

Original Article

Efficacy and Safety of Topical Chamomile in Treatment of Oral Lichen Planus

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Abstract

Background: Management of oral lichen planus remains a clinical challenge. Topical corticosteroids are considered as the first-line therapy, but have undesirable side effects. Chamomile is a herbal remedy that has high treatment success potential due to its anti-oxidant, anti-inflammatory and anti-cancer properties.

Aim: This study aimed to assess the clinical effectiveness of topical chamomile cream versus triamcinolone acetonide in the management of OLP.

Subjects and Methods: This RCT included 34 patients with OLP who were randomly assigned to receive either 2% chamomile cream or 0.1% triamcinolone acetonide in orabase. The outcomes assessed were pain reduction measured by the numerical rating scale and clinical improvement assessed by Thongprasom scale. Patients were evaluated at baseline, after 2, and 4 weeks of treatment.

Results: There was a statistically significant improvement in pain score, total lesion size and Thongprasom score in both groups. However, comparison between the 2 groups resulted in no significant difference for all the outcomes, although TA had a better and faster clinical effect than Chamomile.

Conclusion: Topical application of 2% chamomile cream can be used as a second line-treatment for OLP.

Key words: Lichen planus; Chamomile; RCT; Triamcinolone Acetonide.

Introduction

Oral lichen planus (OLP) is a chronic inflammatory T cell-mediated disease affecting the skin and mucous membranes, including the oral mucosa, and is characterized by periods of remission and exacerbation (Hegarty *et al.*, 2002). OLP affects 1- 2% of the general population with a female to male ratio of 2:1 and

a malignant transformation rate of 0.4 -5% (Alrashdan *et al.*, 2016). OLP may present in six forms: reticular, papular, plaque-like, erythematous (atrophic), erosive-ulcerous, and bullous-erosive. These forms may be seen individually or in combination (Farhi and Dupin, 2010). Reticular, papular, and plaque-like forms are painless white keratotic lesions while

atrophic, erosive, and bullous forms are painful ranging from mild discomfort to episodes of intense pain (Al-Hashimi *et al.*, 2007; Scully and Carrozzo, 2008).

Patients usually complain of a burning pain sensation which may hinder eating, speech and oral hygiene. Cancerophobia may also be a major concern for the patient due to the potentially malignant nature of the lesion. OLP adds additional stress to the patient and may cause undue anxiety and depression, thus severely reducing the quality of life. Patients in the long run tend to catastrophize symptoms, which also leads to a downward spiral in quality of life (Radwan-Oczko *et al.*, 2018).

Corticosteroids are the go-to medication for the management of OLP due to its anti-inflammatory and immunomodulatory action. They can be administered either topically, systemically, or intra-lesionally. Topical corticosteroids are the main stay in treating mild to moderately symptomatic lesions. Their main effect is to reduce pain and inflammation (Mehdipour and Taghavi, 2012).

Generally, topical corticosteroids may have multiple side effects that usually appear with chronic use. These include mucosal thinning, secondary candidiasis, and adrenal insufficiency (Al-Maweri *et al.*, 2017). Thus, the current trend is to use herbal medicine in the management of OLP (Ghahremanlo *et al.*, 2018).

Chamomile is a candidate for use in both treatment of OLP as well as the prevention of malignant transformation. Its essential oil is rich in components as terpenoids, α -bisabolol and azulenes including chamazulene, flavonoids, apigenin, quercetin, glucosides, and various acetylated derivatives. All of these different components are responsible for the flower's desirable biological properties such as anti-oxidant, anti-inflammatory, and anti-cancer

activities (Srivastava *et al.*, 2011; Ghasemi *et al.*, 2017). The German E Commission has approved chamomile for internal and external use to treat skin and mucous membranes' inflammation including the oral cavity (Blumenthal M *et al.*, 1998).

The aim of the present study was to evaluate the clinical effectiveness of topical chamomile cream in the management of OLP in patients free from any systemic disease.

