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Lycopene versus corticosteroid in the treatment of symptomatic oral lichen planus patients: A randomized double blinded clinical trial

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ABSTRACT

Objectives: This trial is designed to evaluate the clinical effectiveness of oral lycopene (LPN) compared to prednisolone (PSN) in oral lichen planus (OLP) symptomatic patients.

Materials and Methods: 40 patients suffering from atrophic/erosive OLP were included in this double-blinded randomized clinical trial. Patients were equally and randomly assigned into 2 groups: LPN was administered in 10 mg/day (Group 1, n=20) and PSN was given as 40 mg/day (Group 2, n=20); for 8 successive weeks. Outcome measures included the visual analogue scale and clinical scoring. The un-stimulated salivary MDA was also assayed at baseline, then at weeks: 2, 4 and 8 after therapy.

Results: In both groups, the reduction of pain and clinical scores was statistically significant ($p<0.05$) at weeks (2, 4 and 8) after administration as well as the mean expression levels of salivary MDA ($p<0.05$). A non-significant difference was recorded between both groups at each time point ($p\geq0.05$).

Conclusions: Prednisolone and oral lycopene are similarly effective in the treatment of symptomatic OLP patients.

Key words: Oral Lichen Planus, Lycopene, Anti- oxidant, Pain, Malondialdehyde

INTRODUCTION

Oral lichen planus (OLP) is a chronic inflammatory mucocutaneous disease of unknown etiology that affects 0.5 – 4% of the adult population; with a higher incidence in middle-aged females [1,2]. OLP may appear as reticular, papular, plaque like, atrophic, and bullous-erosive. The erosive and atrophic forms are often symptomatic and need effective therapeutic interference [3], because clinically these categories are related to oral cancer development [4].

However, the basic mechanisms directing OLP toward the development of oral cancer have not been clearly addressed yet. Reactive oxygen species (ROS) were reported as a corner stone in the inflammation-mediated carcinogenesis [5]; through their interaction with polyunsaturated fatty acids (PAFs) in membranes or lipoproteins, leading to lipid peroxidation.

The management of this disease is aiming at pain alleviation and remission of the symptoms. This could be achieved through the use of different corticosteroids. However, despite the efficacy of corticosteroids, many side effects are to be considered before using it [19]. Some cases are also resistant to corticosteroid therapy. Therefore, searching for new effective treatment modalities with fewer side effects is considered a real clinical need.

The uncontrolled production of lipid peroxides may lead to oxidative stress, with notable destruction to cell integrity. Numerous markers have been recommended to observe the lipid peroxidation process. Malondialdehyde (MDA) is a common product of PAFs peroxidation that is increased secondary to oxidative stress [6].

Currently, the ability of oxidative stress coupled with the diminished antioxidant enzyme expression has been suggested in the pathogenesis of OLP [7]. Moreover, decreased serum carotenoid's levels have been reported in patients with LP [8]. In 2011, a notable lower serum level of lycopene was monitored in symptomatic OLP cases [9].

Lycopene (LPN) is a red-colored carotenoid that has a variety of therapeutic properties like inhibition of cancer cell proliferation, antioxidant activity, inducing phase II, interference with growth factor stimulation, control of transcription and restoration of gap junctions. Lycopene has also a unique antioxidant activity via its physical and chemical quenching

ability of singlet oxygen [10]. However; the direct evaluation of this anti-oxidant role in OLP wasn't assessed. Hence, the present study evaluated the salivary malondialdehyde (MDA) as a quantitative indicator for the anti-oxidant capacity of the treatment as well as evaluation of the effectiveness of oral LPN compared with prednisolone (PSN) in the management of symptomatic OLP-patients.

