

Original Article

The Efficacy of Topical Sesame Oil in Orabase Versus Topical Triamcinolone in Orabase on Oral Lichen Planus and Salivary Level of Oxidative Stress Biomarker (MDA): Randomized Clinical Trial

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ABSTRACT

Objectives: To compare the effectiveness of topical sesame oil in the formulation of a gel and topical triamcinolone acetate 0.1% in dealing with the signs and symptoms of OLP. **Patients and Methods:** This randomized, controlled trial had thirty four patients who were randomly allocated to receive either sesame oil gel or triamcinolone acetate 0.1% gel thrice daily for 4 weeks. We assessed pain using the visual analogue scale and erythema and ulceration using the Thongprasom score and salivary MDA by ELISA. **Results:** Patients improved significantly in both groups, however change in the triamcinolone group occurred significantly faster than the sesame oil group. The Thongprasom score differed significantly between both groups ($p < 0.001$) favoring the triamcinolone group. The MDA level was statistically insignificant between both groups. **Conclusion:** Sesame oil can relieve pain but not as quickly as triamcinolone acetate, additionally, it has no detectable effect on improving the clinical picture of OLP.

Keywords: Triamcinolone acetate; Sesame oil; Thongprasome scale; Visual Analogue Scale

Introduction:

Oral lichen planus (OLP) is a chronic immune dysregulatory mucosal disease of uncertain etiology (Abbas et al., 2014). It affects about 0.4% to 5% of the world population (Alrashdan et al., 2016). OLP is classified as a potentially malignant disorder by the WHO with a rate of malignant transformation of 1.09% particularly in erythematous and erosive OLP (Alrashdan et al., 2016; Iqbal et al., 2020).

In Egypt, the prevalence of oral lichen planus is reported to be 1.43% with 2:1 female to male ratio particularly in the 4th and 6th decade of life. The percentage of the symptomatic forms in Egyptian patients is 59.37% atrophic and 20.3% erosive OLP (Mostafa and Ahmed, 2015). Symptoms may range from mild discomfort to extreme pain that can be associated with difficulty in eating, speech and oral hygiene. Additionally, the premalignant nature of this

disease causes anxiety, stress and cancerphobia for patients. It also affects their quality of life and may even worsen their symptoms (Radwan-Oczko et al., 2017).

The goal of OLP management is not curative but symptomatic relief, acceleration of healing and reducing the chances of malignant transformation (Gupta and Jawanda, 2015). Corticosteroids are the gold standard and the first line of treatment of OLP as they reduce inflammation and pain due to their potent anti-inflammatory and immune-regulatory effects (Gorouhi et al., 2007; Gupta et al., 2017).

The long-standing nature of OLP mandates prolonged management. Moreover, the repeated episodes of exacerbation increase the incidence of facing corticosteroids' side effects which range from mucosal thinning, burning sensation, hyperpigmentation, delayed wound healing and secondary candidiasis to more serious systemic adverse events as adrenal insufficiency, hypertension and osteoporosis (Al-Maweri et al., 2017). As oxidative stress is a key player in the pathogenesis of OLP, natural antioxidants derived from nature are being pursued as a replacement or an adjunct to corticosteroids to overcome their long-term side effects (Keshari et al., 2015; Amirchaghmaghi et al., 2016).

Sesame oil was used as a unique natural oil rich in lignans (sesamin, sesamol, and sesamolol) and tocopherols which have antioxidant and anti-inflammatory activities as they down-regulate oxidative stress, lipid peroxidation and Malondialdehyde levels. Sesamin and sesamolol hinder NF κ B activation via suppressing I κ B-kinase which degrades I κ B. I κ B is an inhibitory protein responsible for preventing NF κ B binding to DNA (Harikumar et al., 2010 and Woo et al., 2019).

