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ORIGINAL RESEARCH

Efficacy of Spirulina 500 mg vs Triamcinolone Acetonide 0.1% for the Treatment of Oral Lichen Planus: A Randomized Clinical Trial

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Abstract

Aim: The present study aimed at evaluating the efficacy of spirulina 500 mg in reducing the burning sensation and lesion size in oral lichen planus (OLP).

Materials and methods: A total of 60 subjects who attended the oral medicine specialty clinic with histopathologically confirmed OLP and having symptoms of burning sensation were recruited for the study. They were randomly divided into two groups: group A (30) subjects were prescribed Spirulina 500 mg twice daily along with only a week application of topical triamcinolone acetonide 0.1% thrice daily; group B subjects were prescribed topical triamcinolone acetonide 0.1% alone thrice daily for 8 weeks. Both the groups were followed up posttreatment monthly for three consecutive months.

Results: Data were recorded, and statistical analysis by using ANOVA one-way test, and Chi-square test were performed, which showed statistically significant *p*-value (<0.005) for the parameters "burning sensation" and "size of the lesion". When compared between groups, group A showed a favorable outcome of the intervention.

Conclusion: Spirulina 500 mg supplementation twice daily could be effective adjunct therapy with steroids to treat OLP.

Clinical significance: This research allowed us to delve into spirulina as one of the treatment modalities for OLP. Further studies are needed as it is a rich source of proteins and vitamins and demonstrates potent anti-inflammatory, immunomodulatory, and antioxidant actions.

Keywords: Burning sensation, Oral lichen planus, Spirulina, Triamcinolone acetonide, Visual Analog Scale score.

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Introduction

Lichen planus is a mucocutaneous immune-mediated disorder involving stratified squamous epithelium that affects oral and genital mucous membrane, skin, nails, and scalp. This condition affects 0.5–2.0% of the general population and most commonly involves middle-aged patients between 30 and 60 years. Females show more predilection than males, with a ratio of 1.4:1.[1,2] Clinically it presents as reticular, papular, plaque-like, erosive, atrophic, or bullous types involving the buccal mucosa, tongue, and the gingiva more commonly.[2] Oral lichen planus (OLP) often presents with a typical bilateral pattern, and a wide range of factors have been implicated in its pathogenesis ranging from viruses like hepatitis C, local factors like plaque and calculus, and psychological triggers like stress-anxiety-depression.[3,4]

It is a T-cell mediated autoimmune disease; the cytotoxic CD8+ T cells trigger the apoptosis of the oral epithelium. The antigen expression or antigen stimulation leads to the migration of CD8+ cells into the epithelium. These migrated CD8+ cells are activated directly by an antigen-binding to major histocompatibility complex (MHC)-1 on keratinocytes or through activated CD4+ lymphocytes. This causes the proliferation of Langerhans cells in conjugation with upregulation of MHC-II expression. The subsequent antigen presentation to CD4+ cells and interleukin (IL)-12 activates CD4+ T helper cells, further activating CD8+ T cells through receptor interaction and interferon γ (INF-γ) and IL-2. The

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activated CD8+ T cells thus kill the basal keratinocytes through tumor necrosis factor (TNF)-α, Fas-FasL-mediated or granzyme B-activated apoptosis, leading to ulceration in the oral cavity.[2]

Corticosteroids are considered the first-line treatment for OLP; apart from them, calcineurin inhibitors, retinoids, dapsone, hydroxychloroquine, mycophenolate mofetil, and enoxaparin have also contributed significantly toward the treatment of the disease.[2] Different treatment regimens were attempted to improve the refractory lesions, but a complete cure of OLP has not been accomplished.

Spirulina (spirulina platensis) is blue-green algae and a rich source of protein and vitamin supplementation with no significant side effects.[5] It also has anti-inflammatory, immunomodulatory, antioxidant, and gastroprotective properties.[6] It has a high protein content (up to 70%), vitamins, like B12 and provitamin A (β-carotenes), and minerals, especially iron. It also contains phenolic acids, tocopherols, and γ-linolenic acid. It has easily digested as it lacks cellulose cell walls.[7] The high levels of phycocyanin, beta carotene, and superoxide dismutase can have a potential chemopreventive role in high-risk oral potentially malignant disorders.[8]

