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Comparison of triamcinolone with pentoxifylline and vitamin E efficacy in the treatment of stage 2 and 3 oral submucous fibrosis: A randomized clinical trial

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Abstract

Objective: The objective of this study was to assess the effectiveness of triamcinolone in combination with pentoxifylline and vitamin E in the treatment of patients with level two and three oral submucous fibrosis.

Methods: The study aimed to compare the efficacy of corticosteroid injections (triamcinolone) versus pentoxifylline and vitamin E in the therapy of patients with stage two and three oral submucous fibrosis. A total of 42 participants with indications and features of oral submucous fibrosis were enrolled between January 2020 and September 2021. The patients' age and mouth opening were evaluated, and descriptive statistics and paired *t*-test were used for analytical investigation.

Results: The study showed a statistically significant improvement in both treatment groups ($p = 0.001$) concerning pre- and post-treatment deviations. However, when comparing the standard differences in treatment outcomes between the two study groups, only mouth opening exhibited a statistically significant difference ($p = 0.001$).

Conclusions: The findings indicate that a treatment regimen combining pentoxifylline and triamcinolone can significantly alleviate oral submucous fibrosis symptoms, including mouth opening, pain, and flaring agitation, thereby enhancing the affected individual's quality of life.

Keywords

Triamcinolone, pentoxifylline, vitamin E, oral submucosa fibrosis, tumor

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Introduction

Oral submucous fibrosis (OSF) is a chronic and debilitating condition characterized by the formation of fibrous tissues and scars in the oral cavity. It is primarily associated with the habitual use of areca nut and related products, leading to mucosal injury and impaired wound healing.[1] As OSF progresses, it causes functional disabilities such as limited mouth opening (trismus), speech disturbances, and difficulty in swallowing (dysphagia).[1,2] The presence of fibrous bands on the lips, cheeks, and soft palate confirms the diagnosis of OSF.[1]

OSF predominantly affects the buccal mucosa and can extend to other areas, including the palate, retromolar area, and faucial pillars. In rare cases, it may involve the throat, larynx, or esophagus, potentially leading to malignant transformation.[1,2] The prevalence of OSF varies by geographic region and is closely associated with cultural practices and lifestyle habits.[3,4]

The pathogenesis of OSF involves chronic inflammation, excessive collagen deposition, and altered extracellular matrix dynamics.[2] Various factors, including genetic predisposition, autoimmune conditions, and nutritional deficiencies, have been implicated in its development.[2,5] Management of OSF has been challenging, and therapeutic approaches aim to improve mouth opening and reduce fibrosis. Treatment modalities include cessation of areca nut use, physical therapy, medications, and invasive surgeries.[2,6] Invasive surgical interventions, however, may be limited by post-operative fibrosis recurrence.[6]

Among the medications used for OSF treatment, corticosteroids have shown promising results in improving mouth opening and reducing inflammation.[7] Synthetic corticosteroids, such as betamethasone, dexamethasone, and methylprednisolone, have been effectively administered intralesionally.[7] Another pharmacological approach involves the use of pentoxifylline, a xanthine derivative, known for its vasodilating capabilities and anti-inflammatory effects.[8] Pentoxifylline has been shown to improve mouth opening and reduce the burning sensation in OSF patients.[9,10] Nutritional support therapy, including antioxidants like vitamin E, has been recommended to address nutritional deficiencies and protect against adverse events such as carcinogenesis.[7] Vitamin E, as an antioxidant, can hinder the effects of tobacco-specific nitrosamines, potentially preventing oral cancer.[11]

Despite the expanding literature addressing OSF, there remain notable gaps and limitations within the existing research landscape. While various studies have shed light on the etiology, clinical presentation, and management strategies of OSF,[7–9] certain aspects of the condition continue to lack comprehensive understanding. For instance, despite efforts to explore therapeutic interventions, there exists a paucity of comparative studies investigating the effectiveness of different treatment modalities for OSF, particularly those targeting clinical stages 2 and 3. Moreover, the mechanisms underlying the progression of OSF, its variable response to treatments, and the long-term implications of various interventions remain areas of ongoing investigation. Thus, this study seeks to contribute to the existing body of knowledge by addressing some of these gaps and providing valuable insights into the comparative efficacy of two distinct treatment regimens for OSF, with a specific focus on stage 2 and 3 cases. The working hypothesis of this study was that the treatment outcomes for the two groups (triamcinolone combined with pentoxifylline and vitamin E) will not differ significantly. This study aimed to assess the efficacy of triamcinolone in combination with pentoxifylline and vitamin E as a treatment approach for patients diagnosed with stage two and three OSF.