Due to the antioxidant effects of sesame oil as well as its anti-inflammatory properties, it can be suggested as a suitable therapeutic candidate for OLP treatment. Furthermore, sesame oil has

anticancer properties through lignans and tocopherols' anti-mutagenic ability (Hsu et al., 2013; Monteiro et al., 2014). Sesame oil has been proven in several trials as a safe and cost-effective drug that is easy to apply (Anilakumar et al., 201; Dharmavaram et al., 2015; Okada et al., 2015; Bigdeli Shamloo et al., 2015; Khaira et al., 2020).

This study examined the effect of topical Sesame oil compared to Triamcinolone acetonide (TA) for managing OLP regarding pain relief, clinical improvement and antioxidant effect.

Subjects and Methods

Study Design:

This is a phase III, two-armed superiority randomized controlled clinical trial. The study protocol is available on clinicaltrials.gov under identifier NCT03738176.

Study Settings:

The study was done at the Oral Medicine clinic, Faculty of Dentistry, Cairo University. The study duration was from September 2018 till November 2021.

Ethical Approval:

The ethical committee of scientific research – Faculty of Dentistry – Cairo University approved this research (Registration Number: 19/3/14). This research was done in accordance with the declaration of Helsinki. The details of the study were clarified to all the participants. All patients gave a written informed consent before admittance to the study. Patients were first assessed for eligibility, then those eligible had the details of the study explained to them. The patients signed a written Arabic informed consent that had all the pertinent information and complications prior to entering the study.

Sample Size Calculation:

We used an effect size of 1.1272141 as reported by Thomas et al. in 2017, a two tailed test, $\alpha=0.05$ and power =0.8 to yield 14 patients needed in each group. A 20% increase in sample size to avoid attrition bias gave a total of 17 patients per group.

Participants:

Eligibility Criteria:

Patients attending the outpatient clinic were screened until reaching the target sample. We included medically free patients with symptomatic (atrophic or erosive) oral lichen planus who had no history of being on corticosteroids or immunosuppressive drugs within 1 month before the study. We excluded patients with lichenoid reaction, or those having other lesions than OLP and pregnant and lactating females.

Intervention :

Sesame oil Preparation:

The Sesame oil gel was prepared from raw sesame seeds, 70% Carboxymethylcellulose, 10% gelatin and 100% distilled water and Methyl para and propyl paraben as a preservative. Several trials were carried out to determine the maximum loading capacity of orabase without showing any signs of separation which was 12 mg (20%). Sesame oil used in this study was cold pressed from raw white Egyptian sesame seeds .

Procedure:

Full medical history, intra and extra oral examination and consent were obtained from all subjects participating in the study . Patients were randomly allocated into two groups of 17 :

Group A: Subjects received topical sesame oil in orabase 3 times /day for a month.

Group B: Subjects received topical Kenacort in orabase (0.1% Triamcinolone) 3 times /day for a month (Bristol-Myers Squibb Company).

The patients in both groups had to apply a thin layer of their assigned treatment. The

subjects were instructed to avoid food, drinks and smoking for 30 minutes after each application. We instructed the patients to report any side effects at any time during the study. We assessed patients at each appointment for possible side effects along with their compliance to their given treatments.

Outcomes:

Pain Intensity:

We used the visual analogue scale (VAS) to determine pain intensity. Patients report the degree of pain according to a 10-cm ruler where a zero score indicated "no pain" and a score of ten indicated "extremely severe pain."

The VAS was measured at baseline and at each follow-up visit (weeks 2 and 4) by the principal investigator.

Clinical Improvement:

Clinical Improvement and reduction in size of the lesion were measured using a periodontal probe and the area of the erosive and atrophic parts were calculated. The lesion was photographed at each visit at a standard distance parallel to the lesion site at a standard angle for documentation. Reduction in clinical sign score was assessed objectively using the Thongprasom score (Thongprasom et al., 1992). These measurements were done at baseline and at the end of the second and fourth weeks.