The phycocyanin inhibits proinflammatory cytokine formation, such as TNFα, suppresses cyclooxygenase-2 (COX-2) expression, decreases the production of prostaglandin E(2), suppresses the activation of nuclear factor-κB by preventing the degradation of cytosolic IκB-α—thus, modulating the mitogen-activated protein kinase (MAPK) activation pathways. Another ingredient of spirulina, β-carotene, has been reported to have antioxidant and anti-inflammatory activities.[9]

Due to the wide range of benefits of spirulina on immune downregulation mechanism and free radicle scavenging action, the present study was aimed at evaluating its efficacy in the overall reduction of inflammation in OLP thereby reducing the burning sensation and the lesional size as a clinical outcome.

Materials and Methods

The present study was conducted on subjects who were clinically and histopathologically diagnosed with OLP, reporting to the oral medicine specialty clinic from January 2019 to November 2020. After obtaining ethical clearance for the study from the institutional ethical committee with approval number PMVIDS&RC/IEC/OMR/DN/0314-2019. All the subjects who reported to the department with a burning sensation in the mouth and clinical evidence of OLP were informed about the study as well as the medications. Informed consent was duly signed by all subjects and the study was conducted following the code of ethics of the world medical association (declaration of Helsinki). Confidentiality was maintained in every stage of the study.

The study consisted of 60 subjects with OLP. They were randomly divided into two groups (A and B), with 30 in each group. This was a randomized, prospective, single-blinded trial. The inclusion criteria consisted of subjects between 18 and 70 years aged, of either gender, and only those subjects with visual analog scale (VAS) scores between 5 and 8. The exclusion criteria consisted of subjects who were already under medications for OLP, subjects with chronic medically compromised conditions and subjects allergic to spirulina and steroids, and also pregnant individuals.

A complete clinical examination was performed. Clinical parameters like the burning sensation and size of the lesion were evaluated on an evaluation sheet. Burning sensation on VAS was assessed with a grading of 0–10. The lesion size was measured using a Vernier caliper, and clinical assessment was based on the Thongprasom scale. According to the Thongprasom scale, the scoring ranges from 0 to 5; A score of 0 is designated for no lesion or normal mucosa; score 1 is designated for mild white striae with no erythematous area; score 2 for white striae with an atrophic area (<1 cm); score 3 for white striae with an atrophic area (>1 cm); score 4 for white striae with an erosive area (<1 cm); score 5 for white striae with an erosive area (>1 cm).[10] At each subsequent visit, measurements of each lesion were planned to be carried out at the triage area with strict COVID-19 prevention protocols.

Group A subjects were prescribed spirulina 500 mg (Healthvit company, Gujarat) two times a day for 8 weeks along with 0.1% triamcinolone acetonide oral paste thrice daily for a week. Spirulina was continued for the entire 8-week treatment period with a 3-month follow-up, however, the oral steroid paste was discontinued after a week. The follow-up period considered was at the end of the first month after cessation of treatment, the end of the second month, and the final follow-up at the end of the third-month posttreatment cessation. Group B subjects were given topical triamcinolone acetonide oral paste three times a day for a period of 8 weeks if the symptoms persisted and followed up similar to group A patients. The application of the steroid oral paste was tapered accordingly based on the burning sensation and the size of the lesion. The subjects were asked to report back if any side effects were noted on the following drug administration.

All the clinical parameters were noted at every 7-day interval for 8 weeks, and later, monthly follow-ups were done for 3 months. The data thus obtained was subjected to the statistical analysis using IBM SPSS version 27 windows operating tool. The parameters VAS score for burning sensation and size of the lesion (based on the Thongprasom scale) were noted on each visit. The data thus obtained were entered, and statistical analysis was carried out using the Chi-square test and ANOVA test with variance at p-value <0.005.

Results

A total of 60 subjects were included in the present study and divided randomly into group A and group B consisting of 30 subjects each. The following were the individual characteristics considered for the analysis:

Gender and Lesional Site Characteristics

The participants in the study included were 41 females and 19 males. A clear indication of a high incidence of lesions in the female population. The reticular type of lichen planus was more common [26 subjects (43.4%)] followed by the erosive and atrophic types. The most common site for the lesion involvement seen was right and left buccal mucosa in 34 (56.7%) subjects, and the site with less prevalence was the tongue (6.7%).

