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CLINICAL EVALUATION OF ADJUNCTIVE ORAL SYSTEMIC VITAMIN E THERAPY IN PATIENTS WITH EROSIVE ORAL LICHEN PLANUS (A RANDOMISED CONTROLLED CLINICALC TRIAL)

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ABSTRACT

BACKGROUND: Oral lichen planus (OLP) is a chronic autoimmune disorder. It mostly involves the skin, mucous membrane, and rarely the scalp and nails. It is an inflammatory condition driven by T-cells. Traditional treatment for OLP is topical steroids, which are frequently used to treat lesions with mild to moderate symptoms. Recent treatment modalities for oral lichen planus include micronutrients as antioxidants, including vitamin E, that modify the immune system function.
AIM OF THE STUDY: The purpose of this study is to assess the clinical response to adjunctive oral systemic vitamin E therapy in erosive oral lichen planus patients.
MATERIALS AND METHODS: 50 patients participated in this randomized, controlled clinical study. The erosive OLP patients were split into two parallel groups: 25 in group A, patients were administered oral systemic vitamin E adjunctive to topical corticosteroids. Group B: 25 patients received topical corticosteroids alone. Clinically, treatment responses were evaluated according to Thongprasom et al. scoring system before and after both treatment modalities.
RESULTS: After 4 and 8 weeks of treatment, there was a significant decline in the Thongprasom scores in the research groups. Both the mean score values for the outcomes after four and eight weeks were more prominent in the test group. Throughout the clinical experiment, the test and control groups were statistically different.
CONCLUSION: Systemic vitamin E adjunctive to topical corticosteroids has shown promising effects in the management of OLP with no side effects.
KEYWORDS: Vitamin E, erosive oral lichen planus, randomized-controlled clinical trial.
RUNNING TITLE: Vitamin E for oral lichen planus treatment.

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INTRODUCTION

Oral lichen planus (OLP) is a chronic autoimmune disorder. It mostly involves skin, mucous membrane, and rarely the scalp and nails. It is of unknown cause, although many etiological factors are thought to be related to the development of oral lichen planus, such as the hepatitis C virus, drugs, contact allergens like dental restoration, and smoking (1-3).

It is an autoimmune disease in which a T-cell mediated immune response abnormally attacks the basal cells of the epithelial layer and recognizes them as an antigen (4). Cytokines that have been released by Th1 lymphocytes lead to the accumulation of both CD4 and CD8 T cells, which are responsible for the apoptosis of keratinocytes (5).

Oral lichen planus is clinically present as bullous, atrophic, plaque-like, reticular, erosive, and papular. The most prevalent variety is the reticular pattern, which appears as asymptomatic white, lacy lines on the buccal mucosa bilaterally. Patients with erosive and atrophic types report a sensation of pain that is made worse by spicy meals (6). Oxidative stress (OS) has an important role in the etiology of OLP. Oxidative stress is the result of imbalance between oxidant and antioxidant substances, resulting in an increase in the level of reactive oxygen species (ROS) and reactive nitrogen species (RNS) at the expense of antioxidants (7). Antioxidants are of two types: endogenous antioxidants such as glutathione reductase, glucose-6-phosphate dehydrogenase, and ferritin; and exogenous antioxidants as trace elements

and vitamins. Antioxidants can defend against oxidative stress (8). Vitamin E is naturally present in foods; it is a lipid-soluble constituent present in cell membrane structure. It has multiple functions due to its antioxidant activity, which neutralizes free radicals and reactive oxygen species by scavenging them (9–11). The cell membrane is shielded by vitamin E by preventing lipid peroxidation (12). Vitamin E plays a direct role in T cell-mediated immune response through helping the native helper CD4 T cells to be activated, lymphocyte proliferation, IL-2 production, signaling of antigen-presenting cells, and membrane-associated molecule rearrangement. Other functions include lowering the production of inflammatory mediators such as pro-inflammatory cytokines and prostaglandin E2 (PGE2) and delayed hypersensitivity reactions (13,14), or indirectly by inhibiting macrophage production of PGE2 that suppresses T cells (15).

