any inflammatory-vesicular disease, pregnancy and nursing.

Saliva sampling: Non-stimulated saliva was obtained from patients at 8-11 a.m in the oral medicine department. Subjects were asked to refrain from eating, drinking, smoking or tooth brushing for 60 minutes prior to sampling. Also, subjects were requested to refrain from eating high carbohydrate or caffeine foods and drinks and were asked to rinse their mouth 10 minutes prior to sampling. They were seated on a chair with their head bending forward and saliva was collected in sterile, screw top, plastic falcon tubes using the spitting method. Three milliliters of saliva was collected. Time to reach this volume was measured by a chronometer to assess the salivary flow rate. By dividing the saliva volume by the time spent to collect this amount, the salivary flow rate was calculated in minutes [9]. After collection, the tube was capped, placed over dry ice and transferred to a laboratory. The samples were centrifuged at 3000 rpm at 4°C for 10 minutes and stored

at -20°C until the experiment.

Patients were clinically examined and the level of pain and burning sensation of ulcers was assessed before and after the intervention using a numerical scale. The scale was comprised of a 10cm line with 0 indicating no pain and 10 indicating maximum pain. The patients expressed their level of pain and burning sensation using this scale. Scores 1-3 indicated mild, 4-6 indicated moderate and 7-10 indicated severe pain.

Salivary TAS, SOD and GPx were assessed using Biorex diagnostic kit, Pars Pakhsh co. Made in Switzerlan, and spectrophotometry, Hatch co. Made in England. In the first session, level of pain of each patient was determined using the numerical scale and demographic information of subjects including age, gender and occupation and medical history, presence or absence of RAS lesions at the time of saliva sampling, number and location of lesions, frequency of occurrence of RAS, size of lesions in millimeter (using a ruler), healing time and history of any kind of allergy were all recorded. Patients were ensured about the confidentiality of their information. The treatment protocol was triple blind in such a way that in the intervention group, bottles containing 3% propolis mouthwash and in the control group, bottles containing placebo were administered. Propolis, Sorentech Co. Mashhad. Iran, and placebo were both poured into similar bottles and coded. A third party was only aware of the codes. The patient, the examiner and the analyzer were not aware of the content of bottles (propolis or placebo). Patients were instructed not to use any other medication during the course of study (such as antibiotics, antiseptics, or analgesics) due to possible drug interference or cross-reactions. Also, patients were informed about the possible allergic reactions secondary to the consumption of mouthwash and were instructed to discontinue its use if any allergic reaction occurred. Subjects were instructed to use the mouthwash three times a day for three months at a specific time. Also, they were instructed to rinse saline solution for 30 seconds prior to using the mouthwash and then fill the bottle cup up to the indicator line, rinse the mouthwash for 5 minutes and then swallow it. They were requested to refrain from eating and drinking for 30 minutes afterwards. Patients were contacted by phone every month to know about the occurrence of new RAS lesions, level of pain, frequency of occurrence of lesions and number of lesions. At baseline and at three months (end of intervention), saliva samples were collected from patients and TAS and level of SOD and GPx were assessed in the saliva.

Statistical analysis

Quantitative variables were reported as mean and standard deviation. Qualitative variables were reported as number and percentage. To compare quantitative variables between the two groups, first normality of variables was tested using Shapiro-Wilk test. For variables with normal distribution, Student's t-test and for variables with non-normal distribution, Mann Whitney test were used. The difference in each variable at three months compared to baseline was calculated and the mean values were compared between the two groups. Pearson and Chi square tests were used to compare qualitative variables between the two groups. Fisher's exact test was also applied wherever appropriate. All data were analyzed using SPSS version 21 (Microsoft, IL, USA) and $P<0.001$ was considered statistically significant.

Results

A total of 45 patients with RAS were evaluated; out of which, 15 had RAS at the time of saliva sampling while 30 did not have aphthous lesions at the time but reported a history of RAS for more than three times a year. The intervention group comprised of 22 RAS patients (48%) including 14 females (63.6%) and 8 males (36.4%) with a mean age of 28.18±7 years (range 18 to 53 years). The control group included 23 RAS patients (51.1%) including 13 females (56.5%) and 10 males (43.5%) with a mean age of 21.13±6 years (range 18 to 43). Oral and dental examinations revealed that 21 patients (46.7%) had very good, 21 (46.7%) had moderate and 3 (6.7%) had poor oral hygiene. There were 41 (91.1%) non-smokers and 4 (8.9%) smokers. Also, 24 (53.3%) subjects reported RAS in at least one first-degree relative while 21 (46.7%) reported no family history of RAS. The main causes of RAS (as believed by the patients) were stress (82.2%), nutrition (35.6%), trauma (11.1%), hormonal changes (6.7%) and dry mouth (6.7%).