SUBJECTS AND METHODS

Study design

A randomized double blinded clinical trial was applied on 40 patients suffering from symptomatic OLP. The design of this trial (50CCT21-021) was accepted by the Ethics Committee of Al-Azhar University (Girls Branch). This treatment protocol was applied in accord with the Declaration of Helsinki

Participants

Eligibility criteria

Inclusion criteria: Patients suffering from symptomatic OLP (Atrophic/Erosive). The included cases were having oral lesions of at least 10 mm in their widest dimension. Patients were free from any systemic disease except for OLP [11].

Exclusion criteria: Lichenoid reactions, malignant lesion or infective oral involvement. In addition, patients who received topical therapy for OLP in the last 2 weeks or systemic therapy in the last 4 weeks [12]; or any lichenoid inducing drugs. Pregnant or breast feeding women were also excluded.

Study setting

The participating patients were recruited in a consecutive order from the Oral Medicine clinic, Faculty of Oral and Dental Medicine, Al-Azhar University (Girls Branch), Cairo, Egypt. This study was performed between August 2017 and October 2018.

Allocation concealment

Randomisation

In this randomized and controlled intervention clinical attempt, all the participating patients were randomly assigned, using a computer-generated table to one of the following equal treatment groups (20 patients each) in a double-masked design. Group 1 was assigned for patients who received oral LPN. Group 2 included those patients who received a systemic PSN.

Blinding

- This is a double randomized trial where patients were blinded about the treatment groups. Each drug was provided as coated tablets in an opaque containers denoted as A and B treatment.
- The treatment was delivered by the dental practioner who had no access to the treatment codes denoted on the container.
- Assessor blinding: Post- operative assessment was carried out by blinded examiner.

Intervention

Pre-treatment measures: A detailed history was taken from each patient including: the systemic condition, duration as well as disease and drug history using diagnostic chart. Giving verbal and written oral hygiene instructions. The aim of the study, the steps, and the treatment plan were explained and clarified for each participant. Oral mucosal incisional biopsies measuring 5-7 mm; including a healthy and integrate tissue zone, were taken from the most representative lesion area. The definite diagnosis of OLP cases (Figure 1) was assessed in accordance with the modified criteria of OLP [13].

Application of intervention

- Patients in group [1] received systemic treatment with lycopene (LYCOPENE 10mg 60 Soft gels, Biovea, Egypt), twice daily for eight consecutive weeks.
- In group [2], patients received oral prednisolone capsules 20 mg (Wysolone, Wyeth India) two capsule per day (total dose was 40 mg) in morning for eight consecutive weeks of treatment. Then the prednisolone dose was tapered to 30 mg/day for two weeks, then to 20 mg/day for next two weeks and finally to 10 mg/day for the last two weeks. Both drugs were administered with unique drug code to mask the identity of drugs.

Outcomes assessment

Each patient was evaluated immediately before active treatment (T0), then during the treatment course, after 2 weeks (T1), 4 weeks (T2), and 8 weeks (T3) [14] after completion of therapy. The following scores were used in this study:

		Paired Differences	T	df	Sig. (2-tailed)				
		Mean			Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		(P-value)
							Lower	Upper	
Pair 1	CLINICAL.S BEFORE-CLINICAL.S 2 WEEKS	1	0.72548	0.16222	0.66047	1.33953	6.164	19	0.0001
Pair 2	CLINICAL.S 2 WEEKS -	0.65	0.48936	0.10942	0.42097	0.87903	5.94	19	0.0001

	CLINICAL.S 4 WEEKS								
Pair 3	CLINICAL.S 4 WEEKS - CLINICAL.S 8 WEEKS	0.8	0.41039	0.09177	0.60793	0.99207	8.718	19	0.0001
Pair 4	CLINICAL.S before - CLINICAL.S 4 WEEKS	1.65	0.19	0.167	1.3	2	9.903	19	0.0001
Pair 5	CLINICAL.S before - CLINICAL.S 8 WEEKS	2.45	0.13	0.185	2.06	2.84	13.27	19	0.0001