Salivary Malondialdehyde (MDA) Level:

Salivary sample collection:

Whole unstimulated saliva was collected at baseline and after one month of treatment in the two groups using standard techniques (Navazesh, 1993). Patients were asked to lean forward and spit saliva into a graduated tube for 5 minutes.

Saliva samples were then centrifuged and the supernatant was used for determination of MDA level using the "Double Antibody Sandwich" technique via ELISA Kit (Cat No. MBS263626) by Biosource (USA, NY).

Sequence Generation and Allocation Concealment :

Random sequence was generated using Microsoft Excel and was implemented by N.A. as was the allocation concealment which was done using the telephone after the primary investigator enrolled each participant.

Blinding:

The principal investigator acted as the outcome assessor and was not blind to the allocated treatment nor was the patient due to the nature of the treatment.

Statistical methods

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the data's normality. Normally distributed data were summed using mean and standard deviation while non-normal distributions were explored using median and range. Categorical data were expressed as percentages. We used the t-test to compare between groups with normally distributed variables while the Mann-Whitney test was used for non-normal distributions. Comparisons of numerical variables over time were done using the repeated measure ANOVA, Friedman test and Wilcoxon test as fits the data. The Chi square was used for categorical variables. P-value was set at ≤ 0.05 . Analysis was done using SPSS version 24.

Results:

From September 2018 till November 2021, 34 patients were included in the study. The CONSORT flow diagram is presented in Figure (1). Table 1 demonstrated the clinical characteristics of the study participants.

The VAS score differed significantly over time in each single group individually. While intergroup comparison showed statistical superiority for group B (table 2).

The lesion size differed significantly over time in each single group was statistically insignificant for group A while a significant reduction in lesion size was seen in group B ($p < 0.001$) throughout the three time intervals (table 3). Figures 1 and 2 show clinical pictures for patients receiving treatment A and B respectively.

Before treatment, the median and range of MDA level was 3.5(2.4-10.6) for Group A and 3.2(1.2-8.6) for Group B with no statistical significance ($p = 0.357$). After treatment, the median and range for MDA was 3.5(1.2-25.9) for Group A and 2.4 (1.2-8.7) for Group B without any significant difference between both groups ($p = 0.838$). Additionally, there was no statistical significance in the level of MDA over time in each single group ($p > 0.05$). Patients in group B did not complain of any side effects. In group A, two patients complained of burning sensation, while three patients complained on unpalatable taste.

