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Evaluation of the efficacy of *Echinacea* on clinical indices of Erosive Oral Lichen Planus: A randomized double-blind clinical trial

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ABSTRACT

Background: Oral lichen planus (OLP) is a chronic immune-mediated mucocutaneous disorder, with an unknown etiology. Since, both pain and discomfort are observed in patients with the erosive type, many drugs have been studied to alleviate pain and clinical symptoms. The present study aimed to assess the effectiveness of systemic *Echinacea* on clinical indices of OLP.

Materials and Methods: In this randomized, double-blind, placebo-controlled trial, 70 patients with erosive OLP were randomly divided into two groups, and each was treated with *Echinacea* tablets or placebo, 3 times a day, for 35 days. In addition, betamethasone lotion (0.1%) or nystatin (100,000 units) mouthwash were used by patients. The pain severity (visual analog scale [VAS]), lesion size, and the number of lesions were assessed at baseline and on days 10, 25, and 35 after study initiation. Finally, the obtained data were analyzed by statistical software, and Mann–Whitney test, Wilcoxon test, KaplanMeier, Chi-squared, and paired *t*-test.

Results: The VAS scores in the *Echinacea* group were significantly reduced at each visit compared to the placebo group ($P < 0.001$). We observed a significant difference between the two groups ($P < 0.01$).

Conclusion: We showed that *Echinacea* is an effective and complementary therapy for OLP. Furthermore, in short-term usage, *Echinacea* is almost completely tolerable.

Key Words: *Echinacea purpurea*, lichen planus, visual analog scale pain, wound healing

INTRODUCTION

Oral lichen planus (OLP) is a common chronic mucocutaneous disorder and its pattern varies according to different types of the lesion including reticular, papular, plaque-like, bullous, atrophic, and erosive.[1,2] Lesions involve buccal mucosa in 80%–90% of cases.[3] Erosive OLP is the most advanced type of OLP with atrophic and erythematous ulcers covered by pseudomembrane, mucosal erosion, and white lace-like patterns.[4] About 0.4%–3.7% of lesions develop malignancy and atrophic and erosive types show more malignancy potential which results in a worse prognosis.[5,6]

Although the etiology of OLP is still unknown, the dysregulation of the T-cell mediated immune system is the most likely cause.[7,8] It has been shown that the upregulation of cytokines such as Tumor necrosis factor-α (TNF-α), interferon-ɣ (IFN-ɣ), and

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interleukin-1 (IL-1) is mostly responsible for the occurrence of OLP.[9,10]

Even though various therapeutic approaches have been provided to reduce pain and heal the lesions, corticosteroids have been the cornerstone drug for OLP management.[11] Other treatment modalities such as calcitonin inhibitors, immunostimulators, retinoids, low-level laser therapy, and photodynamic therapy have also been used to treat OLP.[12]

However, despite the common use of corticosteroids, various side effects including adrenal suppression, secondary candidiasis, and increased blood pressure may occur.[11] Due to the reported side effects, many herbal drugs with anti-inflammatory and antioxidant effects have been suggested for the management of OLP.[13]

Echinacea is one of the medicinal plants which has been known for its immunomodulation effects. It has also shown anti-inflammatory, anti-oxidative, anticarcinogenic, antimicrobial, antihypertensive, and antidiabetic properties. Furthermore, it has been recognized to have minimum toxicity and side effects and is safe for a wide range of patients.[14,15]

Its anti-inflammatory activity is performed through the downregulation of important inflammatory mediators such as TNF-α, IL-1 β, IL-6, IL-8, IFN-γ, and increased production of anti-inflammatory cytokines such as IL-4 and IL-10.[16-18]

Even though OLP is one of the common inflammatory diseases of oral mucosa and the use of corticosteroids has various side effects in reducing pain and clinical symptoms of OLP, no study was found on use of *Echinacea purpurea* extract in the management of OLP. Accordingly, this study aimed to evaluate the efficiency of systemic *E. purpurea* extract in the management of erosive OLP.