Traditional treatment for OLP is topical steroids, which are frequently used to treat lesions with mild to moderate symptoms (16). Recent treatment modalities for oral lichen planus include micronutrients as antioxidants that modify immune system function (17).

The aim of this study is to assess the clinical response to adjunctive oral systemic vitamin E therapy in erosive oral lichen planus patients. The research's null hypothesis is that there won't be any statistically significant differences, considering clinical improvement in erosive oral lichen planus patients, between the test group treated by adding vitamin E supplementation to topical corticosteroids and the control group treated by corticosteroid therapy alone.

MATERIALS AND METHODS

Study design and setting:

A randomized controlled, double, blinded clinical trial was used in this study following the CONSORT guidelines. Fifty erosive OLP patients were recruited, and two parallel groups were formed (18). Patients were randomly selected from the outpatient clinic of the Faculty of Dentistry, Oral Medicine, Periodontology, Diagnosis, and Radiology, Alexandria University, Egypt. According to the 2003 amended WHO criteria for oral lichen planus, the chosen subjects had erosive oral lichen planus, which was diagnosed clinically and histopathologically (19). The Alexandria University Faculty of Dentistry's Research Ethics Committee gave the study its approval (IRB No. 001056-IORG 0008839). The purpose and nature of the study were explained, and informed consent was obtained from each participant. The 2013 amendment to Helsinki's code for clinical trials on humans was followed while treating patients (20).

Patients were included in the study when they satisfied the following criteria:

1. Patients who clinically and histopathologically confirmed that they had erosive OLP according to modified WHO criteria.
2. Patients decided to accept the prescribed drugs and had erosive OLP.
3. Ability to complete this trial.
4. Age between (30-60) (21).

Patients were excluded when:

1. Previous three months, they have been getting any systemic therapy, such as systemic steroids, other immunosuppressive medications, or nonsteroidal anti-inflammatory drugs.
2. Pregnant and breast-feeding females.
3. Patients were suffering from systemic diseases.
4. Patients whose biopsy specimens revealed any dysplastic alterations in their lesions.
5. Patients who were smoking or tobacco users in any form, were not included.
6. Patients with both lichenoid contact reactions and lichenoid drug reactions.
7. Patients with cutaneous lichen planus lesions (22).

Grouping:

Patients with oral lichen planus, equal in severity (erosive type) were split into two equally sized groups:

Group B (control group): 25 patients were administered topical corticosteroids: triamcinolone acetonide 1% oral gel "Kenacort-A Orabase" * three times daily for 8 weeks, applied after meals and at night with avoidance of foods and drinks for 30 minutes after the application (23).

Group A (test group): The other 25 patients were administered topical corticosteroids. In addition, one capsule of 400 mg oral systemic vitamin E supplement* was prescribed once daily in the morning (24).

- 1% oral gel “Kenacort-A Orabase”-Merham.
- Vitamin E 400 – PHARCO Pharmaceuticals.

Clinical procedures

1. Before the treatment, comprehensive data registration, medical and dental histories were taken from selected patients.
2. Accurate extraoral and intraoral clinical examinations were carried out for each patient.
3. Scaling, root planning, removal of any traumatic factors, oral hygiene instructions, and maintenance of good oral hygiene have been done for each selected patient (25).

Objective assessment

Baseline, week four, and week eight following therapy, the whole treatment response and aspects of the oral lesions were noted using the scoring system developed by Thongprasom et al. Score 5 was assigned to patients having white striae with erosive areas >1 cm2, score 4 for patients with white striae and erosive areas <1 cm2, score 3 for those having white striae and atrophic areas >1 cm2, score 2 for those having white striae and

atrophic areas <1 cm2, score 1 for those having only white striae, and score 0 for normal mucosa (Thongprasom et al. criteria 2003) (26).

Randomization and Allocation Concealment:

The selected patients fulfilling the inclusion criteria were assigned at random to groups A (test) and B. (control) by a simple randomization procedure (computerized random numbers). Patients' allocation and blinding procedures were made according to CONSORT (Consolidated Standard of Reporting and Trial) guidelines (27). Both patient and the examiner who registered scores were blinded.