Table1: Paired t-test values for Clinical score at different study times

		Paired Differences	t	Df	Sig. (2-tailed)				
		Mean			Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		(P-value)
							Lower	Upper	
Pair 1	VAS BEFORE - VAS 2 WEEKS	2.1	0.85224	0.19057	1.70114	2.49886	11.02	19	0
Pair 2	VAS 2 WEEKS - VAS 4 WEEKS	1.5	0.68825	0.1539	1.17789	1.82211	9.747	19	0
Pair 3	VAS 4 WEEKS - VAS 8 WEEKS	1.1	0.71818	0.16059	0.76388	1.43612	6.85	19	0
Pair 4	VAS before - VAS 4 WEEKS	3.6	0.05886	0.152	3.28	3.92	23.66	19	0.0001
Pair 5	VAS before - VAS 8 WEEKS	4.7	0.08042	0.249	4.196571	5.203429	18.9	19	0.0001

Table2: Paired t-test results comparing the VAS at different study times

	N	Mean	Std. Deviation	Std. Error Mean
CLINICAL.S Before	20	3.6	0.88258	0.19735
CLINICAL.S 2 WEEKS	20	2.6	0.59824	0.13377
CLINICAL.S 4 WEEKS	20	1.95	0.68633	0.15347
CLINICAL.S 8 WEEKS	20	1.15	0.74516	0.16662
VAS BEFORE	20	7.65	0.74516	0.16662
VAS 2 WEEKS	20	5.55	0.68633	0.15347
VAS 4 WEEKS	20	4.05	0.68633	0.15347
VAS 8 WEEKS	20	2.95	0.82558	0.1846

Table3: Mean and standard deviation for Clinical score values VAS at different study times

	Paired Diff	T	df	Sig. (2-	

		erences			tailed)				
		Mean				Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference	
								Lower	Upper
Pair 1	MDA before - MDA 2W	22.8	20.95258	4.68514	12.9939	32.6061	4.866	19	0
Pair 2	MDA 2W - MDA 4W	26.9	23.17644	5.18241	16.0531	37.7469	5.191	19	0
Pair 3	MDA 4W - MDA 8W	32.9	23.72185	5.30437	21.7978	44.0022	6.202	19	0
Pair 4	MDA before - MDA 4W	49.7	29.38868	6.57151	35.9457	63.4543	7.563	19	0
Pair 5	MDA before - MDA 8W	82.6	38.17329	8.53581	64.7344	100.466	9.677	19	0

Table4: Paired t- test results comparing the MDA values at different study times

	Mean	N	Std. Deviation	Std. Error Mean
MDA before	395.55	20	34.96987	7.8195
MDA 2 W	372.75	20	41.13505	9.19808
MDA 4W	345.85	20	42.25396	9.44827
MDA 8W	312.95	20	51.40395	11.49427

Table5: Means and standard deviation values for MDA at different study times

Primary outcome

Clinical scoring (CS): The representative lesion was characterized by being the most severe and clear lesion, and diagnosed by inspection using CS [15] as following:

- 0 means no lesion/normal mucosa.
- 1 means mild white striae/ no erythematous area.
- 2 means white striae with atrophic area <1 cm 2.
- 3 means white striae with atrophic area more than 1 cm 2.
- 4 means white striae with erosive area <1 cm 2.
- 5 white striae with erosive area more than 1 cm 2.

Secondary outcomes

Visual analogue scale (VAS): It consisted of a 10-cm horizontal line marked 0–10 (0 no pain; 10 most severe pain experienced). Each patient was asked to mark the scale at the follow-up time points [16].

Saliva collection for malondialdehyde (MDA) assessment: Five milliliter of unstimulated whole salivary samples was expectorated in dry plastic vials. Salivary samples underwent the following steps:

- Centrifuged at 2000 g for 10 min.
- The supernatants were stored at -70oC until further analysis.
- Salivary samples were taken at the same time of day (10–12 am) and at least 2 hrs after the last food or drink intake.

