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Evaluation of low level laser therapy versus topical steroids in management of symptomatic oral lichen planus by detecting the level of salivary interleukin-6: Controlled clinical trial

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Abstract---Background: Oral lichen planus (OLP) is a relatively common chronic inflammatory immune-mediated disease affecting the oral mucosa with episodes of exacerbations and remissions. The current study was aimed to compare between the therapeutic outcomes of using low level laser therapy (LLLT) and topical steroids in management of symptomatic OLP and to correlate between the salivary levels of interleukin-6 (IL-6) in relation to the clinical scores (CS) and pain visual analogue scores (P-VAS) before and after treatment. Subjects and methods: 40 participants were included in this study and were divided into 4 groups of 10 participants each. Group (I) included ten symptomatic atrophic or erosive OLP patients and received topical steroid (triamcinolone acetonide 0.1%). Group (II) comprised also of ten patients having symptomatic OLP and managed with LLLT using 810 nm diode laser. Group (III) included ten patients

with asymptomatic reticular OLP. Group (IV) included ten healthy volunteers having no oral or skin lichen planus lesions. Results: Clinical and biochemical analysis revealed that the mean values of (CS), (P-VAS) and IL-6 salivary concentrations before treatment were statistically significantly higher than after treatment in both groups (I) and (II), where group (I) showed a higher value of percentage change in salivary IL-6 concentration than group (II) yet the difference was not statistically significant denoting that both topical steroids and diode laser photobiomodulation can be used effectively in management of symptomatic OLP. Conclusions: LLLT may be considered as an alternative modality in treatment of symptomatic OLP especially when corticosteroids are contraindicated or in the case of suspected resistance. Salivary IL-6 was positively correlated with (CS) and (P-VAS) in OLP patients and could be used as a non-specific biomarker for monitoring the effectiveness of OLP treatment modalities.

Keywords---low level laser therapy, interleukin-6, oral lichen planus, biomarkers.

Introduction

Oral lichen planus is a relatively common chronic immunomediated disease affecting oral mucosa and characterized by episodes of exacerbation and remission. The accurate prevalence of OLP is still contradictory and doubtful. The disease has a female gender predilection and usually affecting middle-aged individuals [1].

Clinical presentations and manifestations of OLP are relatively diverse and in certain instances clinicians face difficulty in identification of atypical lesions. The manifestations of OLP range from just painless roughness in the mucosal lining of the oral cavity to mucosal atrophy or ulcerations where patients' complains are usually burning sensation and sensitivity to hot, citric or spicy foods and beverages [2].

World Health Organization (WHO) in 1997 differentiated OLP lesions into seven morphological subtypes including reticular, papular, plaque-like, atrophic, bullous, erosive and ulcerative. The atrophic-erosive subtype is usually associated with pain and burning sensation that affects the patient's quality of life and interferes with food intake that may lead to serious consequences [3].

The characteristic histopathological features of OLP include basal cell hydropic degeneration and a marked band-like lymphocytic infiltrate under the epithelium. Additional microscopic findings involve the presence of abundant eosinophilic colloid or cytoid bodies along the epithelial-connective tissue interface known as Civatte bodies, saw-tooth shaped rete ridges, acanthosis with variable thickness of spinous layer, hyperkeratosis and ulceration [4].

Although OLP has been and still remains the focus of extensive research, there is no current consensus on its precise etiology. Several predisposing factors are

implicated in its etiopathogenesis by alternating antigen specificity and disrupting self-tolerance of basal keratinocytes, thus targeting them for the cell-mediated immune damage. These predisposing factors can be broadly categorized into internal and external factors. Internal risk factors include genetic background, psychological disorders and systemic diseases as diabetes mellitus, hypertension and thyroid dysfunction. External predisposing factors comprise infectious agents, food allergies, habits, trauma and exogenous agents associated with lichenoid lesions as dental restorative materials, some medications and organ transplantations [5].