MATERIALS AND METHODS

Participants

In this randomized, double-blind, placebo-controlled trial, 70 patients with at least one erosive OLP lesion (20–60 years old) were selected who were referred to Department of oral medicine, Isfahan Dental School. The Thongprasom score[19] more than one was included in this study. The exclusion criteria were as follows: presence of any malignant or viral involvements in the mouth; the presence of extra OLP lesions; a history of receiving topical therapy for OLP in the last 2 weeks; life-threatening and systemic diseases such as diabetes, high blood pressure, ulcerative colitis, and Crohn's disease; a history of organ transplant; pregnancy and lactation.

Interventions, randomization, and blinding

In this randomized double-blind clinical trial, 70 patients with erosive OLP randomly (simple randomization and block randomization) divided into two groups (Groups A and B). Each patient in group A was instructed to take an Echinacea tablet (Immustim, Goldaru corporation, Isfahan, Iran, consisted of 114 mg of dried extract of leachate shoots of Echinacea) and a table spoon (15 ml) of mouthwash containing a spoon (15 ml) of diphenhydramine HCL elixir 12.5 mg/5 ml (diphenhydramine, Pursina Pharmaceutical Co., Tehran, Iran), nystatin oral drop 100,000 units (Nistat, Jaber Ebne Hayyan Pharmaceutical Co., Tehran, Iran) (20–25 drops), betamethasone lotion 0.1% (Betamethasone-Najo 0.1%, Iran Najo, Tehran, Iran) (5–10 drops) and a spoon of aluminum-magnesium suspension 240 mg/ml (Pursina Pharmaceutical Co., Tehran, Iran) every 8 hour for 5 weeks and group B were instructed to take a placebo tablet with the same mouthwash as group A every 8 h for 5 weeks.

The patients were asked to use the medication after eating and washing their mouth and not to eat, drink, or smoke for at least 30 min later. Both patient and clinician were double blinded for the type of medication.

Clinical assessment

The assessment was performed at 10.25 and 35 days after baseline for the severity of pain (visual analog scale-[VAS]), lesion size, and the number of lesions by a clinician who was blind to patients allocated groups. The lesion size was measured in each visit according to the Thongprasom *et al*. criteria as follows: 5 = white striae with erosive area more than 1 cm^2; 4 = white striae with an erosive area <1 cm^2; 3 = white striae with atrophic area more than 1 cm^2; 2 = white striae with an atrophic area <1 cm^2; 1 = mild white striae, no erythematous area; 0 = no lesion, normal mucosa.[20] Patients ranked the severity of pain and burning sensation on a 10 cm VAS from 0 (no pain) to 10 (extreme pain) at the baseline and each visit. In each visit, patients were asked about any side effects such as nausea, vomiting, abdominal pain, and constipation after taking the prescribed drugs by a checklist.

Statistical analysis

The obtained data were analyzed by SPSS version 20.0 (SPSS, Inc., Chicago, IL, United States). Data were expressed in terms of mean and standard deviation (mean ± standard deviation) or frequencies and percentages. Due to nonnormal distribution in each treatment group, we used the Mann–Whitney test to compare means between groups and the Wilcoxon test was administered to compare means within groups at different intervals. KaplanMeier, survival analysis, Chi-squared, and paired *t*-test were performed as well ($\alpha = 0.05$).

Ethical considerations

All participants were informed about the study and signed a consent form according to the Declaration of Helsinki ethical standards. The ethical code was IRCT20200223046591N1.

RESULTS

70 patients participated, 54 females and 16 males with the age range of 20–60 years (50.36 ± 7.82) completed the study without dropping outs. The demographic characteristics are listed in Table l.

Complete healing of erosive lesions (score 0 of Thongprasom criteria) was observed in 16 cases in the *Echinacea* group and the final VAS score was reduced to 0.

The Thongprasom score, VAS score, and the number of lesions were reduced in both groups at the first, second, and third visits, and there was significant difference ($P < 0.001$) between the two groups at each visit [Table 2 and Figures 1, 2]. Furthermore, the adverse effects (abdominal pain) were observed in 3 cases in the *Echinacea* group.

