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Assessment of Effectiveness of Ozonated Olive Oil Fused With Corticosteroids for the Management of Oral Erosive Lichen Planus: A Novel Approach

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***Abstract*---**Erosive lichen planus is counted amongst the most debilitating conditions of oral cavity which has multifactorial etiology and malignant turnover potential. It has been documented that ozonated olive oil have healing, anti-inflammatory, antimicrobial and antioxidant properties and thus have great potential in management of the ulcerative lesions. Present study is aimed to evaluate and compare the efficacy of using ozonated olive oil combined with

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systemic steroid and antioxidant in the management of erosive lichen planus. Materials and methods: Eighty patients with a confirmed clinical and histopathologic diagnosis of erosive OLP were randomly allocated into four groups. Group I, II, III and IV were prescribed systemic Prednisolone 40 mg/day,soft-gel capsule lycopene (6 mg/day), combination therapy of systemic steroid (40mg/day) along with ozonated olive oil and combination therapy of lycopene (16 mg/day) and ozonated olive oil respectively. OLP clinical course was assessed by measuring severity of pain, burning sensation (VAS), clinical signs (scale of Thongprasom) and efficacy of the treatment(efficacy index methods of Liu set). Patients were monitored on regular follow up.

***Keywords*---**combined therapy, corticosteroids, lycopene, oral lichen planus, ozonated therapy.

Introduction

Oral lichen planus (OLP) is a chronic inflammatory mucocutaneous condition that is probably of multifactorial origin; often idiopathic with an immunopathogenesis involving T-cells.1 It mainly affects skin, scalp, nail, oral cavity (2). In the oral cavity, the buccal mucosa, tongue and gingiva are commonly affected and presents as a symmetrical and bilateral lesion or multiple lesions. It occurs in six clinical variants as reticular, papular, erosive, atrophic and bullous (ulcerative) (3). The epidemiologic distribution of lesions differs in each geographical region, but the most common are reticular and erosive form. The first three types are often present as minor or no symptoms without any complaints with no need for any intervention or treatment, but the other three forms are present with the epithelium damage with painful, and/or a burning sensation and requires urgent need of interventions. OLP is considered as a premalignant condition with malignant transformation rate of 0 2%.3 (4).

Oral LP (OLP) is a common disease that afflicts 1–2% of the population, most commonly females than males approximately (1.4:1), with the possible onset in the decade 4-5 of life (4). The aetiology of OLP is still unknown. Several factors have been proposed for the aetiology including genetic background, dental materials, drugs, infectious agents – bacterial and viral infections, autoimmunity – associated with other autoimmune diseases, immunodeficiency, food allergies, stress etc. Also, the pathogenesis is not entirely clear, but it is thought to arise from an immune response presumably involving CD4+ and CD8+ T lymphocytes producing cytokines, interleukin-2, and tumor necrosis factor within the oral epithelium that induce a chronic inflammatory response and keratinocyte apoptosis (3,4).

Various therapeutic approaches have been proposed, but definite cure for this disease entity is still untouched. The large number of therapeutic agents including corticosteroids, retinoid, calcineurin inhibitors, laser, and phototherapy etc2 have been studied and reflected the inadequacy of any one agent to control the symptoms in all the patients because of the alteration in disease activity, the

use of a sole and definitive therapeutic modality is challenging. Corticosteroids are the first drug of choice and considered as standard drug for the treatment of this disease due to its anti-inflammatory and anti-immune effects (5). Steroids suppress the inflammatory response by inhibiting synthesis of the two main inflammatory products, leukotrienes and prostaglandins and also suppress cell-mediated immunity resulting in the accelerated healing of OLP patients.

It has been used topically as the first-line drugs, while they are usually reserved systemically for widespread erosive OLP or acute exacerbation (4). Further, most of the corticosteroid agents studied have their own associated adverse effects, which need to be monitored, thus making the choice of treatment modality in majority of cases a difficult decision. Numerous different topical and systemic treatments have been suggested till now for relieving pain, or eliminating the sign and symptoms of the lesion with minimum or no side effects like curcumin, lycopene, Vitamin E, A etc. These serves as one of the cornerstones in the maintenance of the biodynamic of the body with the various actions like antioxidant, anti-inflammatory, anti-analgesics etc. which may prove a better choice for alternative medicine in the OLP.