There are several mechanisms that are postulated in the immune pathogenesis of OLP, these mechanisms include: antigen-specific cell-mediated immune response and nonspecific autoimmune responses. The specific OLP antigen is unknown, although it may be a self-peptide, thus defining OLP as an autoimmune disease. The non-specific mechanisms that are involved in the immune-pathogenesis of OLP include: The disruption of epithelial basement membrane (BM), the release of chemokines (CK), the release of matrix metalloproteinases (MMP), heat shock proteins (HSP), and Langerhans and Mast cells activation. These mechanisms lead to the movement of lymphocytes into the epithelium to cause destruction of keratinocytes [6].

Recently, detection of some biomarkers through biochemical methods as enzyme linked immunosorbent assay (ELISA), immuno-blotting (IB), immuno-precipitation (IP), radioimmunoassay (RIA) and chemiluminescence immunoassay (CLIA) have been introduced for assessment of malignant potentiality of some OLP lesions or monitoring the treatment response to the various therapeutic modalities [7].

Among these biomarkers, measuring salivary cytokines as interleukins IL-4, IL-6, IL-17, IL-18, IFN- γ , and TNF- α , which are higher in their concentration in OLP patients than healthy controls. However, these salivary cytokines are not specific to OLP and can be released in the saliva in many other chronic inflammatory conditions, but they can differentiate between different subtypes of OLP and assess the severity of the condition [8].

IL-6 is one of most important cytokines involved in OLP immuno-pathogenesis. *Zhang and his research team* demonstrated that there was a significant correlation between serum and salivary levels of IL-6 in Chinese OLP patients. The levels of this cytokine in saliva went up with the levels of its serum partner in the OLP group. They also found that salivary levels of IL-6 are greater than the serum levels, and salivary sample is more convenient and safer than blood sample [9].

Several treatment modalities have been introduced for management of symptomatic OLP but all currently available modalities are palliative and not curative. Patient education about the nature of OLP is tremendously significant. Many patients are concerned about the possibilities of its malignancy and contagiousness. They should know the chronicity of the disease and the expected periods of exacerbations and remissions. Treatment of OLP is aimed primarily at eliminating the symptoms and extending the periods of remission [10].

The current available therapeutic modalities of OLP include pharmacological agents as corticosteroids, retinoids, immune modulatory drugs like calcineurin inhibitors, and dapsone. In addition, several non-pharmacological modalities have been used in OLP management such as photodynamic therapy, lasers, Aloe vera and curcuminoid [11].

Corticosteroids are the gold standard in treatment of OLP and they have been the backbone of its management. The Corticosteroids that are used in management of OLP are systemic, intra-lesional and topical corticosteroids. The motivation behind their usage is their ability to modulate inflammatory and immune response. They act by decreasing the lymphocytic exudate and stabilizing the lysosomal membranes. However, long term usage of corticosteroids has many drawbacks as susceptibility to opportunistic infections, mucosal atrophy, and incompetence with some systemic diseases as diabetes, hypertension and decrease in their pharmacological effectiveness with prolonged use [12].

The use of low-level laser therapy (LLLT) as an alternative modality to corticosteroids has been of great interest in the recent years. LLLT, also known as photobiomodulation, is a non-pharmacological, non-invasive clinical application, which has potential analgesic, anti-inflammatory, immunomodulatory, and biostimulating effects, with minimum reported adverse effects [13].

Aim of the Study

The aim of this study was to compare between the therapeutic effects of low level laser therapy (LLLT) and topical steroids in management of symptomatic atrophic or erosive OLP on a clinical and biochemical basis.

Subjects and Methods

Forty participants were enrolled into this study, twenty of them were clinically and histopathologically confirmed to have symptomatic atrophic or erosive OLP during the exacerbation period. Ten other participants were proven clinically and histopathologically to have asymptomatic reticular or papular OLP and the last ten volunteers in the study were healthy individuals having no oral or skin lesions of lichen planus or any other oral lesions. All participants were selected from or recruited to the outpatient clinic of Oral Medicine, Periodontology, Oral Diagnosis and Radiology department Faculty of Dentistry Ain Shams University.