Parameter of Burning Sensation Evaluation by VAS Score

Group A Participants

Mean VAS scores were evaluated at different time intervals, at the first visit and at the third follow-up at the end of 3 months of posttreatment cessation, which were 7.23 ± 1.95 and 0.70 ± 1.66, respectively (Table 1). There was a significant reduction in mean VAS scores from the initial presentation day and the last follow-up visit after 3 months.

Group B Participants

In this group, the mean scores at the first visit and the final follow-up after 3 months were 7.40 ± 2.07 and 3.90 ± 2.91, respectively

Table 1: Mean VAS scores at different time intervals of group A

Descriptive								
VAS								
					95% confidence interval for mean			
	N	*Mean*	*Std. deviation*	*Std. error*	*Lower bound*	*Upper bound*	*Minimum*	*Maximum*
First visit	30	7.2333	1.95965	0.35778	6.5016	7.9651	5.00	10.00
Week 1	30	4.8000	2.78419	0.50832	3.7604	5.8396	0.00	9.00
Week 4	30	2.8000	2.35475	0.42992	1.9207	3.6793	0.00	8.00
Week 8	30	1.2333	1.86960	0.34134	0.5352	1.9315	0.00	8.00
First follow-up	30	0.7667	1.69550	0.30955	0.1336	1.3998	0.00	8.00
Second follow-up	30	0.9000	1.82606	0.33339	0.2181	1.5819	0.00	8.00
Third follow-up	30	0.7000	1.66402	0.30381	0.0786	1.3214	0.00	8.00
Total	210	2.6333	3.09403	0.21351	2.2124	3.0542	0.00	10.00

Table 2: Mean VAS scores at different time intervals of group B

Descriptive								
VAS								
					95% confidence interval for mean			
	N	*Mean*	*Std. deviation*	*Std. error*	*Lower bound*	*Upper bound*	*Minimum*	*Maximum*
First visit	30	7.4000	2.07780	0.37935	6.6241	8.1759	5.00	10.00
Week 1	30	5.6667	2.78337	0.50817	4.6273	6.7060	0.00	10.00
Week 4	30	3.7333	2.54522	0.46469	2.7829	4.6837	0.00	8.00
Week 8	30	2.2667	1.89251	0.34552	1.5600	2.9733	0.00	6.00
First follow-up	30	2.6667	2.29442	0.41890	1.8099	3.5234	0.00	8.00
Second follow-up	30	2.9667	2.39947	0.43808	2.0707	3.8626	0.00	8.00
Third follow-up	30	2.6333	2.28161	0.41656	1.7814	3.4853	0.00	8.00
Total	210	3.9048	2.91350	0.20105	3.5084	4.3011	0.00	10.00

Table 3: One-way analysis of variance (ANOVA) between the VAS scores of group A and group B

ANOVA					
VAS					
	Sum of squares	*Df*	*Mean square*	*F*	*Sig.*
Between group A and group B	1142.067	6	190.344	44.998	0.000*
Within each group	858.700	203	4.230		
Total	2000.767	209			

*Highly significant

(Table 2). Compared to the first and third follow-up visits the values significantly reduced in the group. It was noteworthy that there was a significant reduction in VAS scores from the first visit to the follow-up phase of the study. On one-way analysis of variance (ANOVA) showed a statistically significant difference ($p = 0.00$) between the VAS scores in two groups—group A (spirulina) and group B (triamcinolone) and within the groups (Table 3).

While comparing the VAS scores implying the pain intensity between group A and group B, it was imperative that the mean VAS scores of both the groups at the first visit had similar values and decreased simultaneously until the 8th week (Fig. 1). However, the mean scores of group A subjects showed a plateau in the first and second months of posttreatment follow-up, which again decreased eventually at the final follow-up to 0.7 (Table 1). But the mean VAS scores of group B subjects showed an increase at the end of the first 1-month posttreatment cessation. They eventually decreased at the final follow-up after 3 months to 2.63 (Fig. 1 and Table 2). The interpretation could be drawn that the VAS scores reduced comparatively more in group A than group B participants.