Sample size calculation

The sample size was estimated assuming a 5% alpha error and 80% study power. The mean (SD) Thongprasom score was 1.85 (0.68) for patients treated with vitamin E and 1.36 (0.5) for the control group (28). According to the variance between independent means. Total sample= number per group x number of groups = 25 x 2 = 50 patients.

Software: The sample size was based on Rosner's method, calculated by G*Power 3.1.9.7. (29,30).

Statistical Analysis

Data was analyzed using IBM SPSS version 23, Armonk, NY, USA. Normality was tested for Thongprasom scores using Shapiro Wilk test, and they were found to be not normally distributed. Thongprasom ordinal scores were mainly presented using the median, interquartile range, minimum, and maximum values in addition to the mean and standard deviation. Age was normally distributed; thus, it was presented using mean and standard deviation and compared using an independent t test. Gender was presented by adding to mean and standard deviation the median, interquartile range, minimum and consistent metrics. Age was reported using mean and standard deviation because it had a normal distribution, and it was then contrasted using an independent t test. Chi Square test was used to compare genders that were presented using frequency and percentage. Mann Whitney U test was used to compare Thongprasom scores between groups, while the Friedman test and post hoc analysis were used to assess changes in each group over time, using Bonferroni correction. The significance level was set at a p value ≤0.05 for all two-tailed tests.

RESULTS

The study involved 50 patients with diagnosed EOLP. Most of the affected sites in the oral cavity were the buccal mucosa, followed by the tongue, palate, and gingiva.

Clinical evaluation results showed a statistically significant decrease in Thongprasom scores along trial time points from baseline, after 4 weeks, and after 8 weeks in each studied group (p value≤0.05). In (Table 1), additional comparisons between the test and control groups were displayed. The Mean±SD of Thongprasom scores was (4.60±0.50, 1.72±0.54, 0.36±0.49) at baseline, after 4 weeks, and after 8 weeks in the test group, respectively. In the control group, the Mean±SD was (4.44±0.51, 3.04±0.79,1.96±0.89) at baseline, 4th week and 8th week in sequence.

There was a significant difference between the studied groups at the 4th week, with Mean±SD (1.72±0.54) for the test group and (3.04±0.79) for the control group. In the 8th week, the Mean±SD was (0.36±0.49) for the test group and (1.96±0.89) for the control group, with a statistically significant difference. The p value was 50.00 for the test group and 40.611 for the control group, so it was a statistically significant at p value ≤0.05.

Demographic information of all selected participants, including sex and age, was stated in (Table 2), where comparisons between the test and control groups revealed that no statistically significant difference was present. Age was reported using mean and standard deviation because it had a normal distribution and then it was contrasted using an independent t test. Gender was presented using frequency and percentage, and Chi-Square test was used to compare them.

Table 1: Thongprasom Scoring system.

Score 0	Normal mucosa
Score 1	Only white striae
Score 2	White striae and atrophic areas <1 cm2
Score 3	White striae and atrophic areas >1 cm2
Score 4	White striae and erosive areas <1 cm2
Score 5	White striae with erosive areas >1 cm2

Table 2: Comparison of the study and control groups' Thongprasom scores.

		Test group (n=25)	Control group (n-25)	Test (*P* value)
Baseline	Mean±SD	4.60±0.50	4.44±0.51	1.121 (0.262)
	Median (IQR)	5.00 (1.00)	4.00 (1.00)	
	Min - Max	4.00 – 5.00	4.00 – 5.00	
4 weeks	Mean±SD	1.72±0.54	3.04±0.79	5.045 (<0.0001*)
	Median (IQR)	2.00 (1.00)	3.00 (2.00)	
	Min - Max	1.00 – 3.00	2.00 – 4.00	
8 weeks	Mean±SD	0.36±0.49	1.96±0.89	5.345 (<0.0001*)
	Median (IQR)	0.00 (1.00)	2.00 (2.00)	
	Min - Max	0.00 – 1.00	0.00 – 3.00	
Test (*P* value)		50.00 (<0.0001*)	40.611 (<0.0001*)	
Pairwise comparisons		P_1=0.001* P_2<0.0001* P_3=0.001*	P_1<0.0001* P_2<0.0001* P_3=0.059	

*Statistically significant difference at p value≤0.05. P1: comparison between baseline and 4 weeks, P2: comparison between baseline and 8 weeks, P3: comparison between 4 weeks and 8 weeks.