Inclusion criteria

Participants involved in this study were male and female patients, aged from 25 to 60 years. They were systemically healthy individuals according to the American Society of Anesthesiologists (ASA class I) and have no skin lichen planus lesions or any oral lesions other than OLP.

Exclusion criteria

The participant excluded from this study were smoker patients, pregnant or breast-feeding females, vulnerable patients as prisoners and mentally retarded

individuals and OLP patients with history of drug induced lichenoid lesions or hypersensitivity to the topical corticosteroid used in this study or any of its ingredients, in addition to patients gave previous history of drugs potentially effective on OLP such as antimalarial agents, retinoid, corticosteroids or immunosuppressive drugs from less than 2 weeks for topical medications, and 4 weeks for systemic medications prior to starting the study and in case of loss of pliability or flexibility of OLP lesions ^[14].

Ethical procedures

All subjects enrolled into this study were provided with detailed verbal and written information about the study and to insure complete understanding and agreement to each step they were asked to sign a written informed consent before their participation. The study protocol was approved by the Ethical Committee of Faculty of Dentistry Ain Shams University and took the number (FDASU-Rec IM 180608).

Study design

The forty participants involved in the study were equally distributed into four groups of ten participants each:

- *Group (I)* Included ten patients having symptomatic atrophic or erosive OLP and managed with topical steroid (triamcinolone acetonide 0.1%) oral paste four times per day (after each meal and at bed time) for four successive weeks.
- *Group (II)* Included ten patients having symptomatic atrophic or erosive OLP and managed with low level laser therapy using 810 nm diode laser twice weekly for four successive weeks with maximum of eight sessions.
- *Group (III)* Included ten patients with asymptomatic reticular or papular OLP and considered as positive control group.
- *Group (IV)* Included ten healthy volunteers having no oral or skin lichen planus lesions or any other oral lesions.

Study and treatment protocol

At first clinical presentation, information related to patient history including: age, gender, disease process, medical history, drug history, family history, and clinical signs and symptoms were documented for each patient. Patients having OLP were examined clinically by a magnifying mirror and using spot light for the oral lesions, the distribution of the lesions and the affected areas were recorded, also their skin was examined and there were no extra-oral manifestations.

Before initiation of the study participants were subjected to full mouth rehabilitation including instructions to self-performed plaque control measures, full mouth supra and sub-gingival scaling and root debridement and removal of any local irritating factors (fractured tooth, poor restorations or prosthesis) if needed.

A punch biopsy was taken to confirm the diagnosis of OLP. The biopsy site was carefully selected to avoid areas that are completely denuded of epithelium and to include keratotic areas and part of normally looking mucosa, and then 6 mm punch biopsy was carried out. The punch is gently inserted into the mucosa with a rotating motion to facilitate cutting the tissue to the appropriate depth. Tissue forceps and a scalpel were used to remove the biopsy sample. The site of the biopsy was sutured by 000 black silk sutures. Biopsies were fixed in 10% neutral buffered formalin. The volume of fixative should be at least 10 times the volume of the sample to avoid improper fixation or autolysis, then fixed biopsy is processed for hematoxylin and eosin (H&E) staining