Evaluation of Size of Lesion

Subjects in group A, at the first visit, the Thongprasom scale showed a score of 2 in nine individuals followed by scores of 3 and 4 in seven subjects, a score of 5 in five subjects, and least score in 2 of them. As the number of visits increased the scores showed a gradual decrease till the first follow-up visit. At the final follow-up, a significant number of subjects had no lesion ($n = 16$) followed

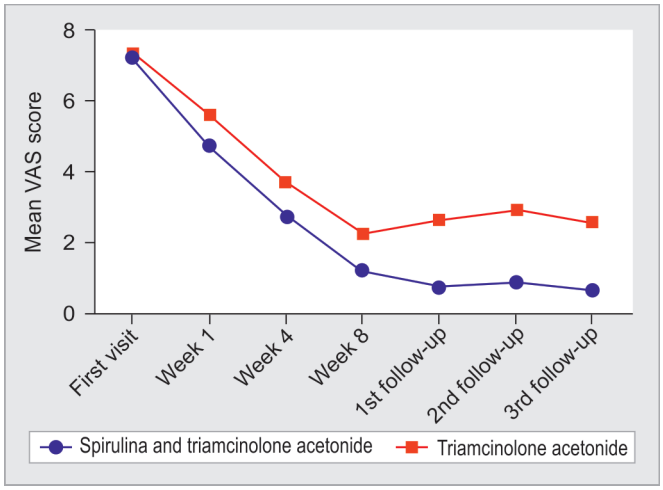

Fig. 1: Comparison of visual analog scores (VAS) indicating a change in pain intensity between spirulina and triamcinolone acetonide and triamcinolone acetonide groups

Table 4: Chi-square analysis of the lesion size at different time intervals in group A

		Lesion size							
		None	*Score 1*	*Score 2*	*Score 3*	*Score 4*	*Score 5*	*Total*	*p value*
	First visit	0	2	9	7	7	5	30	0.000*
	Week 1	1	3	10	9	4	3	30	
	Week 4	1	10	12	5	2	0	30	
Time	Week 8	4	12	13	1	0	0	30	
	First follow-up	7	14	9	0	0	0	30	
	Second follow-up	11	15	3	0	0	1	30	
	Third follow-up	16	10	3	1	0	0	30	
Total		40	66	59	23	13	9	210	

*Highly significant

Table 5: Chi-square analysis of the lesion size at different time intervals in group B

		Lesion size							
		None	*Score 1*	*Score 2*	*Score 3*	*Score 4*	*Score 5*	*Total*	*p value*
	First visit	0	3	7	8	8	4	30	0.000*
	Week 1	0	6	6	11	3	4	30	
	Week 4	0	9	10	8	3	0	30	
Time	Week 8	3	10	11	4	2	0	30	
	First follow-up	4	14	8	2	1	1	30	
	Second follow-up	4	18	3	3	0	2	30	
	Third follow-up	3	21	2	2	0	2	30	
Total		14	81	47	38	17	13	210	

*Highly significant

by score 1 ($n = 10$), score 2 ($n = 3$) and score 3 ($n = 1$) (Table 4). The Chi-square analysis showed a statistically significant p-value ($p < 0.05$) association between the size of the lesion and time intervals (Table 4).

Similarly, in group B subjects, at the first visit, there were eight individuals with scores of 3 and 4, respectively, followed by scores of 2 in seven, score 5 in four, and score 1 in three subjects. As the number of visits increased, the scores declined till the 8th week. By the final follow-up after 3 months, a significant number of subjects had a score of 1 ($n = 21$) followed by no lesion in three of them (Table 5). The Chi-square analysis showed a statistically significant p-value ($p < 0.05$) between the size of the lesion and the time intervals of presentation (Table 5).

When both the groups A and B were compared for lesion size, group A subjects showed faster healing than group B at different time intervals (visits).

