COMPARISON EFFECTIVENESS OF THE BIOADHESIVE PASTE CONTAINING LICORICE 5% WITH BIOADHESIVE PASTE WITHOUT DRUG IN THE MANAGEMENT OF RECURRENT APHTHOUS STOMATITIS

VAJEHALLAH RAEESI[1], FATEME ARBABI-KALATI*, NARJES AKBARI[2], HAMED HAMISHEKAR[3]
[1]Assistant Professor, Department of Internal Medicine, Birjand University of Medical Sciences, Birjand, Iran - *Oral medicine department, Zahedan University of Medical Sciences, Zahedan Iran - [2]Dental Research Center, Birand University of Medical Sciences, Birand Iran - [3]Drug Applied Research Center, Tabriz University of Medical Sciences

ABSTRACT

Background*: Recurrent aphthous stomatitis (RAS) is one of the most common oral mucosa diseases.*

The treatment of RAS is principally directed towards reducing the pain and duration of each episode of ulceration. This study evaluated the efficacy of licorice bioadhesive paste 5% to control the pain and reduce the necrotic zone and erythematose and healing time of Recurrent aphthous ulcer.

Methods*: We performed a randomized,double blind,clinical study. A total of 60 patients, with a history of recurrent aphthous stomatitis and currently suffering from ulceration were selected from patients referred to the School of Dentistry in Zahedan. The patients divided three groups.*

A) group with routin managment. B) group with Licorice bioadhesive paste 5%,C) group with bioadhesive paste without Licorice.

The effects of the following variable were investigated: pain, Area of the Lesion and necrotic zone and Time of the complete healing of the ulcers.

Result*: Recorded data using statistical software 19spss version using test Paired T Test, T-Test student and ANOVA for repeated data assessment was performed. A significant reduction in VAS was Recorded following application of the Licorce Bioadhesive paste 5% on days 1, 3, 5 compared control and placebo groups.*

Licorce Bioadhesive paste 5% cause a significant reduction in the area of necrotic zone in 1,3, 5 compared with control group.

Conclusion*: According to the results of this study , Licorce paste can be effective in the reduction of pain and of the necrotic zone of RAS.*

Key words*: Recurrent Aphthous Stomatitis (RAS), Licorice bioadhesive past.*

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Introduction

Recurrent Aphthous stomatitis(RAS) is an inflammatory disease with unknown etiology. It appears with single or multiple oral ulcer, RAS is the most common oral ulcer. It is reported to occur in 5-25% of the normal population but depending upon the group examine it my affected 50% of the population[1,2].

Local soreness and pain are classical prodromal symptoms that appear 24-48 hours before occurrence of ulcer, a typical aphthous ulcer is a painful round or oval lesion a bout 1- 5 mm with necrotic center covered with yellow grayish pseudomembrane and there is an erythematous halo[1,2].

Base on clinical appearance, RAS is divided to 3 groups : minor, major and herpetic form[3,4].

Minor ulcer is the most common type and seen in 80% of patients. The diameter of these ulcer are 3-10 mm and heating without scar in 7-14 days. These lesions make severe pain in eating or speaking[5, 6].

In spite of wide studies carried out for RAS, the etiology of it is unknown, but most affected people are healthy but trauma, stress, family history, atopy, drug reaction, hormonal factor, immunological disorder and microbial factor, may play a role in etiology of disease[7, 8].

There is no definitive cure for RAS and treatment usually focus on reduction of pain and healing time of lesions. Different methods are used, palliative therapy is used for minor ulcer and topical glucocorticoids are used for major ulcers.

Till now topical steroid is the best method for management of RAS, it seems has many side effects including fungal infection, mucosal atrophy and systemic absorption. Licorice is one of the most herbal drug in Iran. Glicric acid in licorice can inhibit an enzymatic way of cycloxigenaz and lipoxigenaz. In the other hand, it can prevent the production of oxygen free radical also prevents of cell immigration, the recent event results in inhibit of arachidonic acid metabolism. All of them reduce inflammatory reaction[9]. Licorice has been used in the treatment of various rang from tuberculosis to peptic ulcer, but there is a few study about licorice effect on oral lesions, so we design this study to evaluate the effect of bioadhesive paste containing 5% licorice extract in management of RAS.