Subjects and Methods

Study Design:

This is a phase III superiority parallel arm randomized clinical trial with an allocation ratio of 1:1. The study protocol was registered on the trial registry website: clinicaltrials.gov under identifier NCT03793634. The Ethical Committee of the faculty of dentistry, Cairo University approved the current study, under approval number 1911, and all procedures were in accordance with the declaration of Helsinki. Patients were informed about the nature and objectives of the study. All participants read, approved, and signed a written informed consent form.

Participants:

The present study was conducted at the Oral Medicine clinic - Faculty of Dentistry - Cairo University from January 2019 to March 2020.

Patients were included if they met the following criteria: 1) older than 18 years of age, 2) had symptomatic OLP based on the clinical and histopathological 1978 WHO criteria (Kramer *et al.*, 1978), 3) were not on corticosteroids for the previous 6 months 4) had no systemic diseases (Javadzadeh *et al.*, 2008) and agreed to take one of the study medications. Patients who had other

lesions than OLP, lichenoid reaction (Carbone *et al.*, 2003; Javadzadeh *et al.*, 2008) or were smokers or pregnant were excluded from the study.

Interventions:

The sample size was calculated using G*Power version 3.1.9.2 according to the effect size reported by Thomas *et al.* (Thomas *et al.*, 2017) with alpha level of significance of 0.05 and 80% power. The sample size produced was 14 patient per group and an increased to 17 patients per group to make up for any potential dropouts, giving a total of 34 patients.

The subjects were randomly assigned to receive either topical chamomile cream or triamcinolone acetonide. Simple randomization was done using www.randomizer.org. Allocation concealment was done through placing the treatment assignment in sequentially numbered, opaque, sealed envelopes.

Group A (intervention group): included 17 patients who were instructed to use chamomile 2% cream (trade name: camisan cream manufactured by EIPICO pharmaceutical industry).

Group B (control group): included 17 patients who were instructed to use triamcinolone acetonide 0.1% (trade name: kenacort in orabase manufactured by Glaxo smithkline pharmaceutical industry).

All patients were instructed to apply the medication 3 times a day after breakfast and lunch and before sleep. They were also told not to drink or eat for at least 30 minutes after treatment application. The patients were not blinded in this study; however, the outcome assessor did not know the patients' treatment assignment.

The Primary outcome of this study was pain assessed using the numerical rating scale (Chainani-Wu *et al.*, 2007), while the secondary outcomes were 1) total lesion area in centimeter² measured using a periodontal probe, 2) clinical score according to Thongprasom *et al.* (Thongprasom *et al.*, 1992), and 3) side effects of treatment. The study outcomes were assessed at baseline, after 2 and 4 weeks (T0, T2, T4).

Statistical analysis was performed using SPSS (version 20). Quantitative variables were described by the mean, standard deviation (SD) while qualitative categorical variables were described as frequencies and percentages. Shapiro-Wilk test of normality was used to test the normality hypothesis of all quantitative variables for a further choice of appropriate parametric and non-parametric tests.

Mostly for pain analysis, the variables are found to be normally distributed thus, paired sample t-test was used for comparing measurements within each group while independent samples t-test was used for comparing the differences between the two groups. The lesion size variables were not normally distributed so the non-Parametric Wilcoxon Signed Ranks test was used for comparing lesion size within the group while Mann-Whitney test was done to compare the differences between the two groups. For categorical variables, the Chi-squared test was applied for all contingency tables. Pearson correlation coefficient was used to measure the correlation of quantitative variables. Significance level was considered at $P < 0.05$. Two Tailed-tests are assumed throughout the analysis for all statistical tests.

Results

Figure 1 demonstrates the flow of patients throughout the study. The demographic data of the study participants are shown in table (1). The primary outcome of this study was pain

measured by NRS. A significant difference was seen right away between baseline and the second week in both the TA ($p=0.000$) and Chamomile groups ($p=0.000$). The improvement continued through to week 4 where a significant difference was seen in comparison to that reported in week 2 ($p(\text{TA})=0.000$, $p(\text{C})=0.0005$). TA was superior to chamomile during the second week in pain relief, however, Chamomile's analgesic effect caught up with that of TA during the 4th week.