Discussion

Oral lichen planus (OLP) is the intraoral counterpart of cutaneous OLP, affecting 1–2% of the population. About 15% of patients with OLP develop cutaneous lesions.[11] When compared, the proportion

of affected women is higher than the men, the same as in this study. The mean age of prevalence of the lesion reported was approximately 55 years.[12]

Typically, out of six clinical forms of OLP, reticular OLP is the most common form and relatively asymptomatic with a 43.3% prevalence. In our study, reticular lichen planus was found to be more common, but subjects were symptomatic with a burning sensation. The erosive, atrophic, and bullous forms are most symptomatic, often debilitating, and prompt to seek care.[13]

Due to varied clinical fluctuations in the disease representation, the management of OLP varies considerably. Several topical drugs have been suggested for oral lesions, such as steroids, calcineurin inhibitors (cyclosporine and tacrolimus), retinoids, and ultraviolet phototherapy. Topical steroids are widely used and accepted as the primary treatment choice among them.[11] However, they can produce adverse reactions, including secondary candidiasis, nausea, intolerance for oral use, refractory response, mucosal atrophy, delayed healing, and systemic absorption.[14] The adverse effects can also be attributed to the direct absorption of topical steroids via oral mucosa or ingestion following incorrect preparations.[4]

In OLP patients, there is higher oxidative stress, imbalance in the antioxidant defense system, and lipid peroxidation. There is increased oxidative DNA damage in the epidermis and protein modification in the dermis. Thus, antioxidant supplements like spirulina can potentially inhibit these defects and prevent the associated symptoms.

Spirulina, a unicellular blue-green alga, has a variety of health benefits and therapeutic properties. It also acts as an antioxidant and anti-inflammatory agent.[15] It contains multiple antioxidants like phytonutrients; beta-carotene, zeaxanthin, c-phycocyanin, vitamins like vitamin B1, vitamin B2, vitamin D3, vitamin B6, vitamin B12, and folic acid. These antioxidants can be pro-oxidants, thus helping in oxidative stress. Antioxidants in spirulina also offer generalized protection against free radicals.[16] Antioxidant-rich compounds and dietary compounds could also contribute to overall oral cancer chemoprevention and can also contribute to the potential reversal of premalignant lesions or conditions.[17]

Spirulina has shown promising results for treating oral leukoplakia[18] and oral submucous fibrosis.[8] Paul et al. evaluated that the oral antioxidant spirulina capsule (broken and powder is topically applied, four times a day) could be used as adjuvant therapy in the initial management of leukoplakia and was well tolerated without any side effects. The study concluded that the primary action was against free radicals formed due to stress, exposure to toxic chemicals, drugs, and poor diets.[19] Additionally, a study by Shetty et al. demonstrated that oral antioxidant spirulina could be used as adjuvant therapy in the initial management of oral submucous fibrosis (OSMF) patients with no side effects. The subjects in the experimental group were administered spirulina 500 mg twice daily along with biweekly intralesional steroids such as betamethasone 4 mg/mL for 3 months. The other group was treated with a placebo. The spirulina group showed better treatment outcomes concerning the mouth opening and burning sensation.[20] Similarly, Mulk et al. compared the efficacy of spirulina with pentoxifylline in the treatment of oral submucous fibrosis and found that spirulina capsules of 0.5 gm given twice daily for 4 months were more effective in decreasing the burning sensation when compared to pentoxifylline 400 mg given twice daily for 4 months.[8] Another study by Mahendra et al. put forth that spirulina gel, when applied for 120 days, as an adjunct to scaling and root planning, significantly improved the gingival condition in patients with chronic periodontitis.[21]

Though there are multiple studies regarding the management of symptomatic OLP using various antioxidants,[22] spirulina-based studies in OLP are lacking. Hence, there is a need for such studies.

The present study demonstrated that the group that received spirulina and triamcinolone performed better than the group that received only topical steroids. The patients in both groups showed a statistically significant improvement (p <0.000) in all the assessed parameters.

The shortcoming of this study included a small sample size and a lower duration of the follow-up. It is possible that the lesions might recur after 3 months of follow-up. Antioxidants are known to have a beneficial effect on various disorders on their prolonged usage. The duration of their supplementation in the present study was short; hence, the results may require further validation with a large sample size and extended follow-up. The other drawback included was the criteria implemented for the evaluation of lichen planus, where only the linear assessment of symptoms was done based on a VAS.

Conclusion

The exact etiology of OLP is still not understood. Though topical steroids remain a mainstay of treatment for symptomatic OLP, adding spirulina as an adjuvant can improve overall management; this effect could be attributed to the multiple antioxidant ingredients. Spirulina may be helpful to increase the refractory period between the remissions and may help manage recalcitrant lesions not responding to conventional therapy. However, more extensive studies with a bigger sample size across different population groups could further strengthen the role of spirulina as an adjuvant to topical steroids in OLP management.

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