Table 3: Demographics of the study groups.

		Test group (n=25)	Control group (n-25)	Test (*P* value)
Age: Mean±SD		53.08±7.01	51.36±8.30	0.792 (0.432)
Gender: n (%)	Males	3 (12%)	1 (4%)	1.087 (0.609)
	Females	22 (88%)	24 (96%)	

* Age and gender were compared by independent t test and Chi Square test.
n: Number of patients, SD: Standard deviation

DISCUSSION

There is a suggestion that the pathophysiology of OLP may be influenced by an elevated level of oxidative stress and a difference in the antioxidant defense system (31). Antioxidants, such as vitamins, are substances that can neutralize ROS (32). In this trial, we provided systemic vitamin E as an adjunctive to topical corticosteroids, because vitamin E is a potent scavenger with a crucial role in protecting cell membrane from free radical damage (33)

Kharaeva et al. (34) noted that people with sever forms of psoriasis may benefit from taking vitamin E supplements. Elgoweini et al. (35) discovered that systemic vitamin E may represent a valuable adjunct therapy for vitiligo. In a case report study, Petruzzi et al. (2005) (36) comprised two patients: one healed completely after four weeks, while the other remained resistive.

Thongprasom score is typically preferred by investigators due to its ease of application in the practice and the lack of any technical computation (37). While the scoring system that was invented by Escudier et al. (2007) (38) who integrated site scores with activity scores for a score for severity. 17 oral sites were used in this system, which rendered it a sophisticated scoring system for the clinicians (39). Another score was created by Park et al. (2012) (40) which correlates the objective and subjective findings. This might give a misleading result as the reticular pattern of OLP is asymptomatic, which increases the scores mistakenly (41) Therefore, we selected Thongprasom scoring system to record the size of the lesions before and after the treatment.

In the current trial, the Thongprasom scores significantly dropped in both groups under study, but the reduction was significantly greater in the test group. These results correspond to the results of Abdeldayem et al. (28) study, that prescribed systemic vitamin E adjunctive to topical corticosteroids in the test group and corticosteroids plus placebo in the control group for four weeks for those with erosive lichen planus treatment. In the two study groups, it showed a statistically significant reduction in the clinical lesion size that was more noticeable in the experimental group compared to the control group. Moreover, Petruzzi et al. (2007) (42) in a case series study comprised 10 cases; total recovery was accomplished in eight of them, while modest progress was identified in the other two. In a cross-over study with a two-week elimination period, Bacci et al. (43) compared topical vitamin E to placebo. Topical vitamin E was used as a sole treatment for reticular OLP. There was a significant variation in the surface area of the lesions and Thongprasom scale scores between the two groups. The current study did not find any unfavorable effects related to the therapy. None of the patients in the studies by Abdeldayem et al. (28), Petruzzi et al. (2005) (36), Petruzzi et al. (2007) (42), and Bacci et al. (2017) (43) had any side effects.

The remarkable improvement in the clinical outcomes in the test group can be attributed to vitamin E potent effects. Vitamin E is a powerful chain-breaking antioxidant that suppresses the generation of reactive oxygen species molecules (44). Additionally, vitamin E acts on T cells directly by modulating cell membrane integrity, function, and signaling. Moreover, vitamin E has an anti-inflammatory effect by lowering interleukins (IL-1, IL-6), tumor necrosis factor (TNF-α), and prostaglandin E2 (PGE2) (45). This explains why vitamin E played a significant role in OLP regression in this study. The findings of this study demonstrated that treatment using oral vitamin E as an antioxidant adjunctive to topical corticosteroid could be a potentially effective method for patients with OLP.

The present study included some limitations, such as a brief follow-up period and an uneven gender distribution.

It will be recommended to attempt topical vitamin E formulations and to use large number of participants.

CONCLUSION

Systemic vitamin E adjunctive to topical corticosteroids has shown promising effects in the management of OLP with no side effects.

CONFLICT OF INTEREST

It is stated by the authors that they have no competing interests.

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