Figure (1): Biopsy punch used in obtaining the biopsy *

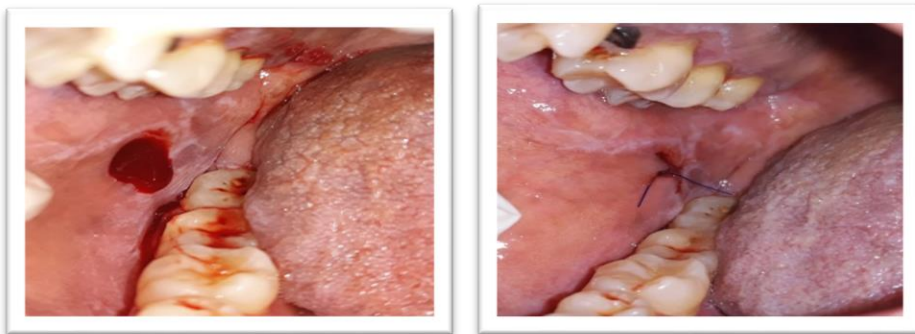


Figure (2): Biopsy and suturing techniques

Un-stimulated salivary samples were taken to detect the level of IL-6 for all groups at the baseline and after four weeks of treatment in group (I) and (II). Samples were obtained by asking participants to swallow first then tilt the head forward, saliva were collected by aspiration using sterile syringe and immediately stored in Eppendorf tubes, and then they were freezed at or below -20 °C to prevent bacterial growth and further degradation of salivary samples. Salivary IL-6 levels were assessed by using Human IL-6 ELISA Kit supplied by Bioassay® Technology Laboratory Shanghai, China - Cat.No : E0090Hu.

*Biopsy Punch Miltex®, Inc. York PA 17402 USA made in Japan.

Patients in group (I) were instructed how to use the medication Triamcinolone acetonide 0.1% in orabase (Geo Oralog®)** by drying the affected areas then applying a thin layer of the medication onto the symptomatic oral lesions four times a day (after each meal and at bed time) without eating and drinking for 30 minutes after application.

Patients in group (II) received low level laser therapy, they were subjected to 810 nm diode laser (Photon Plus (3W) Zolar®)*** twice weekly for four successive weeks with maximum of eight sessions with a total exposure time of eight minutes in four successive applications of two-minutes each with one-minute rest in between and the exposure parameter will be adjusted to output power of (3W) and frequency of (30 Hz) and energy of (180 Joule) with a continuous non contacting mode and the delivery system is by using 300 micrometer diameter and 5 mm long fiberoptic tip that was focused to the affected mucosa until blanching of tissue occurred. The patient and the operator protected their eyes from the laser beam by wearing protective special eye glasses supplied with the device



Figure (3): Zolar Photon Plus® soft tissue diode laser system

The clinical score values (CS) and pain visual analogue scale (P-VAS) were measured before and throughout the treatment period in groups (I) and (II) while they were measured at the baseline only in groups (III) and (IV). The salivary samples were taken before and after treatment in both groups (I) & (II), while in groups (III) and (IV) samples were taken once at baseline.

** Geo Oralog Triamcinolone Acitonide 0.1% 15 gm – Oral paste Marcyrl Pharmaceutical Industries El Obour City the west extension blook 20005- Egypt.

*** Photon Plus (3W) Zolar® Soft Tissue Diode Laser - Zolar technology & Mfg Co Inc 6315 Shwason Drive, Unit 7-8, Mississauga, Canada.

Results

The results of the current study revealed that mean and standard deviation (SD) values for (CS) before treatment showed that group (II) (4.40 ± 0.70) had the highest mean value, followed by group (I) (4.20 ± 0.790). Pairwise comparisons showed values of group (I) & (II) to be significantly higher than other groups

($p < 0.001$). After treatment, Group (II) (2.70 ± 0.95) showed a significantly higher mean value than group (I) (1.90 ± 0.57) ($p = 0.037$). Regarding the percentage change, group (I) (53.17 ± 15.92) had a higher value of percentage change than group (II) (40.17 ± 15.04) yet the difference was not statistically significant ($p = 0.077$).