Oxidant-antioxidant imbalance resulting in excessive accumulation of ROS and oxidative stresses which role and importance is clearly seen with the OLP patients who are more susceptible to an imbalance of antioxidant-oxidative stress status.6 Ozone therapy has gained a prominent consideration in the medical and dental fields due to its physicochemical properties which has gained a prominent consideration in the medical and dental fields (7). It possess strong antimicrobial activity (against bacteria, viruses, yeasts and protozoa), a powerful oxidising agent, anti-hypoxic and immunostimulating, anti-inflammatory. Ozone therapy is an alternative non-medication therapy that has also been introduced as a treatment option in the management of OLP.

Ozone application in form of oil is used over the aqueous ozone therapy due to its cost effective, easy manipulation nature and better shelf life of the medication (8). To our knowledge, this is the first study of its kind to investigate the effectiveness of ozonated olive oil with the steroid, and antioxidant in the treatment of erosive lichen planus, with the hope that the findings will help and provide its potential role and clinical significance in the management of erosive lichen planus. Hence, the aim of this study is to evaluate and compare the efficacy of using ozonated olive oil in combination with systemic steroid and systemic antioxidant in the management of erosive lichen planus.

Materials and Method

The present prospective, randomized, double-blind study was conducted in the Department of Oral Medicine and Radiology, ITS-CDSR, Ghaziabad, India. Eighty systemically healthy individuals of either sex, aged between 30 and 60 years with clinically and histopathologically diagnosed (diagnostic criteria according to American Academy of Oral and Maxillofacial Pathology, 2016) (9) or symptomatic erosive OLP were included in the study. Patient with any active systemic disease and undergoing with any medication (topical/systemic corticosteroids, immunosuppressant's etc), OLP with dysplasia, candidiasis and oral lichenoid

lesions, pregnant or lactating ladies were excluded from the study. Ethical approvals were obtained from the Legal and Ethical Committee of the institute. All the patients were explained about the study and an informed consent was obtained by the patients who were further evaluated by the investigator.

Eighty patients were randomly allocated into four groups (n=20). Group I were treated with systemic Prednisolone 40 mg per day in the two divided doses, Group II were administered with softgel capsule lycopene 16 mg/day in two divided doses, Group III were given a combination therapy of systemic steroid (40mg per day in two divided doses) and ozonated olive oil and Group IV were given combination therapy of lycopene (16 mg/day in two divided doses) and ozonated olive oil. Patient was advised to avoid drinking or eating for 15–20 min after using topical intervention. Treatment response was recorded at baseline (T0), after 1 week (T1), 2 week (T2), 3 week (T3) and 4 week (T4). First follow up visit was after an additional 2 weeks of 4th week (T5) and 2nd follow up (T6) visit after 1 month of T5. At 50% reduction in lesion sign and symptoms steroid dose was tapered by 20 mg/day for next 1 week, then to 10mg/day for 1 week, 5mg/day for the next 1 week and finally 2mg/day for last week. Blood glucose level, serum electrolytes, complete blood counts and blood cortisol levels were recorded at the start and at the end of the treatment. Any adverse effect relates to any therapy was also being noted and discontinuation of the intervention was done if any reported. OLP clinical course was assessed by measuring severity of pain, burning sensation, clinical signs and efficacy of the treatment.

- Pain & burning sensation scoring: The severity of pain was determined using a visual analogue scale (VAS) from 0 to 10 where 0 corresponds to “no pain” and 10 to “the worst possible pain”. The symptoms data were then scored according to the following classification: score 3: severe pain/discomfort (7<VAS<10); score 2: moderate pain/ discomfort (3.5<VAS<7); score 1: mild pain/discomfort (0<VAS<3.5); score 0: without pain/discomfort (VAS=0).
- Clinical sign scoring was done by scale of Thongprasom et al.[1] (1992): 5 (white striae with an erosive area > 1 cm2), 4 (white striae with an erosive area < 1 cm2), 3 (white striae with an atrophic area > 1 cm2), 2 (white striae with an atrophic area < 1 cm2), 1 (mild white striae only), and 0 (no lesions, normal mucosa).[1]
- Efficacy of the treatment was done according to the methods of Liu set.al.[10] Treatment efficacy index (EI) was calculated, using the following formula: [(Total score of the lesion before treatment – Total score of the lesion after treatment) / Total score of the lesion before treatment] X100.