As for lesion size reduction, both treatments yielded a significant effect by the end of the study duration ($p=0.000$ in both groups). However, TA had a faster effect than Chamomile by week 2, and while there was no significant difference between the two groups by week 4, there was a considerable clinical difference in favor of TA as seen in table 2. Similarly, the Thongprasom score improved significantly in both groups separately, but with no significant difference between the 2 groups.

As for side effects, two patients in the TA group reported undesirable taste, while in the Chamomile group, four patients reported undesirable odor and five patients reported an undesirable taste.

Discussion

A definitive treatment for OLP remains elusive despite the current medical advances. Management aims at controlling the symptoms in addition to lesion size reduction and prevention of possible malignant transformation (Ghahremanlo *et al.*, 2018). We aimed to evaluate Chamomile as a natural treatment alternative to the conventional topical corticosteroids.

Up to our knowledge, this study is the first randomized control clinical trial to compare the effect of commercially available chamomile

cream with topical triamcinolone acetonide in the management of OLP.

The results of the present study showed that the use of chamomile cream can significantly reduce pain sensation, and reduce clinical signs in patients with OLP. These results were achieved by the second week of treatment which might indicate the ability of Chamomile to induce rapid clinical change. These results are similar to Lopez Jornet *et al.* (2016) who compared the effect of 2% chamomile oral gel to placebo in the management of OLP. The authors found a statistically significant difference between the two study groups (Lopez Jornet and Aznar-Cayuela, 2016).

Other studies used drugs which incorporated constituents of the treatment under investigation. For example, Amirchaghmaghi *et al.* (2015) used quercetin tablets as combination therapy with dexamethasone mouth wash in the management of OLP (Amirchaghmaghi *et al.*, 2015). Quercetin was given in a systemic form twice daily, unlike the current study which supplied topical treatment three times daily. The authors found no statistically significant difference between quercetin tablets and placebo.

Topical Chamomile has been investigated in other diseases. For instance, Andishe Tadbir *et al.* (2015) used chamomile for the treatment of aphthous ulcer which -like OLP - is an immunologically mediated oral disease (Andishe Tadbir *et al.*, 2015). The authors compared the effect of chamomile extract in orabase versus triamcinolone acetonide in orabase in the treatment of aphthous ulcer. They found that while chamomile was as effective in pain reduction as TA, it had a significantly lower ability at reducing ulcer size. This is somewhat similar to the findings of the current study.