Methods

S*tudy design*

This randomised controlled double blind study has been carried out 60 patients with RAS. They were recently reffered to the clinic of oral medicine at the school of dentistry in Zahedan University of Medical Sciences (zaums), Zahedan, Iran for regular visits during the April of 2010. This study was approved by Ethical committee of Zahedan University of medical sciences before the patient's enrolled.

All patients filled and signed consent forms. This study is registered on Iranian Registry of clinicul trial and its code is IRCT 201011273133 N2, it is available on www.irct.it and www.who.int/trialsearch

Patient selection

The inclusion criteria was presence of painful aphthous ulcer without parstisia or anasteasia.The exclusion criteria were systemic disease, pregnancy, systemic drug therapy for RAS during 3 past months, topical drug therapy. Also patient with major ulcer, patients who have suffered lesions more than one day, patients who have more than one lesion were excluded.

Study procedure

Before procedure all patients under went careful examination by an oral medicine specialist. Patients were divided in 3 groups by block randomization method.

Patients in group A received routine palliative therapy (including dephenhydramin mouth wash).

Group B: patients received bioadhesive paste containing 5% of licorice extract, 4 times in a day. Three times after meal and one time before sleeping for 5 days. We advised patients to keep away of eating, drinking and smoking for an hour after applying drug.

Patients in group C were treated by bioadhesive paste without licorice extract which were similar in shape, taste and color to licorice tape. Patients, applied drug in same way as patients in group B.

For evaluating the efficacy of treatment, pain, size of ulcer with erythematous halos, and necrosis diameter were recorded by the blind examiner on 0, 1, 3, 5 days of study.

Visual analogues scale (VAS) was used for pain evaluation the patients were requested to record the level of pain of ulcer in follow up period.

The size of ulcer with erythematous halos, and necrosis zone were measured with periodontal prob.

The bioadhesive paste

The grounds roots of liqourice were defatted using n-hexan and then obtained powder were dried using rotary evaporator. Extraction was done by 50% methanol solution using maceration technique. Obtained extraction was filtrated and then dried in rotary evaporator (Heidolph, Laborota 4002). Deglycyrrhinization was done in acidic medium. For this mean, powders were purred in distillated water and pH adjusted with 20% sulfuric acid solution. Finally precipitated glycyrrhizine was separated from the medium. For neutralization of the medium, calcium hydroxide was also added. Obtained extraction was dried in rotary evaporator and used for preparation of bioadhesive formulate[10].

Licorice extract powder, gelatin, pectin and sodium carboxy methyl cellulose were milled in a plenary ball mill (PM100, Retsch, Germany) and sieved in an automatic sieve shaker (AS200,

Retsch, Germany). The size fractions under 45 μm were separated and dried an overnight in a 60 ºC oven (Behdad, Iran) for complete dehydration. The same proportion of mucoadhesive excipients (gelatin, pectin and NaCMC) were mixed together completely after addition of licorice extract (5% w/w of total formulation weight). Powders were mixed with Plastibase (5% poly ethylene in liquid paraffin) in the ratio of 40/60 at 2000 rpm (IKA, Germany) until a substantially homogeneous ointment was obtained. A placebo formulation were prepared in the same method without licorice extract. Both formulations were filled into the identical tubes and coded randomly to be used in the double blind manner.

Statistical analysis

Data were analyzed by spss version 19, statistical significancy was tested by student t test, paired t test and repeat measurement ANOVA, the level of statistical significance was set at a tow-tailed value of 0.05

Results

Sixty patients enrolled in this study were divided in three groups. Demographic data of the patients showed in table 1, as the table shows distribution of age, sex and most common place of lesions were the same in different groups.

