

Topical Application of Tocopherol with Corticosteroid in Reducing the Early Signs and Symptoms of Oral Submucous Fibrosis Patients

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Abstract

Objective: The aim of this study was to compare the topical application of steroid alone or with combination use of steroid and tocopherol in reducing oral mucositis in Oral Submucous Fibrosis (OSMF), patients.

Methods: In Pakistani population a rapidly advancing premalignant condition, Oral submucous fibrosis (OSMF), is present which has deteriorated the quality of life. The study was conducted in Department of Oral Medicine & Diagnosis, College of Dentistry, Ziauddin University Karachi, from December 2013 till July 2015. Randomly selected 76 patients with diagnosed OSMF, with history of chewing areca/betal nut or other similar products, with burning sensation on having spicy ingredient, trismus > 20mm with or without palpable fibrous bands on the buccal mucosa intraorally with rigidity and blanching were included in the study. Total 38 out of 76 patients were given a combination of topical tocopherol application 100mg and betamethasone (betonil 0.1%) twice daily and remaining 38 were on topical rinse of betamethasone (betonil 0.1%) alone. OSMF patients were clinically examined to assess the mouth opening and other clinical symptoms during three months and were followed up for next two months.

Results: In the amelioration of early signs and symptoms of OSMF topical tocopherol combination with steroid application was found to be significantly efficacious. Objective signs of OSMF were reduced with improved mouth opening in 69.56% ($p < 0.05$) of the cases.

Conclusion: This study has shown that tocopherol, appears to be an effective drug in treating the early signs of OSMF.

Keywords: Oral mucositis, tocopherol, oral submucous, premalignant

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Introduction

Leukoplakia, lichen planus, oral submucous fibrosis (OSMF), oral epithelial dysplasia, erythroplakia are premalignant lesions which precede oral cancer. The main aetiological risk factor of oral cancer in Southeast Asian decent is chew-

ing tobacco and betal nuts¹. OSMF proceeds with the gradual disease resulting in harmful effects on the affected part of the oral cavity. It is mostly present with vesicle and ulcer formation leading to fibrosis of the oral mucosa causing trismus and difficulty in eating if left untreated²⁻⁴.

OSMF often causes diffuse involvement of the oral cavity and other upper gastrointestinal parts and clinically becomes visible as whitish mucosa lacking elasticity. Epithelial dysplasia has been found in approximately 7-26% of OSMF tissues, and 7% malignant transformation is suggested in long-term studies¹. The early signs and symptoms of oral mucositis include redness, erythematous ar-

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reas that lead to ulceration with elevated painful desquamative patches and burning sensation with inability to take hot or spicy foods^{2,3}.

OSMF management can be divided in two wide treatment modalities: medical and surgical⁴. The medical management includes phasic injections of hyaluronidase at intervals, hydrocortisone, placental extract, triamcinolone plus vitamin, and iron supplements. Minimal improvement of mouth opening can be treated with intraregional steroids giving satisfactory results. Severe trismus is best treated by the surgical means. Instead of continuing the limited available modes of therapy, the idiopathic nature of this condition indicates new avenues for its management⁵⁻⁷.

In 1922 Herbert Evans and Katherine Scott Bishop discovered vitamin-E in which they found "anti-sterility factor-x" which is essential for reproduction in rats⁷. In 1924 Barnett Sure labelled the substance as "Vitamin-E" which is known as tocopherol⁸. In the Journal of Biological Chemistry in 1936 Evans first published the chemical formula of Vitamin-E⁷. The rationale for the topical use of tocopherol functions as an antioxidant and helps protecting cell membranes from lipid per-oxidation by trapping the peroxy radicals^{9,10}. It also inhibits carcinogenesis, thus reducing the risk of developing oral cancer whereas steroids provide initial symptomatic relief by reversing capillary permeability and suppressing migration of neutrophils, thus reducing inflammation and preventing fibrosis and collagen deposition⁷. Use of tocopherol favors the community because of its cost effectiveness, readily available, and well-tolerated among the population.

The aim of this study was to compare the topical application of steroid alone or with combination use of steroid and tocopherol in reducing oral mucositis in Oral Submucous Fibrosis.