The EI was categorized into 5 rank scale as follows: healed: 4: EI=100%; marked improvement: 3: 75%≤EI<100%; moderate improvement: 2: 25%≤EI<75%; mild improvement: 1: 0<EI<25%; no improvement: 0: EI=0. Two clinicians who evaluated the outcomes weekly (before and immediately after every week and in all further follow up visits) were blinded to the allocation group. Later, data were tabulated and subjected to statistical analysis using SPSS (statistical package for social sciences) software.

Results

Table 1
Clinical sign scoring with chi- square and p value at different follow up intervals in all four groups

Clinical sign scoring		Groups				Chi-square value	p-value
		Group I	Group II	Group III	Group IV		
T0	3	0	0	2	0	6.353	0.385
		0.0%	0.0%	10.0%	0.0%		
	4	9	9	7	9		
		45.0%	45.0%	35.0%	45.0%		
	5	11	11	11	11		
		55.0%	55.0%	55.0%	55.0%		
T1	4	7	5	13	11	11.313	0.010*
		35.0%	25.0%	65.0%	55.0%		
	5	13	15	7	9		
		65.0%	75.0%	35.0%	45.0%		
T2	3	0	0	3	1		
		0.0%	0.0%	15.0%	5.0%	36.339	< 0.001*
	4	14	8	17	19		
		70.0%	40.0%	85.0%	95.0%		
	5	6	12	0	0		
		30.0%	60.0%	0.0%	0.0%		
T3	2	0	0	2	0		
		0.0%	0.0%	10.0%	0.0%	21.104	0.002*
	3	16	9	18	17		
		80.0%	45.0%	90.0%	85.0%		
	4	4	11	0	3		
		20.0%	55.0%	0.0%	15.0%		
T4	1	0	0	11	3	74.991	< 0.001*
		0.0%	0.0%	55.0%	15.0%		
	2	8	0	9	9		
		40.0%	0.0%	45.0%	45.0%		
	3	12	13	0	8		
		60.0%	65.0%	0.0%	40.0%		
	4	0	7	0	0		
		0.0%	35.0%	0.0%	0.0%		
T5	0	0	0	7	3	124.570	< 0.001*
		0.0%	0.0%	35.0%	15.0%		
	1	0	0	13	0		
		0.0%	0.0%	65.0%	0.0%		
	2	20	4	0	14		
		100.0%	20.0%	0.0%	70.0%		
	3	0	16	0	3		
		0.0%	80.0%	0.0%	15.0%		
T6	0	0	0	11	4	118.892	< 0.001*
		0.0%	0.0%	55.0%	20.0%		
	1	0	0	9	6		
		0.0%	0.0%	45.0%	30.0%		

	2	20	5	0	10
		100.0%	25.0%	0.0%	50.0%
	3	0	15	0	0
		0.0%	75.0%	0.0%	0.0%

Table 1 depicts the clinical sign scoring values based on the scale (1). In all four groups(Group I- Prednisolone, Group II- Lycopene, Group III- combination therapy of steroid and ozonated olive oil and Group IV- combination therapy of systemic lycopene and ozonated olive oil) at different follow up intervals starting from the baseline till the 3 months of follow up. Clinical sign score 4 at T1, score 3 and 4 at T2, score 3 at T3 and score 1 and 2 at T4 was significantly more among Group III and IV as compared to Group I & II. Clinical sign score 0 and 1 at T5 and T6 was significantly more among Group III and IV as compared to Group I & II with the significant p- value.

Table 2
Treatment efficacy index with chi- square and p value at different follow up intervals in all four groups

Treatment efficacy index (EI)		Groups				Chi-square value	p-value
		Group I	Group II	Group III	Group IV		
T0	0	20	20	20	20	< 0.001*	1.000
		100.0%	100.0%	100.0%	100.0%		
T1	0	6	14	0	0	43.362	<
		30.0%	70.0%	0.0%	0.0%		0.001*
	1	14	6	14	13		
		70.0%	30.0%	70.0%	65.0%		
	2	0	0	6	7		
		0.0%	0.0%	30.0%	35.0%		
T2	1	9	18	0	11	33.083	<
		45.0%	90.0%	0.0%	55.0%		0.001*
	2	11	2	20	9		
		55.0%	10.0%	100.0%	45.0%		
T3	1	7	16	0	4	65.829	<
		35.0%	80.0%	0.0%	20.0%		0.001*
	2	13	4	10	12		
		65.0%	20.0%	50.0%	60.0%		
	3	0	0	10	4		
		0.0%	0.0%	50.0%	20.0%		
T4	1	7	14	0	0	75.547	<
		35.0%	70.0%	0.0%	0.0%		0.001*
	2	13	6	8	14		
		65.0%	30.0%	40.0%	70.0%		
	3	0	0	12	6		
		0.0%	0.0%	60.0%	30.0%		
T5	1	0	3	0	0	61.340	<
		0.0%	15.0%	0.0%	0.0%		0.001*
	2	14	17	0	6		
		70.0%	85.0%	0.0%	30.0%		
	3	6	0	13	12		