Previous drug therapy for RAS from highest to lowest were diphenhydramin (31/7%), herbal drugs (21/7%), topical corticosteroid (18/3%) and antibiotics (3/3%),fifteen patients (20%) didn't use any drug before that.

Analytic results of this study for degree of pain, necrotic zone, size of lesion with erythemathous halo and healing time are presented as follows:

Degree of pain

At the beginning of the study, there was no difference in degree of pain between Groups (p=0.7), figure1.

On 1st, 3rd and 5th days of study statistically significant differences were observed in degree of pain (p <0.001).

Post hoc Tukey analyzed showed in a day after treatment. There was statistically significant difference between group B and group C as well as between group A and group C (p <0.001). But there was no statistically significant difference between group A and group C (p =0.1), pain decreased in group B.

		group			Total
		control	licorice	placebo	
sex	female	13	18	16	47
		65.0%	90.0%	80.00%	78.30%
	male	7	2	4	13
		35.0%	10.0%	20.0%	21.70%
Age		24.30	26.80	24.45	25.18
location	lip	11	14	11	36
		55%	70%	55%	60%
buccal		3	4	8	15
		15%	20%	40%	25%
Floor of the mouth		0	1	0	1
		00%	5%	0%	1.7%
palate		1	1	1	1
		5%	5%	5%	5%
Mucobucal fold		5	0	0	5
		25%	0%	0%	8.3%
frequency	≤3 in year	6	9	13	28
		30%	45%	65%	46.7%
	4-5 in year	8	9	5	22
		40%	45%	25%	36.7%
	5-10 in year	6	2	2	10
		30%	10%	10%	15%

Table 1: demographic characteristic of patients.

After 3rd and 5th days of treatment there were statistically significant difference between group B and group A as well as between group B and group C (p <0.001) and between group C and group A, pain reduction in group C was more than group A.

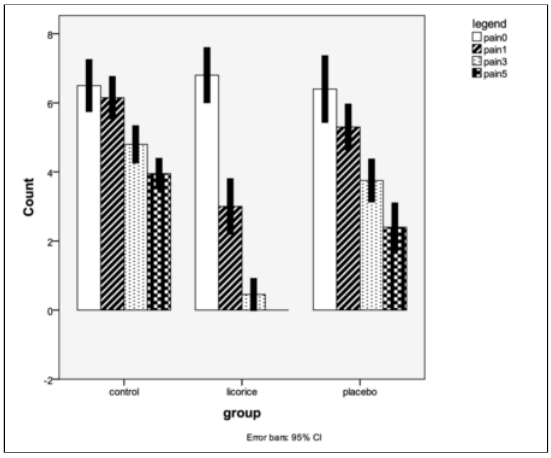

Figure 1: pain intensively in three groups of patient.

Necrotic zone

There was no statistically difference between groups before treatment (p=0.06), figure 2.

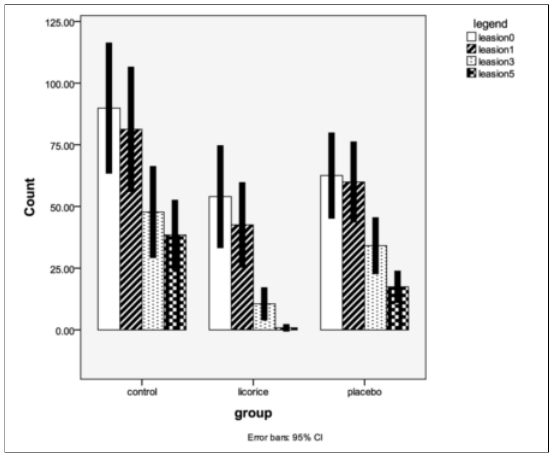

Figure 2: necrotic zone in three groups of patient.

During 1st, 3rd and 5th days of study, there was statistically significant difference between groups.