Number of aphthous lesions: Before the intervention, 10 in the intervention (25.5%) and 5 in the control (21.7%) group had RAS. After the intervention, 6 (36.4%) in the intervention ($P=0.092$) and 20 (86.9%) in the control group had RAS. Number of aphthous lesions in the two groups of propolis and placebo was not significantly different at baseline; but after the intervention, number of new aphthous lesions was significantly less in the intervention (propolis) group

(P<0.001).

Location of aphthous ulcers: In terms of the location of aphthous lesions, no significant difference was noted between the two groups before or after the intervention. The most common site of involvement was buccal mucosa before and non-keratinized lip mucosa after the intervention (P=53.3).

Size of aphthous ulcers: Size of lesions was not significantly different between the two groups before the intervention. After the intervention, lesions in the intervention group were significantly smaller than in the placebo group (P<0.001).

Frequency of occurrence: No significant difference was found between the intervention and control groups in frequency of occurrence of aphthous lesions at baseline. However, after the intervention, this difference was statistically significant. In the intervention group, the frequency of occurrence of aphthous lesions significantly decreased from shorter than once every two weeks to longer than once every three months (P<0.00).

Healing time: No significant difference was noted in healing time of aphthous ulcers between the two groups at baseline. After the intervention, the healing time in the propolis group was significantly shorter than in the placebo group (P<0.001). Sixteen subjects in the intervention group did not develop RAS at all for three months and of 6 subjects who developed RAS during the three months, 5 made a full recovery in less than a week.

Intensity of pain: No significant difference was noted in the intensity of pain of aphthous ulcers between the two groups at baseline. But, after the intervention, the intensity of pain was significantly less in the intervention group (P<0.001). One subject in the intervention group reported no pain at all when developed an aphthous ulcer and the remaining 5 reported mild to moderate pain. Based on the numerical scale, the two groups were not significantly different in terms of pain on the first day after developing the ulcer before the intervention. After the intervention (on the first day after developing the ulcer), the pain score was significantly lower in the intervention group (P<0.001). Before the intervention, on the third day after development of ulcers, the two groups were not significantly different in terms of pain scores. However, after the intervention, the intervention group had significantly lower pain score on the third day after the occurrence of ulcers (P<0.01). The same result was obtained with regard to the level of pain on the 7th day after the occurrence of ulcers (P<0.001).

Salivary antioxidants: At the end of the study, 10 patients were lost to follow-up. In the remaining 35 patients, TAS and level of SOD and GPx were not significantly different before and after the intervention (Table 1). As seen in Table 1, TAS increased and level of SOD and GPx decreased in the intervention group. However, these changes were not significant.

Discussion

Recurrent aphthous stomatitis is a common oral mucosal condition with an unclear pathogenesis. Since the etiology of aphthous ulcers has not yet been fully understood, a definite treatment for this condition does not exist. Recent studies have shown that the oxidative stress due to an oxidant/anti-oxidant imbalance can play a role in its occurrence. Considering the role of oxidative stress in development of inflammatory lesions, it appears to play a role in the occurrence of RAS, since it is also an oral inflammatory condition.

Considering the high prevalence of RAS, the probable role of oxidative stress in its occurrence and absence of a definite treatment, this study aimed to assess the efficacy of propolis mouthwash for treatment of RAS as a new therapeutic strategy. The results showed significant differences in number and size of lesions, frequency of occurrence, healing time and intensity of pain in the intervention group compared to controls.

The efficacy of propolis for treatment of RAS has also been discussed in a few previous studies. Samet et al, [18] in a double blind clinical trial in 2007 evaluated the efficacy of daily use of 500mg propolis capsules by 19 patients with RAS for 6 months. They reported a significant reduction in number and healing time of aphthous ulcers and an improvement of quality of life of subjects in the interventation group. patients reported lower frequency of RAS during the 6-month study period. Over 50% reduction in the frequency of RAS was noted in 60% of patients in the propolis and 11% of subjects in the placebo group. Also, the intensity of pain in both groups decreased by 50%; but the difference in this regard was not significant between the two groups. These findings were attributed to the positive effect of propolis on the immune system of patients. Their results were in accord with our findings [18]. Fa'iz A Al-Sultan [19] in 2003 evaluated the effect of different concentrations of propolis extract and topical