Patients and Methods

Probability sampling technique with random selection was used. Seventy six patients (32 female and 44 male), aged 18 to 54 years with diagnosed OSMF were included in the study. It was conducted in the Department of Oral Medicine & Diagnosis,

College of Dentistry, Ziauddin University, Karachi from December 2013 till July 2015.

Inclusion criteria were patients who had 5 year history of chewing areca/ betel nut or any trade products, burning sensation on having any spicy food, trismus >20mm with or without palpable fibrous bands on the buccal mucosa intraorally with rigidity and blanching clinically.

Exclusion criteria included patients on anticoagulant therapy and those with Vitamin K related clotting abnormalities, rationale being that studies have shown that Vitamin E may increase the bleeding⁷. Histopathologically proven OSMF transforming into malignancy were also excluded.

Patients were explained about the premalignant condition and its transformation rate and a written consent was taken. All patients were advised to follow the provided instructions including stopping the habit of using areca nut in all its form, avoiding hard or spicy food and maintaining optimum oral hygiene.

Sample size was estimated depending on a power calculation. At level of significance $\alpha = 0.05$ with estimated standard deviation 1.2 and power 0.9. A randomized controlled clinical trial on patients diagnosed with OSMF were randomly divided into two groups and treated for 12 weeks. Group 1 was patients administered topical application of vitamin E and betonil drops 0.5 ml twice daily (after breakfast and before sleep). While, group 2 patients were administered just topical use of betonil 0.5 ml twice daily. The soft gelatinous capsule of Vitamin E (Evion) of 200mg was used, patients were advised not to exceed the maximum daily recommended dose (25 IU / Kg) emptied into the oral cavity. Patients were instructed to pierce the capsule by sterile lancet and apply twice daily on the buccal mucosa. Vitamin E in the capsule is in oil consistency and is easily washed away by saliva. Based on previous studies¹¹ the problem was overcome by applying vitamin E with acceptable consolidation with chlorhexidine gel, which has good adherence to mucous membranes. However, patients were advised to see the clinician immediately in case of development of any signs of an allergic reaction to

vitamin E such as hives, difficult breathing, swelling face, lips, tongue, or throat.

In 1995 Lai DR et al presented the classification for OSMF¹² based on mouth opening. In the same year Khanna and Andrad¹³ classified OSMF according to the clinical and histological characteristics of mouth opening. In 2011 Chandramani Moreet al¹⁴ presented staging of OSMF highlighting the condition symptoms and fibrotic bands presence. In 2014 Santosh Patil¹⁵ mentioned flexibility of cheek in grading of OSMF. Hence, in the present study we modified and classified our patients based on the studies mentioned¹²⁻¹⁵.

The criteria included, stage 1 with vesicles and ulceration with stomatitis and/or blanching of oral mucosa, mouth opening / cheek flexibility up to or >35 mm. Stage 2 included fibrous palpable bands in buccal mucosa and/or oropharynx, with /without stomatitis, mouth opening / cheek flexibility between 25 till 35 mm. While stage 3 included presence of palpable fibrous bands in buccal mucosa and/or oropharynx, and in any other parts of oral cavity, with / without stomatitis, mouth opening / cheek flexibility between 15 and 25 mm and Stage 4 was interincisal mouth opening less than 15 mm

Visual Analog scale (VAS) for pain was recorded at baseline for burning sensation before the start of treatment and at the end of every week for a period of 12 weeks. VAS was based purely on patient's response scoring from 0 to 10 (Score 0: no pain; Score 10: worst imaginable pain). Mouth opening was also recorded subsequent intervals. Student's t test was used to compare pre and post treatment results with $p < 0.05$ being considered as significant.

Results

In this study, 76 patients were included with diagnosed OSMF, and were randomly divided into two groups with equal number of patients. But differing in the treatment provided to them so that the comparison between the efficacies of two treatments could be described. The data revealed that out of all the patients observed, 57.8% (n=44) were males and only 42.1% (n=32) were females. This sug-

gests a higher incidence of disease in males (Fig. 1). Of all the patients examined, 64% patients complained of both trismus (Fig. 2) and burning sensation.