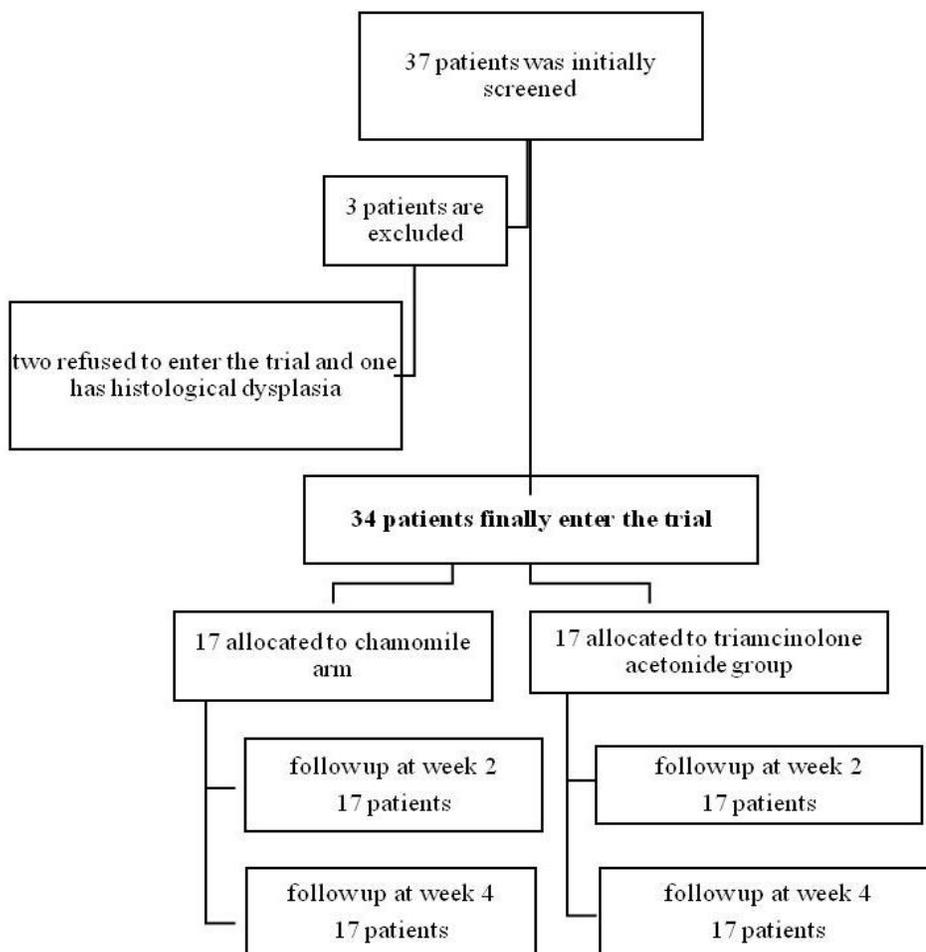


Figure 1: CONSORT flowchart

Table (1): Clinical characteristics of the recruited subjects

	Chamomile (n=17)	TA (n=17)
Age (Mean±SD)	54.47± 7.45	56.41± 7.78
Gender (F/M)	13/4	11/6
Types of oral lichen planus		
Erosive OLP	9 (53%)	8 (47%)
Atrophic OLP	8 (47 %)	9 (53%)
Site Distribution		
Cutaneous Lesion	0 (0%)	0 (0%)
Buccal Mucosa	14 (82.3%)	16 (94.1%)
Labial Mucosa	3 (17.6%)	0
Tongue	6 (35.3%)	5(29.4%)
Palate	2 (11.8%)	2 (11.8%)
Lip	0 (0%)	0 (0%)

Table 2: Comparison between mean values of NRS and Lesion size in the TA and Chamomile groups at baseline, week 2 and week 4.

	NRS		
	Chamomile (Mean ±SD)	TA (Mean ±SD)	p-value
Baseline	7.13 ±1.88	7.57 ±1.79	0.792159
Week 2	4.27 ±2.19	4.79 ±2.12	0.020993
Week 4	3.00 ±2.27	2.06 ±2.25	0.050343
	Lesion Size		
	Chamomile (Mean ±SD)	TA (Mean ±SD)	p-value
Baseline	72.41 ± 70.81	98.45 ± 98.15	0.683000
Week 2	36.94 ± 66.05	55.09 ± 54.70	0.016000
Week 4	30.58 ± 67.70	31.12 ± 36.54	0.140000

Although Chamomile was able to reduce pain, lesion size and Thongprasom score in a statistically significant manner, it failed to bear comparison with TA at 2 weeks. As regards lesion size, TA had significantly greater lesion reducing effect than Chamomile at week 2, however by week 4 there was no significant difference between the 2 groups. This indicates that Chamomile was able to somewhat catch up to the effect of TA, these findings show that TA acts more rapidly in reducing the lesion than chamomile.

Based on the results of this trial, we can conclude that chamomile can act as a standalone therapy for the management of patients with OLP. It can be used as a second line of treatment in OLP, or when side effects of long-term corticosteroids are feared, or even in patients who refuse corticosteroid treatment. The authors recommend that further studies of different Chamomile concentrations be investigated in the treatment of OLP as well as the use of combination therapy with corticosteroids to investigate the possible presence of an added or synergistic effect.

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