	4	30.0% 0 0.0%	0.0% 0 0.0%	65.0% 7 35.0%	60.0% 2 10.0%		
T6	1	2 10.0%	2 10.0%	0 0.0%	0 0.0%	124.110	< 0.001*
	2	12 60.0%	16 80.0%	0 0.0%	0 0.0%		
	3	6 30.0%	2 10.0%	7 35.0%	14 70.0%		
	4	0 0.0%	0 0.0%	13 65.0%	6 30.0%		

Table 2 depicts the treatment efficacy index based on Liu et al. in all four groups (Group I- Prednisolone, Group II- Lycopene, Group III- combination therapy of steroid and ozonated olive oil and Group IV- combination therapy of systemic lycopene and ozonated olive oil) from the baseline till the 3 months of follow up. Treatment efficacy index (EI) score 2 at T1 and T2, score 3 at T3 and T4, score 3 and 4 at T5 and T6 was significantly more among group III and IV as compared to group I & II. Group III showed a marked improvement in treatment efficacy index (EI) from T1, T2, T3, T4, T5 till the T6. In the end of the treatment interval and follow ups 65% and 35% patients scored 4 and 3 i.e. healed and marked improvement which was significantly more than other three groups.

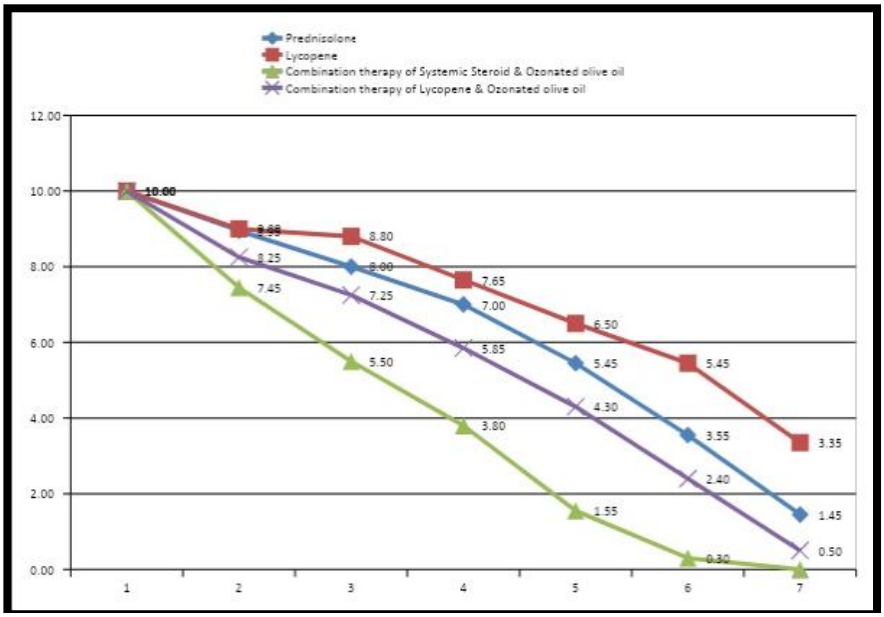

Figure 1. Mean Pain scores at different follow up intervals in all four groups

The figure 1 shows the comparative assessment of mean pain scores at different time intervals in all four groups respectively. Using the one-way ANOVA test there was a significant difference in mean Pain score mean values at T1, T2, T3, T4, T5 and T6 in all groups. Group III showed marked reduction in mean pain values from baseline till the 3 months follow up intervals as 7.45, 5.50, 3.80, 1.55, 0.30

and 0.00 respectively with the significant p- value of < 0.001 which was more than other three groups.