Methods

Study design

This clinical trial employed a randomized control design to compare the therapeutic efficacy of injection steroids with that of pentoxifylline and vitamin E in patients with level 2 and 3 OSF. The study received ethical approval from the ethical review committee of Altamash Institute of Dental Medicine, Pakistan, before commencing the research (AIDM/ERC/12/2021/03), and it followed the principles outlined in the Declaration of Helsinki. The trial was registered on ClinicalTrials.gov under the Trial number NCT05660694 (https://clinicaltrials.gov/). To determine the sample size, the open-epi program (Open Source Epidemiologic Statistics for Public Health, Version 3.01) was used, with an established confidence interval of 95%, a desired percentile of 70%, and a power of 80%, resulting in an estimated sample size of $n=42$ [(DEFFNp(1−p)]/[(d2/Z21−α/2(N–1) + p*(1−p)].[12]

Participants were recruited from the department of oral and maxillofacial surgery if they were diagnosed with OSF. A total of 42 patients were enrolled between January 2020 and September 2021. The study adhered to the CONSORT (Consolidated Standards of Reporting Trials) guidelines, a recognized framework for improving the transparency and reporting of clinical trials. These guidelines were followed to enhance the quality and comprehensibility of our research. By adhering to the CONSORT checklist, we ensured the accurate reporting of essential elements such as participant recruitment, randomization procedures, interventions, outcomes assessment, statistical analysis, and interpretation of results. The approach gave assurance that our study design, methodology, and reporting aligned with established best practices in clinical research, enhancing the credibility and reproducibility of our findings, Supplemental Figure 1.

Randomization procedures and treatment allocation

In this randomized control trial, eligible participants provided informed consent and were randomly allocated into two treatment groups using a computer-generated randomization sequence. Group 1 received intralesional corticosteroid injections, while group 2 received oral pentoxifylline and vitamin E. Allocation concealment was ensured through sealed opaque envelopes opened sequentially during participant enrollment to determine their group assignment, preventing bias in treatment allocation. Neither researchers nor participants were aware of the treatment assignment until after inclusion in the study.

Eligibility criteria

Inclusion criteria:

- Patients with medically confirmed oral submucous fibrosis (OSMF) who had not previously undergone OSMF treatment.
- Patients who were willing to discontinue the use of gutkha, areca nuts, and chewing tobacco.
- Patients who agreed to participate in routine follow-ups were included in our analysis.

Exclusion criteria:

- Patients who had received OSF treatment in the past.
- Medical history of cardiovascular, gastroenterological, nephrological, or metabolic disorders.
- Pregnant and lactating patients.
- Patients with any co-existing disorder of the orofacial region other than OSF that may interfere with the study.

All participants were informed about the nature of the study before obtaining their consent. Demographic and clinical information, including name, age, gender, and relevant behaviors such as smoking, chewing areca nuts, and betel nut use, were collected. Data on the duration of these habits in years and their frequency per day were also recorded.

Data collection

Following the diagnosis, depending on the mouth openness, each patient was told of the problem and its precancerous risk. Prior to the start of the trial, the patients were also told to stop chewing areca betel nuts and smoking areca nut tobacco in any manner. Such participants underwent straightforward random process for selection and staged according to pre-established clinical characteristics suggested by Bailoor et al.[13]

The recruited participants were placed in one of the two groups (1 and 2) and evaluated every month. For 4 weeks, group 1 patients received bilateral buccal mucosa injections of triamcinolone 400 mg combined with lidocaine 1:1 two times per week. For 4 weeks, group 2 patients received one pill of a vitamin E addition each day along with pentoxifylline 40 mg twice daily. Additionally, it was suggested that both groups perform a stick mouth opening exercise twice daily, holding the stick on one side of the mouth for 10 min, and then resting for approximately 10 min before performing the exercise on the opposite side.