The data further revealed that the majority of patients around 48% (n=18) in group 1 and 53% (n=20) were recorded with clinical grade 3 followed by grade 1 with 39% (n=15) and 42% (n=16) respectively (Fig. 3). Interincisal distance was also recorded of all the patients and the results showed that the majority of patients i.e. 26% in each group (group 1 and group 2) were having interincisal opening between 30-34mm (Table 1).

The patients were also examined after the treatment and the results showed that most of the patients were relieved from burning sensation in both the groups, but the frequency of patients with improved symptoms were more in group 1 patients who were using topical tocopherol and betonil as compared to the other group of patients using betonil only. Also, the patients in group 1 showed improvement in their symptoms earlier comparatively (Table 2).

After treatment most of the patients were relieved from burning sensation in both the study groups. Group 1 showed 41% relief in the second week as compare to 28% in study group 2, Table 3. For inter group comparison of the effectiveness of treatment in increasing the mouth opening parameters, student's t test was done that resulted in a value $p < 0.05$ and confidence interval 95% which are statistically significant, and indicated that group 1 patients responded better than group 2. The results suggested that the topical use of tocopherol and betonil was found to be more significantly efficacious as compared to using betonil alone.

Discussion

Early relieve of sign and symptoms of burning sensation and significant improvement in mouth opening were seen in patients falling in Group 1. Group 1 shows 41% relief in the second week as compare to 28% in study Group 2. The clinical status of OSMF patients in our study was assessed according to the clinical staging after the topical

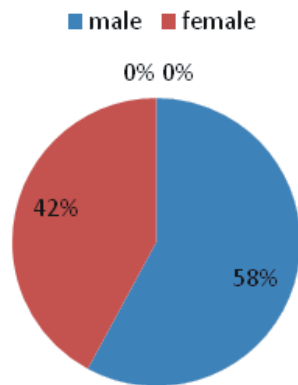


Fig 1. Showing distribution according to gender.



Fig 2. showing clinical picture of patient with trismus

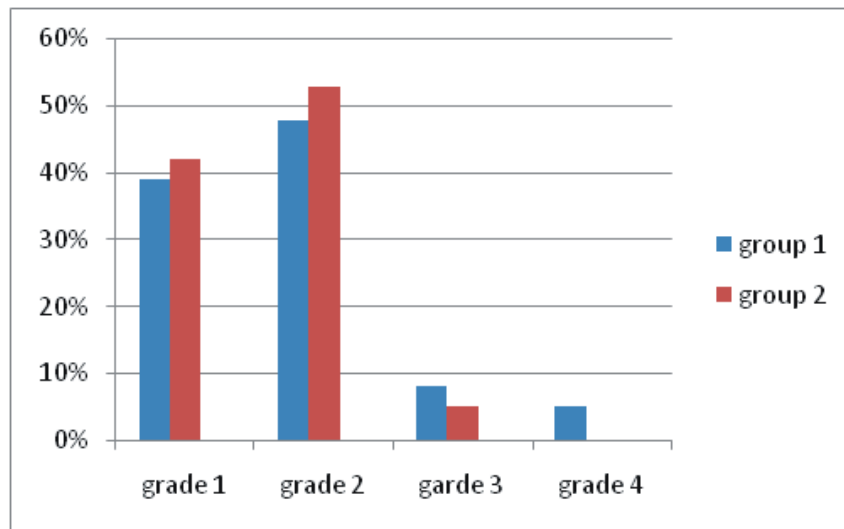


Fig 3. Week wise assessment of patients showing reduction in burning sensation

Table 1. Showing frequency of patients with different interincisal distance

INTERINCISAL DISTANCE	GROUP 1 n (%)	GROUP 2 n (%)
>35 mm	8 (21)	8 (21)
34-30mm	10 (26)	10 (26)
29-25mm	9 (23)	9 (23)
24-20mm	6 (16)	6 (16)
19-15mm	3 (8)	3 (8)
< 14mm	2 (5)	2 (5)

Table 2. Comparing the frequency of patients with improved symptoms in both groups