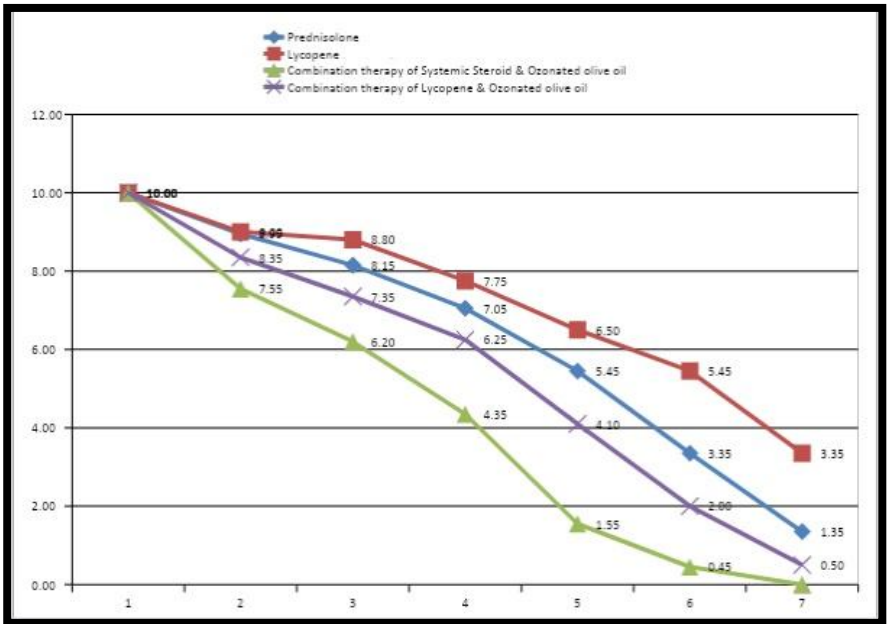

Figure 2. Mean burning sensation scores at different follow up intervals in all four groups

The figure 2 shows the comparative assessment of mean burning sensation score at T0, T1, T2, T3, T4, T5 and T6 in all four groups respectively. There was a significant difference in mean burning sensation score between all four groups. Group III showed marked reduction in mean pain values from baseline till the 3 months follow up intervals as 7.55, 6.20, 4.35, 1.55, 0.45 and 0.00 respectively with the significant p- value of < 0.001 which was more than other three groups.

Figure 3. Pre and post treatment of oral erosive lichen planus with Ozonated olive oil with corticosteroid

Discussion

OLP is a prevalent condition that affects people all over the world. It's thought to be an autoimmune disease that mostly affects women in their middle age. A white lesion with wickham's stria causes burning and pain sensations in the afflicted oral mucosa, causing patients anguish and morbidity (5). Corticosteroids are the most widely adopted therapy option for OLP because of their quick efficacy in managing symptoms. However, due to the considerable adverse effects of long or short-term steroid use, these treatments are limited. In addition to corticosteroids recently, studies on administering natural or herbal origin medications to treat OLP, such as curcumin, lycopene, cedar honey, anthocyanins and quercetin, have been emerged (11) but due to the chronic and recalcitrant nature of oral lichen planus, a definitive cure has yet to be found. Finding safe and effective immunoregulating medicines for OLP, either as a stand-alone treatment or in combination with above mentioned treatment strategies is essential (11).

So, on the contrary to the above mentioned treatment protocols the ozonated olive oil with other modalities has been used to reinforce their therapeutic effect. Its copious therapeutic properties includes immune-stimulant, anti-analgesic, antihypnotic, antimicrobial, biosynthetic activities, anti-inflammatory etc. A total of 80 patients (51 female and 29 males) with clinically and histopathologically confirmed erosive OLP were divided into four groups having an age range from 25-60 years with a mean age of 47.03 ± 4.56 years were included in the study which was slight in contrast with studies done by Mostafa et.al.[12] and Sethi Ahuja U et.al.[5] where mean age was found to be 54.67 years and 44.5 years respectively. The finding of the present study revealed that the combination of ozonated olive oil with systemic corticosteroids and lycopene for instance, showed effective improvement in healing of oral lichen planus lesion size, pain and burning sensation as compared to other group treatment modalities.