Mean and (SD) values for (P-VAS) at the baseline showed significant difference between different groups ($p < 0.001$). Group (II) (7.95 ± 1.32) had the highest mean value followed by group (I) (7.55 ± 1.26). Pairwise comparisons showed value of group (I) and (II) to be significantly higher than other groups ($p < 0.001$). After 1st week of treatment, group (II) (6.70 ± 1.30) had significantly higher mean value than group (I) (5.45 ± 1.01) ($p < 0.031$) while after the 2nd week, group (I) (5.15 ± 1.27) had higher mean value than group (II) (4.45 ± 1.17) yet the difference was not statistically significant ($p = 0.188$). After 3rd week, group (I) (3.90 ± 0.84) had higher mean value than group (II) (3.05 ± 0.90) yet the difference was not statistically significant ($p = 0.063$) and at the end of treatment after 4th week group (I) (2.50 ± 0.85) had a significantly higher mean value than group (I) (1.50 ± 1.08) ($p = 0.045$).

Mean and (SD) values for IL-6 salivary concentration measured in (ng/ml) before treatment showed a significant difference between values of different groups ($p < 0.001$). Group (II) (153.50 ± 16.16) had the highest mean value, followed by group (I) (148.26 ± 20.51) and (III) (119.34 ± 8.75), while the lowest value was found in group (IV) (80.65 ± 6.13). Pairwise comparisons showed values of groups (I) and (II) to be significantly higher than values of other groups ($p < 0.001$). After treatment, group (II) (120.34 ± 18.65) had a higher mean value than group (I) (110.62 ± 11.61) yet the difference was not statistically significant ($p = 0.179$). Regarding the percentage change, group (I) (24.79 ± 7.48) had a higher value of percentage change than group (II) (21.92 ± 4.60) yet the difference was not statistically significant ($p = 0.314$).

Correlations between IL-6 salivary concentrations and (CS) or (P-VAS) revealed that there was a moderate positive correlation between (CS) and IL-6 salivary concentration values which was statistically significant ($r_s = 0.490$, $p < 0.001$), while there was a weak positive correlation between (P-VAS) and IL-6 salivary concentration values that was statistically significant ($r_s = 0.240$, $p = 0.002$).

Table (1): Mean and (SD) values for (CS) in different groups

Follow-up	(CS) (Mean $\pm$ SD)				p-value
	Group (I)	Group (II)	Group (III)	Group (IV)	
Before	4.20 ± 0.79^A	4.40 ± 0.70^A	1.00 ± 0.00^B	0.00 ± 0.00^B	$< 0.001^*$
After	1.90 ± 0.57^B	2.70 ± 0.95^A	—	—	0.037^*

Different superscript letters indicate a statistically significant difference within the same horizontal row *; significant ($p \leq 0.05$) ns; non-significant ($p > 0.05$)

Table (6): Mean and (SD) values for (VAS) in different groups

Follow-up	(VAS) Mean±SD				p-value
	Group (I)	Group (II)	Group (III)	Group (IV)	
Baseline	7.55±1.26 ^A	7.95±1.32 ^A	0.00±0.00 ^B	0.00±0.00 ^B	<0.001*
1st week	5.45±1.01	6.70±1.30	—	—	0.031*
2nd week	4.45±1.17	5.15±1.27	—	—	0.188ns
3rd week	3.05±0.90	3.90±0.84	—	—	0.063ns
1 month	1.50±1.08	2.50±0.85	—	—	0.045*

Different superscript letters indicate a statistically significant difference within the same horizontal row *; significant ($p \leq 0.05$) ns; non-significant ($p > 0.05$)

Table (3): Mean and (SD) values for IL-6 salivary concentration (ng/ml) in different groups

Follow-up	(IL-6) (Mean±SD)				p-value
	Group (I)	Group (II)	Group (III)	Group (IV)	
Before	148.26±20.51 ^A	153.50±16.16 ^A	119.34±8.75 ^B	80.65±6.13 ^C	<0.001*
After	110.62±11.61 ^A	120.34±18.65 ^A	—	—	0.179ns

Different superscript letters indicate a statistically significant difference within the same horizontal row *; significant ($p \leq 0.05$) ns; non-significant ($p > 0.05$)