Measurement of saliva MDA

The salivary levels of MDA were determined by a method based on reaction with thiobarbituric acid (TBA) at 90–100oC [17] and expressed as nano gram/ ml.

In this clinical trial, both the patient and investigator were blind to the treatment intervention, one investigator make all the clinical evaluation steps. Another blind investigator makes the biochemical assessment.

Sample size calculation

Our research design was based on similar studies [18]; the chosen primary outcome was CS. The secondary outcomes were: VAS and salivary MDA. A power analysis was designed to have adequate power to apply a 2-sided statistical test of the research hypothesis (Null hypothesis) that there was no difference between the two groups. Using alpha (α) level of 0.05 (5%) and Beta (β) level of 0.20 (20%), a post-study power indicated that this study had approximately 80% power and significance level = 5; with the predicted minimum sample size (n) was a total of 30 cases i.e. 15 cases in each group. 5 cases were extra-taken in each group to accommodate for any future case loss. Done by IBM™ SPSS™ Sample Power™ Version 3.0.1.

Statistical analysis

Data management and statistical analysis were done using Statistical Package for Social Sciences, Version 21.0 (SPSS, IBM) for Windows. Comparisons between the base line and after treatment at different study times interventions and over time were done by paired T- test. For pain score as well as clinical score, both were expressed as median and range and differences between the 2 groups was tested by the Student- T test was used for changes overtime. Adjustments of the p-value for multiple testing were performed using Bonferroni method.

P value < 0.05 will be considered significant.

RESULTS

Demographic data

The age ranged from 46 to 62 years with a mean of 52.1±4.2. Regarding the gender, 12 (60%) out of the 20 patients enrolled in the test group were females and 8 patients (40%) were males.

Clinical Score results

A statistically significant difference was noticed comparing the clinical score values before and 2 weeks after treatment and through all the follow up time 4 and 8 weeks after treatment as mentioned in (Table 1). The highest mean of clinical score was reported before treatment 3.6 ± 0.88 while the lowest mean of clinical score was noted in week 8 after treatment 1.15 ± 0.74 (Table 1) (figure 1-3).

Visual analogue score results

A statistically significant difference in VAS values was found comparing before and 2 weeks after treatment and through all the follow up time 4 and 8 (Table 2). The highest mean value for pain score was reported before treatment 7.65 ± 0.74. The least mean values of pain score were on week 8 after treatment 2.95 ± 0.82 (Table 2).

Salivary malondialdehyde (MDA)

There was a statistically significant difference in MDA values before and 2 weeks after treatment and through all the follow up time 4 and 8 weeks, 4 and 8 weeks after treatment. The least mean values were on week 8 after treatment 312.95 ± 51.4. The highest mean was reported before treatment 395.55 ± 7.8 (Table 3).

Significant at a p- value < 0.05

	Mean	Standard deviation	Variance
Prednisone	3.65	1.04	1.0816
Lycopene	3.65	0.9333	0.8711
Two weeks			
Prednisone	2.8	0.8335	0.6947
Lycopene	2.4	0.6806	0.4632
Four weeks			
Prednisone	1.95	0.8256	0.6816
Lycopene	1.7	0.5712	0.3263
Eight weeks			
Prednisone	1	1.026	1.0526
Lycopene	0.95	0.7591	0.5763

Table 1: Comparison between clinical score values between the two test groups at different study times.

	Mean	Standard deviation	Variance
Prednisone	7.4	1.0954	1.2
Lycopene	7.65	0.7452	0.5553
Two weeks			
Prednisone	6.15	1.04	1.0816
Lycopene	5.4	0.5982	0.3579
Four weeks			
Prednisone	4.75	1.3328	1.7763
Lycopene	3.9	0.7182	0.5158
Eight weeks			
Prednisone	2.6	1.6983	2.8842
Lycopene	2.35	0.9881	0.9763

Table 2: Comparison between visual analogue score of pain values between the two test groups at different study times.