dexamethasone on RAS. He reported that both topical dexamethasone and propolis extract significantly accelerated the healing of aphthous ulcers; which is also in line with our results. Although most studies state that a minimum of 10 days is required for complete healing of RAS, in the study by Fa'iz A Al-Sultan 50% of patients that used propolis extract and topical dexamethasone made a full recovery after 5 days versus 20% of controls that used placebo. Faster healing in these patients can indicate the role of immunological disorders in development of RAS. This result has also been confirmed in another study [6]; although the latter recommended a minimum dose of 1% for propolis mouthwash/extract. In the current study, we considered 700 mg/kg as the daily effective dosage for propolis [20]. Propolis mouthwash (3%) was administered in our intervention group patients and no side effect was reported in this group. However, Fa'iz A Al-Sultan reported side effects such as redness and itching of oral mucosa following the use of propolis extract (0.5% and 1%) that it made with [19]. It appears that side effects are related to the geographical source from which, the propolis is derived rather than its concentration. Ali and Abdul Rasool [21]. They investigate buccal pastes in different formulation with different combinations of propolis, sesame oil and olive oil, in terms of formulation and clinical efficacy. Both formulations caused a significant reduction in pain in the intervention compared to the placebo group at one day after use. Also, propolis significantly shortened the healing time and decreased the size of ulcers compared to the placebo group. Our study results also showed the same results after three months of using the propolis mouthwash. Khan et al. [22] discussed that patients with a family history of RAS reported at least one of the external predisposing factors. In our patients, thermal, physical and chemical stress and trauma due to foods were among the most common causes of RAS. One patient in our study reported a possible cause to be menstruation and hormonal changes; this relation has been previously reported as well [22].

Karincaoglu et al. [23] showed an increase in catalase in the saliva and a reduction in catalase and SOD of serum in patients with RAS. Momen-Beitollahi et al. [24] compared the level of SOD, GPx and catalase in erythrocytes and TAS of plasma and saliva in RAS patients and controls and reported that the level of SOD was lower in RAS patients but no significant difference was noted in terms of GPx, catalase and TAS. They concluded that the antioxidant system of saliva and plasma is not a suitable index for assessment of RAS patients. Gupta et al, [25] also reported an association between the serum level of antioxidants and development of RAS and showed that the serum levels of SOD and GPx were lower while the serum level of CAT was higher in RAS patients compared to controls. Considering all the above, it can be concluded that TAS is often not significantly different in RAS patients and controls [9,24,26-28], while SOD, which is an antioxidant with enzymatic activity, often has a lower serum level and higher salivary level in RAS patients [23-25,29]. We did not find any difference in TAS between the intervention and control subjects, which confirms the findings of previous studies [24,26-28]; but we did not find any significant difference with regard to SOD. We also assessed the salivary level of GPx, which showed a reduction (although not significant) in the RAS patients. Karincaoglu et al. [23] analyzed antioxidant enzymes and reported significant amounts of SOD, catalase and GPx in the saliva of patients with RAS. They discussed that the reduction in immunity enzyme levels of plasma and their increase in saliva may be due to the fact that at the time of occurrence of aphthous ulcers, defense mechanisms of the saliva, which act via the antioxidant agents, attract the reservoir antioxidants to the area. In general, all these studies focus on the accumulation of antioxidant enzymes in the saliva of patients with RAS and the protective role of these enzymes in control of these lesions. In our study, these three parameters did not show any significant change in any of the two groups. This result may be due to the fact that as stated in previous studies [24], the salivary antioxidant system is not a suitable measure for assessment of TAS in patients with RAS. Although some changes were noted in the salivary level of these parameters, these changes were not significant; this indicates that propolis mouthwash can prevent the occurrence and enhance the healing of minor aphthous ulcers that are not due to a specific systemic condition. However, it cannot quantitatively affect the salivary antioxidants. Also, it was found that propolis mouthwash was not effective on increasing the salivary flow rate for treatment of xerostomia.

This study had some limitations. Finding patients that met our inclusion criteria was difficult. Also, due to the unpleasant taste of mouthwash, most patients were reluctant to swallow it after rinsing. This resulted in some cases of dropouts. Future investigations on larger sample sizes are required to assess the efficacy of different types and concentrations of propolis. Also, attempts must be made to produce a propolis mouthwash with a more pleasant taste and consistency.