Table 1: Demographic and baseline characteristics of the subjects in two treatment groups

Characteristics	*Echinacea*	Placebo	*P*
Age (years), mean±SD	51.71±7.04	49.00±8.42	0.14
Male, *n* (%)	10 (28.6)	6 (17.1)	-
Female, *n* (%)	25 (71.4)	29 (82.9)	-
Pain at baseline VAS (mean±SD)	5.91±2.13	5.83±1.46	0.73
Thongprasom score (mean±SD)	3.11±0.47	3.17±0.56	0.64
Number of lesions (mean±SD)	2.14±1.37	2.00±1.00	0.98

SD: Standard deviation, VAS: Visual analog scale

Table 2: Comparison between the two study groups regarding visual analog scale score, thongprasom score, and the number of lesions at baseline and after 35 days (third visit)

Groups	Mean±SD		*P*
	Echinacea	Placebo	
VAS score			
Baseline	5.91±2.13	5.83±1.46	0.73
Third visit	1.77±1.97	4.74±1.19	0.00
Thongprasom score			
Baseline	3.11±0.47	3.17±0.56	0.64
Third visit	1.20±1.25	2.60±0.55	0.00
Number of lesion			
Baseline	2.14±1.37	2.00±1.00	0.98
Third visit	0.66±0.76	1.74±0.88	0.00

SD: Standard deviation, VAS: Visual analog scale

DISCUSSION

Several medications have been used for OLP including corticosteroids, retinoids, laser, and phototherapy.[21,22] Due to the side effects of corticosteroids, attention has been paid to alternative drugs. Herbal medicine could be a good choice considering its anti-inflammatory and antioxidant properties.[23] Various studies have discussed the efficacy of different herbal drugs versus corticosteroids in treating OLP. *Echinacea* is widely used to prevent or provide early treatments for colds.[24] The role of *Echinacea* on the immune system is mostly through affecting the innate immune responses. There are also reports of anti-oxidant and anti-inflammatory effects induced by *Echinacea*,[25,26] and the present study results could be explained by them.

Different components of this herbal drug (including caffeic acid derivatives, phenols, chicoric acid, and polysaccharides) have been shown to play a role in immune-mediated pathways and therefore affect inflammation or oxidation processes.[14] For example, in a study conducted in 2005, topical *Echinacea* was administered on vocal fold injuries of animal subjects. The results of this study revealed that the healing of vocal fold wounds in the *Echinacea* group is accompanied by a more stable hyaluronan content compared with the control group. This could be explained with the antihyaluronidase properties of caffeic acid in *Echinacea* which could have also affected the OLP lesions healing process.[27] Moreover, *Echinacea* can cause to decrease serum levels of cytokine such as IL-6 and IL-1-beta.[28] Furthermore, the results of the research done by Sun *et al*. indicate that patients with OLP have higher levels of IL-6 compared with healthy controls. They also reported that treatment with levamisole and Chinese herbs can reduce serum