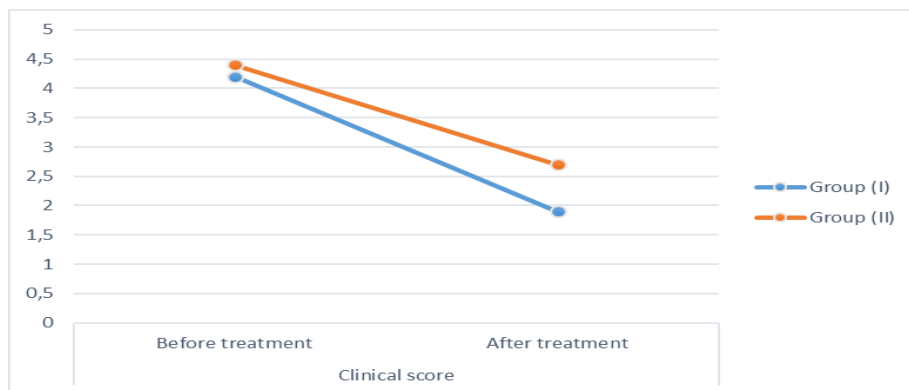


Figure (4): Line chart showing mean values of (CS)

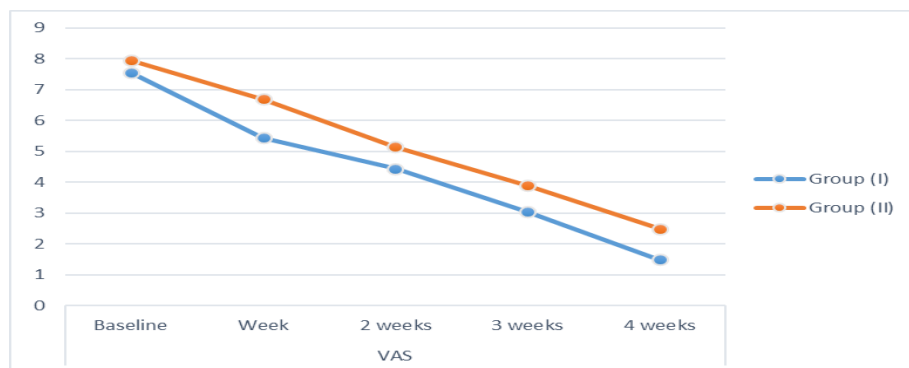


Figure (5): Line chart showing mean values for (P-VAS)

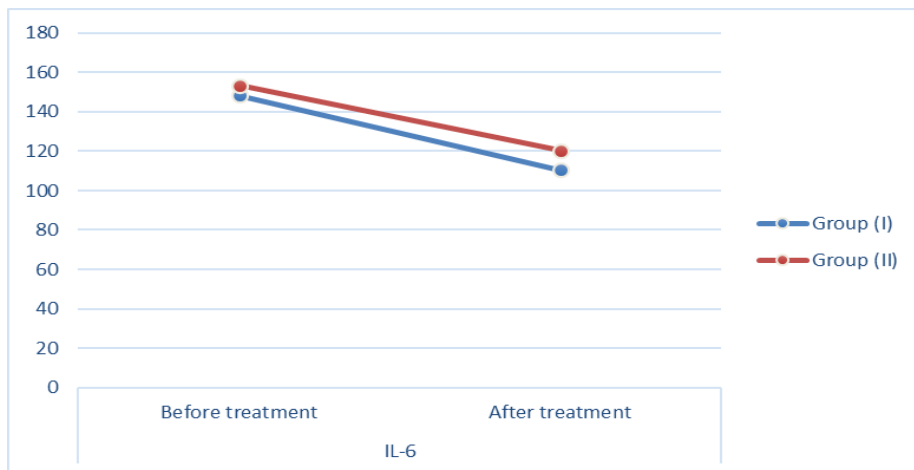


Figure (6): Line chart showing mean values of IL-6 salivary concentration (ng/ml)

Discussion

OLP is a relatively common chronic immune mediated disease. It can be seen in different clinical presentations. The most aggressive subtype of OLP is the erosive/atrophic form which is characterized by pain and burning sensations with episodes of remission and exacerbation. The contemporary available treatment modalities of OLP are palliative and yet there is no definite cure. Topical steroids are the gold standard treatment for OLP.