Significant at a p- value < 0.05

	Mean	Standard deviation	Variance
Prednisone	384.25	47.0172	2210.6184
Lycopene	395.55	34.9699	1222.8921
Two weeks			
Prednisone	380.9	48.6003	2361.9895
Lycopene	372.75	41.135	1692.0921
Four weeks			
Prednisone	357.5	52.1814	2722.8947
Lycopene	345.85	42.254	1785.3974
Eight weeks			
Prednisone	335.4	66.666	4444.3579
Lycopene	308.2	45.1542	2038.9053

Table 3: Comparison between Salivary malondialdehyde values (nmol/L) between the two test groups at different study times.

Significant at a p- value < 0.05

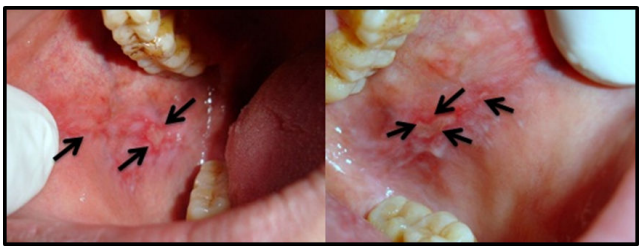

Figure 1: A Clinical photograph showing oral lesion of erosive lichen planus (Black arrows) in 47 years old female patient. A bilaterally distributed lesion was seen in her buccal mucosa.

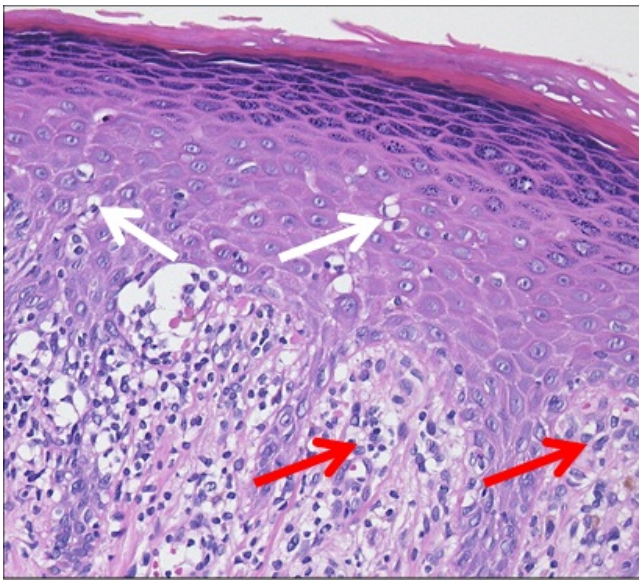

Figure 2: A histologic view showing liquefaction of basal layers (White arrows) and inflammatory cellular infiltrates (Red arrows) in the papillary dermis (H&E X200).

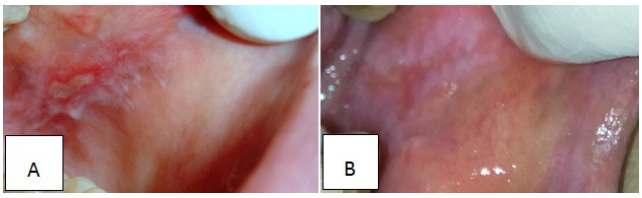

Figure 3: A Clinical photograph showing oral lesion of erosive lichen planus (A) in 47 years old female patient. A marked improvement was noticed at the end of the follow up period (B), in the test group.

DISCUSSION

Among many alternative treatments used to spare corticosteroids in OLP, herbal medicine could be of value as palliative treatment to help decrease the symptoms of the disease and overcome the side effects of corticosteroids [20]. Given that the oxidative stress is believed to have a crucial effect in the pathogenesis of OLP, the use of anti-oxidants would be implied to induce remission in OLP patients [21].