The two groups of propolis and placebo were not significantly different in TAS (P=0.9), SOD (P=0.9) and GPx (P=0.9) (Figures 1-3). Also, the salivary flow rate was not significantly different before and after the intervention or between the two groups of intervention and control (P=0.1).

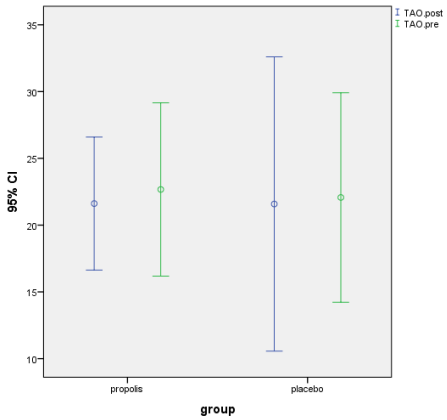

Figure 1. Error bar of the mean and 95% CI of TAS of saliva before and after the intervention.

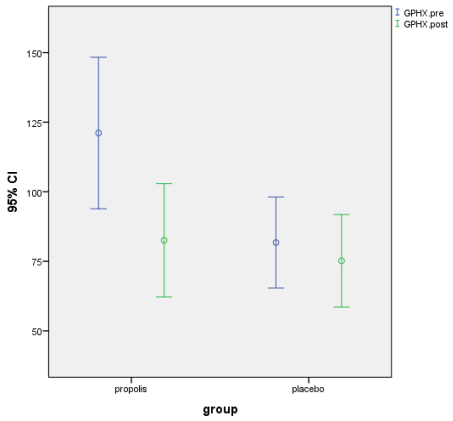

Figure 2. Error bar of the mean and 95% CI of GPx of saliva before and after the intervention.

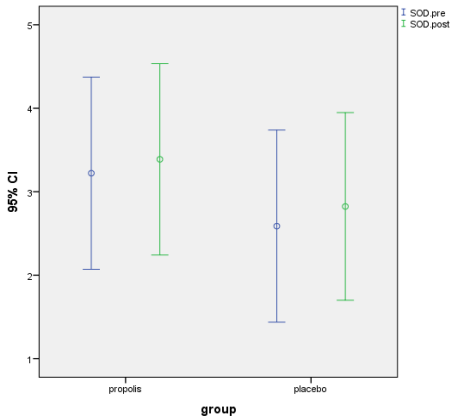

Figure 3. Error bar of the mean and 95% CI of SOD of saliva before and after the intervention.

Conclusion

This study showed that propolis mouthwash significantly decreased the number and size of aphthous ulcers, the severity of pain and the healing time.In addition, the frequency of occurrence of ulcers decreased. However, it had no significant effect on TAS, SOD or GPx; although it resulted in a significant improvement in the intervention group. Propolis had no effect on salivary flow rate.

Table 1. Comparison of TAS, SOD and GPx in the two groups of propolis and placebo.

Group		N	Minimum	Maximum	Mean	Std. Deviation
Propolis	Age	22	18.0	53.0	28.182	7.9859
	GPx.pre	22	51.10	238.50	116.1218	50.87824
	GPx.post	18	31.70	170.30	82.5644	40.98506
	TAS.pre	22	4.70	51.30	23.1805	12.07572
	TAS.post	18	6.30	40.29	21.6150	10.01817
	SOD.pre	22	0.00	8.00	3.1818	2.32249
	SOD.post	18	0.00	8.00	3.3889	2.30444
	Group	22	1	1	1.00	0.000
	Unstimulative saliva.rate.pre	22	.14	1.34	.4982	.33769
	Unstimulative saliva.rate.post	18	.21	1.33	.5844	.31109
	Valid N (listwise)	18				
Placebo	Age	23	18.0	43.0	27.130	6.7373
	GPx.pre	23	10.19	136.30	84.1157	33.73131
	GPx.post	17	17.00	153.30	75.1682	32.41570
	TAS.pre	23	4.30	56.40	20.3213	15.10178
	TAS.post	17	1.00	84.00	21.5824	21.42479
	SOD.pre	23	0.00	8.00	2.4783	2.37160
	SOD.post	17	0.00	7.00	2.8235	2.18619
	Group	23	2	2	2.00	0.000
	S.rate.pre	23	.16	2.05	.6539	.55161
	S.rate.post	17	.16	2.00	.6712	.50113

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