DAYS AFTER TREATMENT	GROUP 1 n (%)	GROUP 2 n (%)
2nd Week	14 (41)	9 (28.1)
3rd Week	11 (32.2)	8 (25)
4th Week	9 (26.4)	15 (46.8)

application of tocopherol drug used in combination with steroid vs alone use of steroid. Also to our knowledge, since this was the first study where topical tocopherol had been used in the treatment of OSMF, we could not compare our results with other studies. However, tocopherol effect is ascribed as an anti-fibrotic and anti-inflammatory agent. It decreases the production of collagen, fibroblast proliferation is reduced and anti-fibrotic cytokine and collagenase synthesis in the basement membrane and connective tissue¹⁶. Whereas application of steroids provide initial symptomatic relief by its anti-inflammatory action by reducing the juxtaepithelial inflammation and thus preventing fibrosis.

Natural sources of vitamin E are found mainly in fresh vegetables, cereals and nuts. It has an antioxidant properties and is used in the prevention of premalignant lesions as it produces free radical reaction. In the study conducted by Starasoler et al.¹⁷ significant results were obtained in topical application of tocopherol in primary herpetic gingivostomatitis. Wadleigh et al.¹⁸ treated chemotherapy-induced oral mucositis by applying Vitamin E topically. Comparison in the Wadleigh study was done between topical application of Vitamin E twice daily and placebo group consist of coconut and soybean oil containing less than 1 mg of Vitamin E. Infected lesions were excluded and only head and neck cancer patients were included in the study. Patients had beneficial effects in this study but it was unable to prove whether the effects produced were due to local effects or its systemic absorption. More recent studies by Ferreira et al.¹⁹ found successful results in prevention of radiation-induced oral mucositis by prescribing prophylactically Vitamin E topically. Yoruket al²⁰ studied recently radiation-induced oral mucositis in rat model by giving prophylactically Vitamin E and L-carnitine. It was given in a dose of 40 mg/kg intramuscularly daily. It down regulated the number of platelets and white blood cells causing radiationmucositis^{20,21}.

Specific activation and detoxification process was found by the antioxidant effect of Vitamin E as mentioned in Chandra Mouli PE et al, and Balwant Rai et al. studies⁹. According to Uplabdh Raghuwanshi et al¹⁶ the decrease amount of Vitamin E can cause or potentiate oral cancer.

Oral submucous carcinoma patients in S Chitra and C S Shyamala Devi²² studies also proved the action of Vitamin-E. Serum glycoproteins and Vitamin E were tested in radiotherapy patients of oral squamous cell carcinoma patients. Glycoconjugate levels were in lower amount and this is helpful in assessing disease progression. Vitamin E is cost effective, easily dispenses and well tolerated by patients. Daily blood Vitamin E varies widely so its toxicity is reported rarely in humans so we can prescribe up to 1600 IU safely with unnoticeable side effects^{23,24}. Recent studies suggest that use of antioxidant lycopene other than Vitamin E has demonstrated improved mouth opening, percentage of which was 69.56% ($p < 0.05$)²⁵.

Conservative use of Vitamins, iron supplements and intralesional steroid injections were used as medical modalities for the treatment in OSMF⁶. Role of Vitamin-E in OSMF patients studied by Soma Gupta et al²⁶ who found a decrease level in grade II and III OSMF cases but not in grade I cases. Vitamin-E mean level was less 9.3 ± 0.3 mg/L as compared to control group 10.1 ± 1.2 mg/L. Superoxide dismutase analyze the enzymatic antioxidant property which prove no change in the progression²⁷.

The main limitation of this study was the fact that patient compliance cannot be evaluated accurately, and therefore, we had to trust the patients and their families regarding the way and timing of using the prescribed drug. However, in future more elaborate studies with a larger sample size with co-existing malignancy along with follow-up are needed to determine the actual role of Vitamin E in initiating and promoting oral malignancy. Patients should be advised to take a balance natural antioxidant diet such as tomato, berries and leafy green vegetables during the treatment course as it can help in reducing the signs and symptoms.

Conclusion

From the present study, it is evident that by topical application of Vitamin E in OSMF patients degree of oxidative damage can be assessed. It improves the treatment by arresting it in early stages and avoiding the possible consequences of malignant transformation.

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Conflict of Interest

Authors have no conflict of interests and no grant/ funding from any organization for this study.

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