For the duration of the experiment, all patients underwent clinical follow-ups at intervals of 30 days. Clinical indicators such as the discomfort associated with wide opening of the mouth, cheek flexibility, along with blanching of the mucosa were noted during each visit to estimate the progression of the illness in both groups that were assessed and entered into a specifically designed questionnaire. Following the discontinuation of medicine, all of the patients included in this objective assessment were monitored for a total of 6 months.

Questionnaire information

The specifically designed questionnaire used to assess the progression of the illness in this study included various items and domains relevant to OSF Supplemental File 1. The specific items or domains in the questionnaire were:

- Mouth opening: This domain assessed the extent of mouth opening in patients before and after treatment, as a primary parameter to compare the efficacy of both treatment regimens.[14]
- Discomfort associated with wide mouth opening: This domain assessed any discomfort or pain experienced by patients during wide mouth opening before and after treatment.
- Cheek flexibility: The questionnaire included an evaluation of cheek flexibility to assess any improvements or changes in the flexibility of the cheeks after treatment.
- Mucosa blanching: This domain assessed the blanching of the oral mucosa, which is a characteristic sign of OSF, to determine any changes or improvements after the treatment.

Statistical analysis

The collected data was analyzed using the Statistical Package for Social Sciences version 25. The Shapiro-Wilk[15] test was used to assess the normality of data distribution. Descriptive statistics and paired *t*-test[16] were employed to compare the efficacy of triamcinolone with pentoxifylline and vitamin E. A p-value of $\leqslant 0.05$ was considered statistically significant.

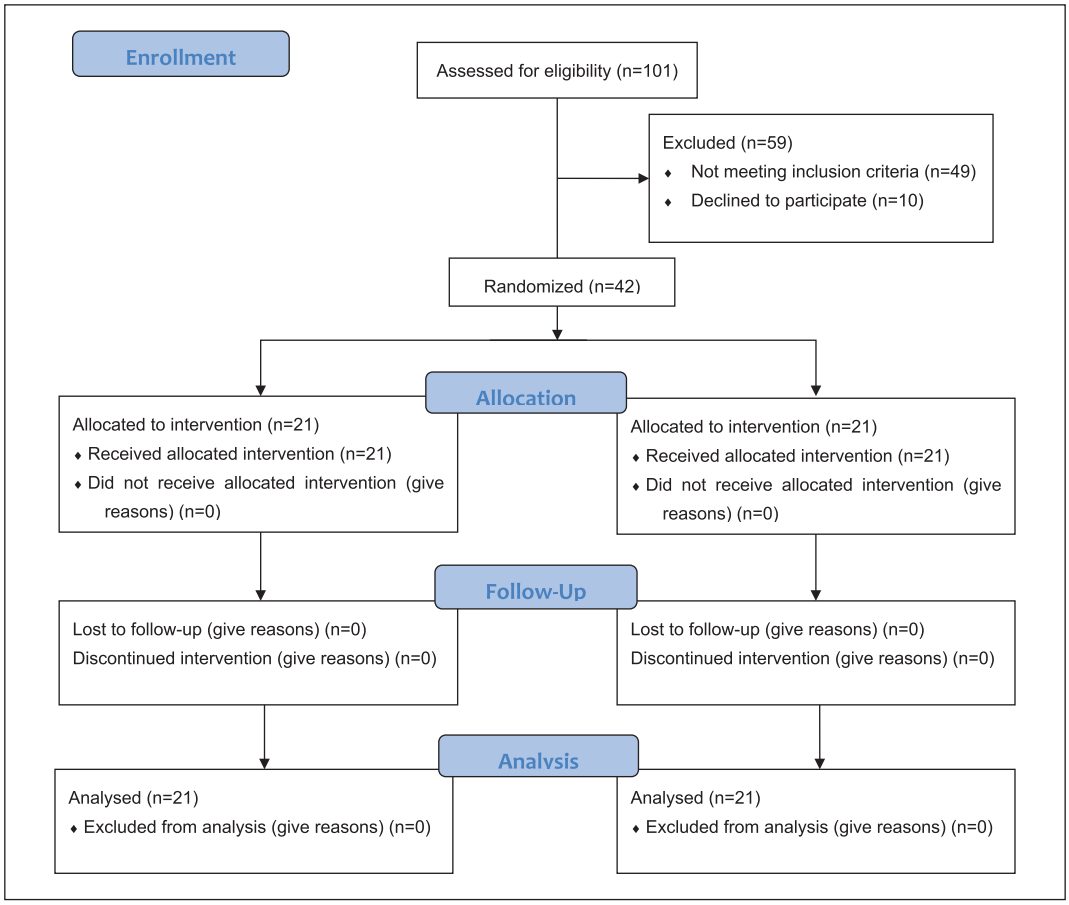

Figure 1. Study flow diagram.