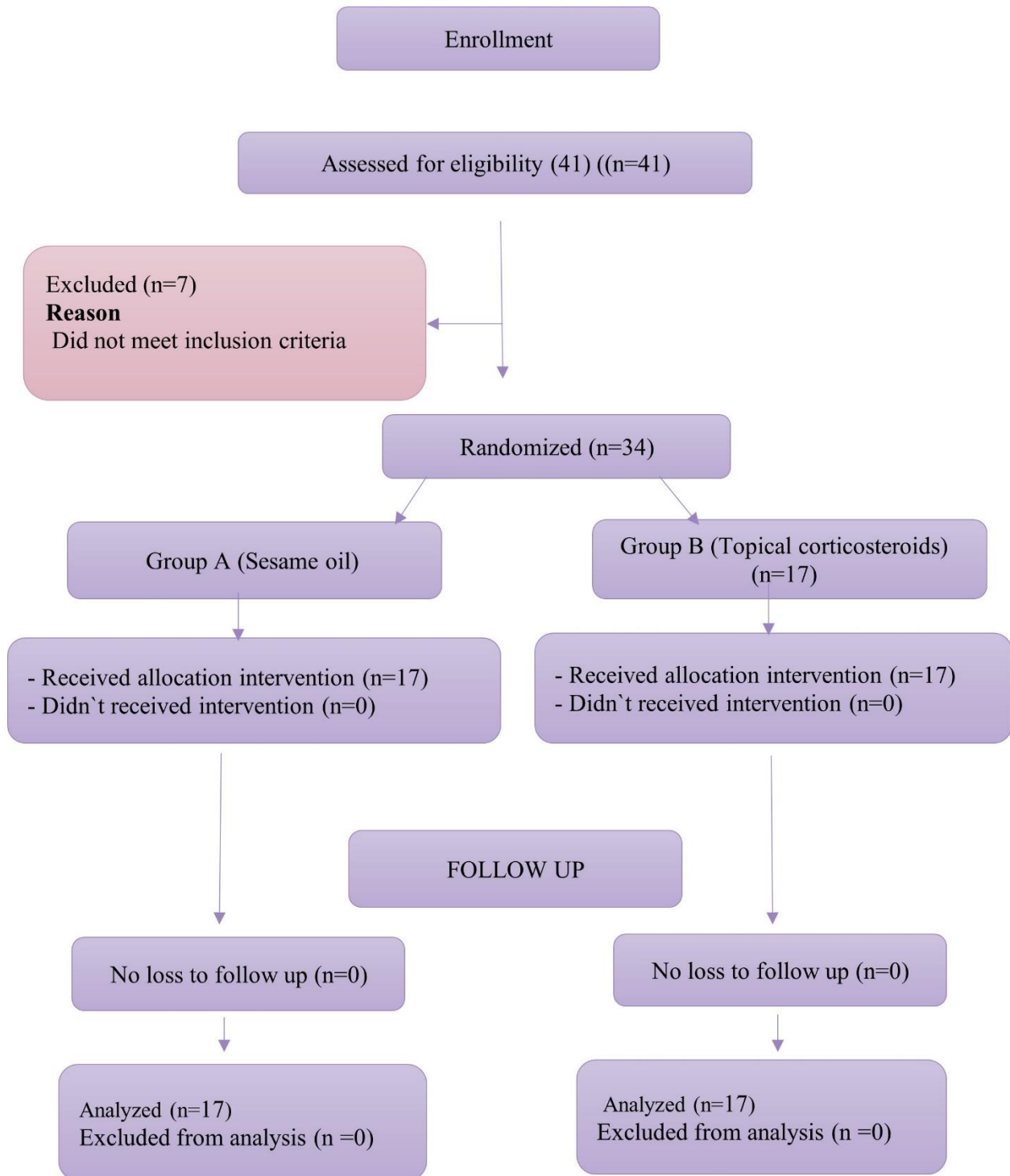


Figure (1): CONSORT Flowchart

Table (1): Clinical characteristics of included patients

Variables	Group	Group A(n=17)		Group B (n=17)		P value
		No	%	No	%	
Age (yrs.)	Mean± SD	52.7±11.9		48.4±9.6		0.21
	Range	34-75		32-66		
Sex	Male (%)	3(17.6)		2(11.8)		1.0
	Female (%)	14 (82.4)		15 (88.2)		
Types of OLP	Erosive	7		8		
	Atrophic	10		9		
Site Distribution	Cutaneous lesion	5		3		
	Buccal mucosa	16		16		
	Tongue	7		6		
	Gingiva	2		1		
	Labial mucosa	3		0		

Table (2): VAS score throughout the study period in both groups

	Group A			Group B			P ¹ value
	Median	Min.	Max.	Median	Min.	Max	
Baseline	7 ^a	5	9	7*	6	9	0.394
Week 2	6	4	9	6	5	8	0.454
Week 4	5 ^a	0	8	2	0	6	0.003
P ² value	<0.001			<0.001			

P1: comparison between 2 groups.

P2: comparison over time in each group separately, similar lower case letters are statistically significant

*: all time interval are statistically significant from each other.

Table (3): Size of the lesion throughout the study period in both groups

SIZE	Group A		Group B		P ¹ value
	Mean	SD	Mean	SD	
Baseline	3.2	1.2	3.4*	0.7	0.456
Week 2	2.9	1.2	2.9	0.8	0.833
Week 4	2.8	1.3	1.2	0.9	<0.001
P ² value	0.218		<0.001		

P1: comparison between 2 groups.