Lycopene is a plant extract that has been used to treat many diseases with oxidative stresses playing a role in their pathogenesis [22]; including OLP [23]. Therefore, the current study evaluates the use of 10 mg of lycopene per day for 8 weeks in management of symptomatic OLP cases. Clinical score was measured before, 2, 4, and 8 weeks after treatment to evaluate the remission of oral signs. Visual analogue scale of pain was evaluated at the same time intervals; along with the salivary malondialdehyde (MDA) as a quantitative indicator for the anti-oxidant capacity of the treatment. The reaction of malondialdehyde with thiobarbituric acid has been widely employed in the spectrophotometric detection of malondialdehyde in several biological samples [24].

The present study reported reduction in clinical score of oral mucositis and pain in 2 weeks after the use of lycopene. These results are in accordance with the findings of Saawarn et al. in 2011 [25]. The authors compared lycopene 8 mg per day for 8 weeks to identical placebo on a sample of 30 symptomatic OLP patients and reported that lycopene has a valuable effect in treating OLP. They also added that oxidative stress may have a potential role in disease pathogenesis.

Moreover, the results of Shekhawat et al. in 2016 were in line with our findings. Their study included 50 symptomatic OLP patients that were randomly assigned into two groups; one received 8 mg lycopene per day while the other group had levamisole in a dose of 50mg 3 times/day for 3 successive days per week; for 8 weeks. Pain was assessed 2, 4 and 8 weeks after treatment and lycopene has shown a more potent and faster therapeutic effect.

Recently, Kushwaha et al. [26] used oral lycopene capsules (4 mg/day) for 8 successive weeks with symptomatic OLP patients. The assessment was done at 0, 2, 4, 6, and 8 weeks intervals to record the clinical and symptomatic improvement in OLP lesions. The authors reported as an effective therapy in relieving patients' symptoms.

Moreover, the use of lycopene in our study revealed a notable decrease in the monitored salivary MDA levels along the duration of study. This result can be explained in the light of its ability to scavenge free radicals [27]. It is worth noting that this was the first clinical report to provide data about the effect of systemic lycopene administration and the oxidative stress biomarker in treating OLP patients. Given that lycopene deficiency has been reported in symptomatic OLP cases and lycopene supplementation significantly decreased the salivary MDA parallel with clinical improvement, a decreased lycopene levels are suggested to have a role in the etio-pathogenesis of OLP for future research. Additionally, lycopene can be successfully used as a sole treatment to manage OLP cases, and as a corticosteroid sparing as recommended by various researchers [19, 22].

Nevertheless, a special concern should be paid to the used dose of lycopene to be used as a corticosteroid sparing line. In this regard, Kushwaha et al. [28] have compared the use of lycopene (4 mg/day) with the systemic prednisolone (40 mg/day) in OLP patients for eight consecutive weeks. The authors reported a significant difference in pain reduction in the prednisolone group. This finding might be attributed to the used dose of lycopene (4 mg), in their model.

In accord, Devaraj et al. [29] examined the immune-modulatory effects of different doses (0, 6.5, 15, or 30 mg lycopene/day for 8 weeks) of purified lycopene supplementation on the oxidative stress biomarkers in healthy volunteers. The authors concluded that purified lycopene delivered a decrease in DNA oxidative damage at the high dose. The aforementioned speculations can explain the good clinical and biochemical results of our study; with further confirmation of the used regimen of lycopene (10 mg/day for 8 weeks); owing to its dose dependent effect.

A possible limitation can be addressed of our study; the relatively short evaluation period. However, this time frame was taken by various researchers [23, 25, & 26]. Indeed, longer

follow up clinical trials are needed to further understand the effectiveness of various therapeutic protocols in treating OLP cases, as recommended by Gupta et al., 2017 [30].

CONCLUSION

According to our data; the oral use of lycopene has a promising clinical advantage in treating symptomatic OLP patients via its immune-modulatory effect on the expression levels of the salivary MDA. This finding indirectly substantiates the hypothesis of the potential role of oxidative stress in the pathogenesis of lichen planus. Further studies should be conducted to assess the maintenance effects of oral lycopene.

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