Post hoc Tukey showed, in a day after treatment reduction in necrotic zone was statistically significant between group A and group B (p=0.01), it was smaller in group B. there was no significant difference between group A and group C (p=0.2) and between group B and group C (p=0.4) .In three days after treatment, there was statistically significant difference between group A and group B (p <0.001) as well as between group B and group C (p=0.02), necrotic zone was smaller in group B . There was no difference between group A and group C (p=0.2).

In five days after treatment there was statistically significant difference between group A and group B (p <0.001), group A and group C (p=0.003) as well as between group B and group C (p=0.02).

Size of lesion with erythematous halo

In the beginning of study, there was no statistically significant difference between groups (p=0.5) and either in one day after treatment (p=0.6)

After three and five days of treatment there was statistically significant difference between groups(figure 3).

Post hoc Tukey showed after three and five days of treatment there was statistically significant difference between group A and group B as well as between group B and group C (p <0.001), Size of ulcer with erythematous halo in group B was smaller, but there was no statistically difference between group A and C (p=0.9).

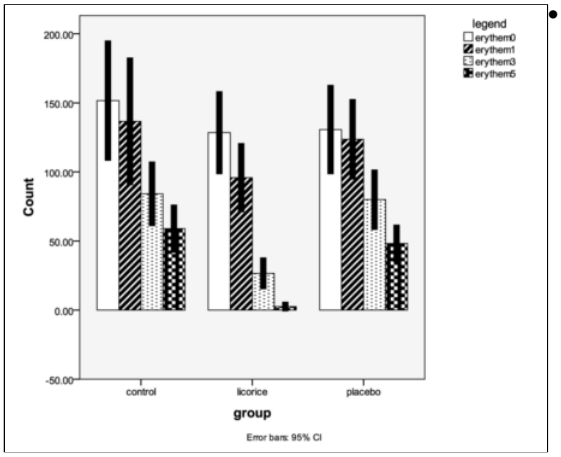

Figure 3: Size of lesion with erythematous halo in three groups of patient.

Healing time

Mean of healing time were 9.2 1.2 days, 4.2 1.3 days and 7.45 1.3 days in group A, B and C respectively. There was statistically significant different between groups (p< 0.05).

Discussion

This clinical trial has been evaluated the efficacy of oral paste containing 5% licorice extract in the treatment of the RAS ,our results showed that topical licorice has a quick and significant beneficial effect in control of pain and size of lesions without side effect.

RAS is a recurrent painful oral ulcer and despite small size can be very painful, there is no curative treatment for RAS and its management is largely toward symptomatic pain relief, so quick reduction pain in patients of group B is very important and valuable results[11].

Licorice is a plant with very anti-inflammatory effects and was used for treatment of many diseases. Different mechanisms were explained for its anti-inflammatory effect including inhibition of glucostroid metabolism and complement[12].

Moghaddamnia et al used bioadhesine pachte containing 1% licorice extract for treatment of RAS. They showed this therapy reduced pain and size of lesion, but compared with the bioadhesine patch without drug this reduction was not significant[11]. They concluded patch therapy was effective on pain control and licorice was not useful, but in this study in group B reduction in nectrotic zone, erythematous halo and pain were significantly more than group A and group C.

Also in our study, healing time in group B was about 4 days and in group C was 7 days and in group A was 9 days.

Saeedi and et al used gels contining 1% and 2% of licorice extract in treatment of atopic dermatitis, their results showed gel contining 2% licorice was effective in reduction of edema, erytheam and itching more than 1% licorice gel. This may be explained difference between our results and Moghaddamnia's study probably anti-inflammatory effect of licorice is dose depended.[13].

Burges and et al showed dissolving oral patch can have the same effect as amelexanox[14]. Because preparation of oral paste with high dose of licorice is difficult. So, the same study with oral rinse or dissolving tablet is suggested.

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Corresponding author
FATEME ARBABI-KALATI
E-mail: F-kalati@yahoo.com