Results

In this clinical trial, a total of 42 participants suffering from OSF were recruited, as shown in Figure 1. Regarding the age of the patients, group 1 had a mean age of 25.48 ± 3.010, while group 2 had a mean age of 25.67 ± 3.483. Group 1 consisted of 18 males and 3 females, whereas group 2 had 15 males and 6 females. As for social habits, the majority of participants in group 1 (42.9%) and group 2 (33.3%) had consumed Ghutka and Chalia. Regarding smoking habits, most of the participants in both groups (14 in group 1 and 16 in group 2) were non-smokers, as shown in Table 1.

After the administration of steroid in group 1, the mean mouth opening before the treatment was 27.14 ± 3.637 mm, and after the administration, the mean increased to 33.43 ± 2.580 mm. For group 2 patients, the mean mouth opening before the administration of pentoxifylline and vitamin E was 25.43 ± 3.995 mm, and after administration, the mean increased to 32.19 ± 3.172 mm (Table 2).

The Shapiro-Wilk test results indicated that the data for mouth opening measurements in both treatment groups (group 1: injection steroids and group 2: pentoxifylline and vitamin E) were normally distributed ($p > 0.05$).

Table 1. Distribution of participant's age ($n = 42$).

Groups	Variables	Mean and SD
Group 1	Age	25.48 ± 3.010
Group 2		25.67 ± 3.483

The statistically significant difference ($p = 0.001$) observed in the intergroup analysis of mouth opening between groups 1 and 2 indicates that there is a significant variation in the treatment outcomes of the two groups. The large t-value of -24.571 further emphasizes the substantial difference in the mean mouth opening between the two treatment groups.

The negative t-value suggests that the mean mouth opening in group 1 (treated with steroid injections) was higher than the mean mouth opening in group 2 (treated with pentoxifylline and vitamin E). This implies that the steroid injections were more effective in improving mouth opening compared to the pentoxifylline and vitamin E treatment in patients with OSF at level 2 and 3.

Table 2. The compassion of patient's mouth opening in both groups ($n = 42$).

Variables		Paired differences					*t*	Dif	*p*-Value
		Mean	SD	Std. Er	95% confidence				
					Lower	Upper			
Group 1 versus group 2	Mouth opening B.S—Mouth opening A.S	−6.762	1.261	0.275	−7.336	−6.188	−24.571	20	0.001

t: the difference between mean values, dif: difference, SD: standard deviation, Std. Er: standard error mean.

It is important to note that the statistical significance of the difference ($p = 0.001$) indicates that the observed variation in mouth opening between the two groups is unlikely to be due to chance. This finding provides strong evidence that there is a true difference in the therapeutic efficacy of the two treatment regimens.

Discussion

OSF is a precancerous condition characterized by a pro-inflammatory state leading to gradual roughening of the submucosa, resulting in visible protrusion and limited mouth opening. Early disease recognition and effective management are crucial in treating OSF. At this stage, cessation of harmful habits and dietary supplementation are recommended, while traditional therapy is offered on a modest scale, supplemented with medical attention. In advanced cases, surgical interventions may be necessary.[17] The purpose of this study was to compare the effectiveness of intralesional steroid injections and oral pentoxifylline with vitamin E in managing stage 2 and 3 OSF patients. We divided the patients into two groups, and their clinical improvement in mouth opening was evaluated as the main parameter to compare the efficacy of both regimens.

The age range for OSF development is wide, but young individuals between 25 and 35 years are more frequently affected. In our study, the participants' age ranged from 25 to 45 years in both groups, consistent with other studies reporting an average age of around 35 years for OSF patients.[17,18] Our study predominantly included male participants in both groups, whereas a study by More et al.[19] reported a higher prevalence of OSF in females. The diversity in outcomes observed in our study could be attributed to its conduct in a tertiary hospital, with patients representing different regions of the country.