P2: comparison over time in each group separately

*: all time intervals are statistically significant



Figure (2): a, b, c: Clinical photograph of a 74-year-old female patient showing atrophic OLP on the right side of the buccal mucosa, erosive OLP on the left side of buccal mucosa and on the lower vermilion border.(Thongprasom score:4,VAS:8). d,e,f: Clinical photograph of the same patient showing partial healing(Thongprasom score:2,VAS:1) after receiving treatment A



Figure (3): a,b: Clinical photograph of a 46-year-old female patients showing atrophic and erosive OLP on the right and left sides of the tongue.(Thongprasom score:5,VAS:8). c,d: Clinical photograph of the same patient showing partial healing (Thongprasom score:1,VAS:0) after receiving treatment B.

Discussion

As far as we know, this study is the first clinical trial to evaluate the effect of topical Sesame oil as a gel in the managing symptomatic OLP. Sesame oil is one of the most used oils in the practice of ayurvedic oil pulling where oil is swished in the mouth for oral and systemic health benefits (Dhaliwal et al., 2017), which made it a perfect candidate for the treatment of OLP. The current study found that Sesame oil can significantly reduce pain over a period of 4 weeks. Sesame oil contains gamma Tocopherol and α -tocopherol which are the two major constituents of vitamin E. Vitamin E has anti-inflammatory activity where it can down regulate dendritic cells migration, cyclooxygenase (Cox)-2 activity and production of prostaglandinE2 (PGE2) and interleukin (IL-12). Also, vitamin E can regulate T-cell function via suppression of tumor necrosis factor (TNF)- α , IL-6 and IL-1 β release (Lee et al., 2018; Lewis et al., 2019). Furthermore, vitamin E has chemo-preventive activity where it can inhibit cancer cell growth and differentiation (Iqbal et al., 2014). Many studies assessed the serum and salivary levels of Vitamin E in OLP (Raietal, 2008; Abdolsamadi et al., 2014; Mohammed and Diajil, 2019). Nagao et al. found that vitamin E levels were lower in both the saliva and serum of OLP patients compared to healthy individuals (Nagao et al., 2001). This justifies the use of vitamin E containing compounds in patients with OLP.

However, the present study found that Sesame oil could not bring about a significant reduction of lesion size over the treatment duration. Moreover, TA had a higher statistically significant effect in reducing lesion size and pain than Sesame oil. In our results, Triamcinolone was effective and safe, where the patients did not complain from any side effects.

On the other hand, studies using formulations that contained Vitamin E produced promising results. Inamdar et al, 2015 treated OLP patients with an aloe vera, licorice and sesame oil gargle

swished twice daily for six weeks. Patients had significantly less pain, redness and functional disturbance after using the prepared formulation.

Dayem et al (2020) used Vitamin E for the treatment of OLP. They used vitamin E systemically as an adjunctive treatment to topical triamcinolone acetonide. They found that the group treated with Vitamin E capsules and topical triamcinolone acetonide showed greater improvement in pain, clinical scores with decrease in salivary total antioxidant capacity.

Topical sesame oil has been researched in other diseases. Dharmavaram et al (2015) used topical Sesame oil for managing recurrent aphthous stomatitis which is an inflammatory disease mediated by immune dysregulation like OLP. Sesame oil turned out to be superior in pain reduction and lesion size. Sharquie et al. (2020) compared the effect of sesame oil and pumpkin oil in the management of recurrent aphthous ulcer and their prophylactic effect. They found that sesame oil showed higher statistically significant effect in the healing of recurrent aphthous ulcer and prophylactic effect up to three months after starting therapy.