Previous studies have compared the outcomes of LLLT and topical steroids in the management of OLP and revealed contradictory results. *ElShenawy and Eldin* concluded from their clinical trial that OLP patients managed with topical steroid showed significant improvement in signs and symptoms as compared to those patients treated with LLLT [15]. Similar results were reported by *Othman and his colleagues* [16]. However, *Jajarm and his research colleagues* reported that OLP patients managed with LLLT showed better clinical outcomes than the management with topical steroids [17]. Furthermore, *Dillenburg and his study co-workers* stated that application of LLLT in management of OLP revealed statistically significant clinical outcomes than topical steroid therapy [13].

There was statistically significant difference between (CS) values before and after treatment in both group (I) and (II) ($p=0.005$ and 0.004) respectively, denoting that both topical corticosteroid and LLLT can be used effectively in management of OLP. After treatment, Group (II) showed a significantly higher mean value than group (I) ($p=0.037$). Thus meaning that topical steroid used in managing OLP in group (I) showed better results than LLLT used in group (II), while the percentage change of (CS) between values before and after treatment in both group (I) and (II) was non-statistically significant ($p=0.077$) denoting that LLLT may be used as alternative in treatment of OLP. This was coincided with the finding of *ElShenawy et al.* in which they reported that topical steroids reduce their (RAE) clinical scores of OLP more than laser therapy [18].

Regarding (P-VAS), there was a significantly higher mean value of percentage change from the baseline to the 1st week and after the 4th week of treatment between group (I) and group (II), ($p=0.008$) ($p=0.021$) respectively denoting that topical corticosteroid is more effective in reducing pain both after 1st week interval and at the end of treatment after 4 weeks rather than LLLT. Although the values during the 1st to 2nd week, 2nd to 3rd week and 3rd to 4th week had no statistically significant differences between group (I) and (II) meaning that topical steroid give a rapid enhancement and relief of pain than LLLT, where both treatment modalities gave nearly equivalent relief after 1 week. These results were coincided with *Jain et al.* study in which they had reported immediate relief of pain with corticosteroid more than with laser photobiomodulation [19].

Regarding the salivary IL-6 levels before and after treatment in both groups, the both treatment modalities leads to a statistically significant difference ($p<0.001$) in IL-6 concentrations before and after treatment which indicates that topical corticosteroids and LLLT are biochemically effective in management of OLP. Furthermore the percentage change of IL-6 concentrations before and after treatment show non-significant value between the two groups ($p=0.314$) indicating that LLLT is an alternative to topical steroid therapy. These results were matching what had been reported by *Ferri et al.* that there was statistically significant reduction in levels of measured cytokines before and after treatment by topical steroid and photobiomodulation [20].

Conclusions

The results of the current study demonstrated that LLLT may be considered as an alternative modality in managing symptomatic OLP especially when corticosteroids are contraindicated or in the case of suspected resistance or incompliance. Whereas, management of symptomatic erosive/atrophic OLP with triamcinolone acetonide 0.1% is slightly more effective than 810 nm diode laser photobiomodulation therapy. The salivary level of IL-6 is higher in the erosive/atrophic subtype of OLP than the reticular form and both are higher than the healthy controls. In addition, treatment modalities as topical steroids and LLLT can cause significant reduction in IL-6 salivary levels so salivary IL-6 could be used as a non-specific biomarker for monitoring OLP and therapeutic agents used for its management.

Conflict of interest

There were no conflicts of interest to disclose.

Authorship statement

We confirm that all listed authors meet the authorship criteria and that all authors agree with the manuscript's content.

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