Group 1 patients received bilateral buccal mucosa injections of triamcinolone 40 mg combined with lidocaine 1:1 twice a week for 4 weeks. Group 2 patients received a daily dose of one tablet of vitamin E supplement in addition to pentoxifylline 40 mg twice daily for the same duration. The intergroup analysis revealed a statistically significant difference in mouth opening between the two groups.

Similar studies have shown significant improvement in trismus and burning sensation with the use of dexamethasone plus hyaluronidase combination, indicating the efficacy of this drug regimen Hasan et al.[20] The consumption of Gutka and Chalia emerged as the most frequent causes of OSF in our study, consistent with earlier research by Patil et al.[18] Notably, all patients exhibited restricted mouth openings with visualized and palpable fibrous bands on the buccal mucosa. Over the 6-month follow-up period after the regimen, mouth opening considerably increased in both groups, aligning with findings reported by Bhambal and colleagues.[21]

In the context of our study, it is essential to consider the role of oxidative stress in the pathogenesis of OSF and its potential implications for our findings. The combination of triamcinolone, pentoxifylline, and vitamin E was investigated with the understanding that oxidative stress contributes to the progression of OSF. By addressing the oxidative microenvironment through antioxidant supplementation and anti-inflammatory agents, we aimed to mitigate the factors that could lead to malignant transformation. This study's focus is on assessing the effectiveness of the combination treatment in patients with level 2 and 3 OSF, which aligns with the increasing recognition of oxidative stress as a crucial factor in the development of OSF and its potential connection to malignant transformation.[22–25] Through our investigation, we contribute to the broader understanding of how interventions targeting oxidative stress might affect the management and outcomes of OSF patients.

Our study has some limitations. Firstly, the sample size was relatively small, and the follow-up period was short, which could impact the generalizability and long-term assessment of treatment outcomes. Secondly, this study was conducted in a single tertiary hospital, potentially limiting the representativeness of the findings to a broader population. Furthermore, confounding factors like variations in OSF grades and the persistence of associated habits may influence treatment efficacy, necessitating consideration in future research. To strengthen the evidence regarding the efficacy of pentoxifylline in different age groups and OSF grades, larger sample sizes and longer follow-up periods should be employed in future studies. Additionally, multicenter trials involving diverse patient populations could improve the generalizability of the findings. Comparative studies exploring the persistence of habits and their influence on treatment outcomes would provide valuable insights. Furthermore, research investigating other potential therapeutic options for OSF management, such as novel drugs or

targeted therapies, may lead to more effective and personalized treatment approaches for this challenging condition.

Conclusion

In conclusion, our clinical trial comparing the effectiveness of intralesional steroid injections with oral pentoxifylline and vitamin E in managing stage 2 and 3 OSF patients demonstrated significant improvements in mouth opening in both groups. The steroid injection group showed superior results compared to the pentoxifylline and vitamin E group. Further exploration of alternative therapeutic approaches and multi-center trials could advance the development of more effective and personalized treatment strategies for this debilitating condition.

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Author contributions

Conceptualization: S.S., S.N., R.Y., A.L., Z.K., S.A., A.M., and N.A.; Methodology: S.S., N.A., S.N., and A.L.; Software: R.Y., N.A., S.N., and A.L.; Validation: N.A., A.L.; Formal analysis: A.L., N.A., and R.Y.; Investigation: S.A., S.S., and N.A.; Resources, S.S., N.A., and S.A.; Data curation: N.A.; Writing—original draft preparation: A.L., S.N., N.A., S.A., and S.A.; Writing—review and editing: A.M., N.A., A.H., S.S., and S.N.; Visualization, S.S., A.L., A.M., and R.Y.; Supervision, A.L., N.A., and A.M.; Project administration: S.S., S.N., R.Y.; Funding acquisition: N.A. All authors have read and agreed to the published version of the manuscript.

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Informed consent

The written informed consent was obtained from all patients involved in the study.

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Data availability statement

The data is available on a reasonable request from the corresponding author.

Supplemental material

Supplemental material for this article is available online.

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