This finding highlights the role of antioxidants in the treatment of OLP and the validity of pursuing this research venue. Contrary to this belief, sesame oil did not have favorable results in the current study where there was no significant lesion size reduction in the Sesame oil group. Possible explanations, would be that the current study used sesame oil from raw sesame seeds which contain small amounts of sesamol as opposed to that present in roasted sesame oil where sesamol is converted to sesamol after roasting (Kumar et al., 2015; Islam et al., 2016). Additionally, the ability of Sesame oil to resist rancidity is mainly due to sesamol and sesamol dimer, which might be the cause of the unpalatable taste experienced by the patients in

group A as the seeds were not roasted (Mostashari and Khaneghah).

Sesamol is the main anti-oxidative and anti-inflammatory component of sesame oil (Hsu et al., 2013). Sesamol can suppress the production of TNF- α and down regulate cytokine release from dendritic cells in concentration lower than sesame oil and with stronger effects than sesame oil (Khorrami et al., 2018). Another explanation would be the use of local sesame seeds to manufacture the oils which could be contaminated with heavy metals (Pb, As, Cu, Cd, Zn). These metals could be from the soil, fertilizers, and even geographical conditions encountered during seed transport. The percentage of heavy metals in the oil differs according to the method of extraction. These include: grinding roasted sesame seed including Ardeh oil; or cold pressed using virgin oil and refined oil, where the refined oil has the lowest amount of heavy metals (De Leonardis et al., 2000; Pehlivan et al., 2008; Rounizi et al., 2020). Moreover, cold pressed Sesame oil may contain aflatoxins due to fungal infection during harvest, transportation, and storage (Li et al., 2009). Sebaei et al. (2020). Found that 37 % of the Egyptian sesame samples included in their study had large amounts of aflatoxin of up to 20 $\mu\text{g}/\text{kg}$.

On the other hand, studies by Hegde et al (2017) and Sawair et al. (2010) investigated alternative treatments used by patients for treatment of recurrent aphthous ulcers. They found that Tahini is the major alternative treatment where all subjects who applied Tahini believed that Tahini was effective in relieving pain and reducing the duration and frequency of ulceration. These results may be due to the difference in composition where Tahini is made from milled and roasted sesame seeds which contain high levels of beneficial nutrients such as calcium, iron, potassium and phosphorus, antioxidants and vitamins (B, C and E) not to

mention a high amount of sesamol (more than 50%) (Gholami et al., 2020).

Under physiological conditions, there are low lipid peroxidations rates (sub toxic conditions) and the cells can survive via activation of signaling pathways that increase the antioxidant proteins and, ultimately, the adaptive stress response. However, under pathological conditions, there are medium or high lipid peroxidation rates (toxic conditions), so oxidative damage overrides cells regeneration, and induces apoptosis (Ayala et al., 2014). Markers of oxidative stress can be used in the surveillance of diseases in response to treatment (Mansourian et al., 2016).

Malondialdehyde is the principal end product of lipid (long chain of polyunsaturated fatty acid) peroxidation, thus, it can be used as a marker for oxidative stress (Shirzad et al., 2013). Results of salivary MDA in our study revealed that no significant difference be it within groups or between them. Mansourian et al. (2016) evaluated the level of MDA in patients with OLP before and after TA treatment and reported similar findings. MDA may not be a specific marker for oxidative stress levels. This might be justified by the chronic nature of the disease, where return to physiologic lipid peroxidations rates takes longer than a month.

In conclusion, the palliative effect of sesame seed products is undeniable through-out numerous studies (Hsu et al., 2008; Wichitsranoi et al., 2011; Roghani et al., 2013; Haidari et al., 2016) Seeds rich in vitamin E have continuously proven to be effective in many mucosal diseases (Iqbal et al., 2013; Bacci et al., 2017; Lewis et al., 2019; Dayem et al., 2020). The findings of the current study suggest that sesame oil alone is not enough to achieve a better therapeutic effect in OLP patients than TA. It can, however, be used to reduce pain experienced by patients and can act as a safe adjunctive drug in treatment of OLP.

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