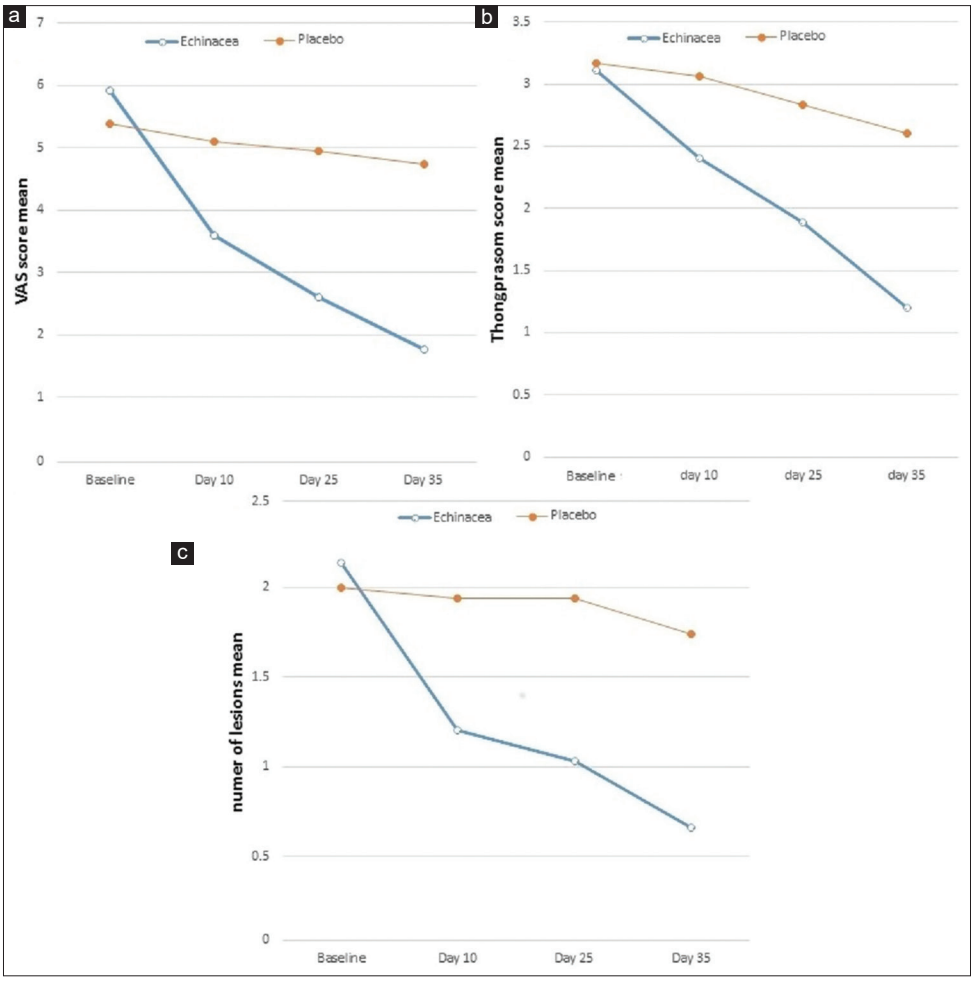

Figure 1: The mean visual analog scale score (a), Thongprasom score (b), and number of lesions (c) in two groups in 35 days.

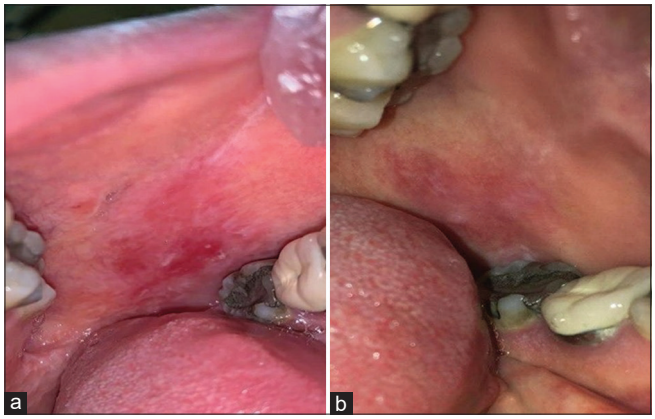

Figure 2: The clinical appearance of the lesion at the baseline (a) and 3rd visit (b).

IL-6 levels.[29] This could be another mechanism by which *Echinacea* is effective in OLP treatment.

There are currently no studies on the role of *Echinacea* in treating OLP, and therefore, no comparison can be made. However, considering other oral conditions, *Echinacea* tablets have been used to treat recurrent oral aphthous ulcers and have been proven to be effective on the number of lesions, pain intensity, and rate of complete improvement.[30] Furthermore, according to a study by Oláh *et al.*, application of topical *Echinacea* extract was significantly more effective than placebo in alleviating symptoms and disease intensity in atopic eczema patients.[31]

In the present study, *Echinacea* was associated with more patient-reported adverse effects than placebo. These adverse effects included three cases of abdominal pain. In general, adverse effects are not commonly reported with using *Echinacea* and short-term usage is either completely safe or could be associated with mild and reversible side effects. The most frequent adverse effects are rashes and gastrointestinal upsets which were observed in our patients.[32]

The limitations of the present study are the small sample size as well as short-time following-up of the

patients. However, this study provides information for better management of OLP, especially in cases where herbal medicines are preferred.

CONCLUSION

Echinacea is an effective complementary therapy for OLP. Furthermore, in short-term usage, *Echinacea* is almost completely tolerable.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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