The patients in both the combination groups i.e. corticosteroid & ozonated olive oil (group III) and lycopene & ozonated olive oil (group IV) showed a statistically significant improvement ($P < 0.001$) in all parameters like pain, burning sensation and clinical sign scoring from the baseline(T0) till the fourth week of treatment (T4) and further 2 months of follow up visits(T5 & T6). The usage of ozone (O3) as a supplemental medicinal method has been steadily expanding among non-pharmacological treatments. Ozone is an extremely unstable that decomposes quickly into regular oxygen (O2). O3 is an extremely strong oxidant, despite not being a reactive molecule, and because of its highly toxic feature, it has been frequently employed as a disinfectant and germicidal agent, including for medical and dental purposes. Furthermore, delivery of O3 in the form of an O2-O3 combination has been shown to increase metabolic activity and have therapeutic effects in a variety of disorders.

Many T-cell-mediated inflammatory disorders are caused by underlying antioxidant response abnormalities. Ozone produces a modest activation of beneficial anti-oxidant pathways, such as the nuclear factor erythroid – related 2 (Nrf2) pathway, which helps restore redox homeostasis, at low concentrations (13). In the accordance of above literature (14) evaluated the effectiveness of ozonized water in association with corticosteroids for the treatment of erosive OLP

and concluded that ozonized water seems to be effective as an adjunct therapy, in combination with topical corticosteroids, for the treatment of erosive OLP in terms of reducing pain and size reduction were significantly higher in ozone-treated group.

Above findings were in consistent with the present study results where patients treated with combination therapy of corticosteroid and ozonated olive oil (group III) showed marked reduction in all clinical parameters i.e pain, burning sensation, clinical sign and treatment efficacy rate. In another study done by author which aimed to assess the effect and adverse reaction of total glucosides of paeony capsule (TGPC) in combination with corticosteroids for the treatment of OLP also showed that combined treatment of TGPC with corticosteroids shows a definite therapeutic effect and may be considered as a safe and effective drug for OLP with minimal side effects (11). In the present study the distribution of Clinical sign scoring at T0, T1, T2, T3, T4, T5 and T6 was compared between four groups and it revealed that the clinical sign score 4 at T1, score 3 and 4 at T2, score 3 at T1 and score 1 and 2 at T4 was significantly more among combination therapy of Systemic Steroid & Ozonated olive oil (group III) and combination therapy of Lycopene & Ozonated olive oil (group IV) as compared to prednisolone (group I) and least in lycopene (group II) alone group. Clinical sign score 0 and 1 at T5 and T6 was significantly more among Combination therapy of Systemic Steroid & Ozonated olive oil and Combination therapy of Lycopene & Ozonated olive oil compared to Prednisolone and Lycopene alone groups (group I and group II respectively).

We also found that corticosteroid administration can improve clinical signs and symptoms in OLP patients, though less efficient in comparison to combination therapy with ozonated olive oil. These findings were consistent with previous studies, which reported that the combination therapy of corticosteroid with the ozone and other herbal products shows improvement in erosive OLP. Combined treatment, on the other hand, is more likely to retain a curative impact since it promptly decreases signs and symptoms, prevents relapse and improves and consolidates therapeutic results as compare to the monotherapy treatments. As systemic corticosteroid regimens in OLP differ according to patient-related criteria such as weight, medical status, the severity of oral lesions, and previous response to therapies proposed, according to Kini et al.[15]In this trial, owing to their need to benefit from Prednisolone as an alternative with the least possible side effects, treatment was started with 40 mg for four consecutive weeks followed by tapered doses which was in line with clinical trial done by Kushwaha et al (16).

Thus, there have been wide comparisons observed between different modalities in previous literature, but the most favourable curing treatment modality has not been yet established for the symptomatic OLP. Although the sample size of the preset study was small, it seems that the combination therapy of ozonated olive oil with the corticosteroid and the lycopene have beneficial effects on the treatment of the erosive OLP signs and symptoms. In the previous literature a wide comparisons is observed between different modalities, but the most favourable curing treatment modality has not been yet established for the symptomatic OLP. So in future more research should be conducted with a bigger sample size which would provide a more accurate forecast of ozonated olive oil's

efficiency in OLP and would further authenticate the role and efficacy of ozonated olive oil in erosive OLP.

Conclusion

On the basis of the present results of the current study and the diversity actions of ozonated olive oil i.e. anti-inflammatory effects, healing, anti-microbial and anti fungal properties etc., it could be concluded that ozonated olive oil may be used as a synergistic or adjuvant therapy with other modalities as it did not exhibits any unwanted adverse effects and may be considered as most favourable curing treatment modality for the symptomatic OLP.

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