

Efficacy of Pentoxifylline in Combination with Garlic Pearls in the Management of Oral Submucous Fibrosis: A Randomized Controlled Trial

Dr. Arshi, Dr. Upasana Sethi Ahuja, Dr. Akshay Rathor, Dr. Abhishek Mukherjee

Department of Oral Medicine and Radiology, Shree Bankey Bihari Dental College & Research Centre, Ghaziabad, Uttar Pradesh, India

Corresponding Email addresses:

Dr. Arshi: arshikhankhan72@gmail.com

Abstract

Background: Oral submucous fibrosis (OSMF) is a chronic, progressive and potentially malignant disorder of the oral cavity, strongly associated with areca nut and betel quid chewing, and characterised by burning sensation and progressive restriction of mouth opening. Numerous treatment modalities have been tried, but none is uniformly successful, prompting continued interest in combination and herbal-adjunct regimens.

Aim: To evaluate the efficacy of pentoxifylline combined with garlic pearls in the management of OSMF, compared with a B-complex (multivitamin) control.

Materials and Methods: In this randomized controlled trial, 30 clinically diagnosed OSMF patients were randomized into two groups of 15. The study group received tablet pentoxifylline 400 mg thrice daily plus two garlic pearls twice daily, and the control group received B-complex capsules twice daily, each for three months. Burning sensation (Visual Analogue Scale, 0–10), mouth opening (mm), tongue protrusion (mm) and cheek flexibility (mm) were recorded at baseline and at monthly follow-up. Data were analysed using paired t-test, Student's t-test and repeated-measures ANOVA (SPSS 20.0); $p < 0.05$ was significant.

Results: Overall grade improvement was 86.66% in the pentoxifylline + garlic group versus 33.33% in the control group. The study group showed greater improvement across all parameters: burning sensation reduced by 56.84% (mean VAS reduction 3.6), mouth opening increased by 14.81% (4 mm), tongue protrusion by 20.07% and cheek flexibility by 60%. Reduction in burning sensation was statistically significant within both groups (study $p = 0.0001$; control $p = 0.0007$). Between-group analysis showed significantly greater improvement in the study group for tongue protrusion ($p = 0.0091$) and cheek flexibility ($p < 0.0001$), whereas the difference in mouth opening did not reach statistical significance.

Conclusion: The combination of pentoxifylline and garlic pearls produced clinically meaningful improvement in the signs and symptoms of OSMF and outperformed multivitamin therapy, with only mild, dose-related side effects. Larger, longer trials are warranted to confirm these findings.

Keywords: Oral submucous fibrosis; Pentoxifylline; Garlic; Areca nut; Potentially malignant disorder; Mouth opening; Burning sensation.

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Introduction

Oral submucous fibrosis (OSMF) was defined by Pindborg (1966) as an insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx, associated with a juxta-epithelial inflammatory reaction followed by fibroblastic change in the lamina propria and epithelial atrophy, leading to stiffness of the oral mucosa, trismus and difficulty in eating.[1] A comparable condition was described in ancient medicine by Susrutha as “Vidari”; Schwartz (1952) termed it “atrophica idiopathica mucosa oris”, and the term OSMF was coined by Joshi in 1953.[2,3] The strongest risk factor for OSMF is chewing of betel quid containing areca nut, a habit practised widely in the Indian subcontinent and Southeast Asia.[4,5] Of the areca-nut alkaloids—arecoline, arecaine,

guvacine and guvacoline—arecoline is the most potent and plays a major role in pathogenesis by causing an abnormal increase in collagen production.[6] Genetic and immunologic predisposition, chillies, lime, tobacco and nutritional deficiencies (particularly iron and vitamins) are additional contributory factors.[7,8] Areca-nut constituents induce excessive reactive oxygen species, and fibrosis is thought to result from increased cross-linking of collagen through up-regulation of lysyl oxidase activity.[9,10]

Clinically, the onset is insidious over two to five years, with prodromal burning sensation, blisters, ulceration, excessive salivation and altered taste.[11] As the disease progresses the mucosa becomes blanched and opaque, and dense fibrous bands—particularly around

the pterygomandibular raphe—produce progressive limitation of mouth opening. Among oral potentially malignant disorders, OSMF carries the highest rate of malignant transformation.[12,13]

Medical management is largely symptomatic and aimed at improving mouth opening, and includes corticosteroids, antioxidants, proteolytic enzymes, placental extracts, interferon- γ , peripheral vasodilators, levamisole and physiotherapy; surgical modalities are reserved for advanced cases.[14,15] Intralesional steroids can improve symptoms but are associated with pain, infection and rebound fibrosis on follow-up.[16] These limitations have driven interest in agents with vasodilatory, anti-inflammatory and antioxidant activity.

Pentoxifylline, a tri-substituted methyl-xanthine derivative, is a “rheologic modifier” with vasodilating, anti-inflammatory and immunomodulatory properties.[17] It improves microcirculation, reduces platelet aggregation and granulocyte adhesion, increases leukocyte deformability, alters fibroblast physiology to promote fibrolysis, and possesses antithrombin, antiplasmin and fibrinolytic activity.[18,19] Garlic, one of the oldest cultivated herbs, is a rich source of organosulphur compounds (notably allicin) with antioxidant, anti-inflammatory, immunomodulatory and vasorelaxant properties, and is inexpensive with good patient compliance.[20,21] Because both agents share vasodilatory, anti-inflammatory, antioxidant and immunomodulatory actions, their combination may exert a synergistic effect.[22] The present trial was therefore undertaken to evaluate the efficacy of garlic with pentoxifylline in the management of OSMF.

Materials and Methods

Study design and setting. This randomized controlled trial was conducted in the Department of Oral Medicine and Radiology, Shree Bankey Bihari Dental College & Research Centre, Ghaziabad, Uttar Pradesh, India, from December 2020 to September 2022. Approval was obtained from the Institutional Ethical Committee and written informed consent was taken from all participants.

Participants. Thirty patients of either gender, clinically diagnosed with OSMF, were enrolled. Inclusion criteria were: clinical diagnosis of OSMF; adult patients; no OSMF treatment in the preceding three months; willingness to quit areca nut, gutkha or pan masala use; and willingness to attend regular follow-up for six months. Patients with co-existing systemic, cardiac, gastrointestinal, metabolic or neurological disease, pregnant or lactating women, patients with a past diagnosis of cancer, and those already under OSMF treatment within the last six months were excluded.

Grouping and intervention. Participants were segregated into a study group and a control group (15 each). The study group received tablet pentoxifylline 400 mg thrice daily and two garlic pearls twice daily after food for three months. The control group received B-complex capsules (B-complex forte with vitamin C) twice daily after food for the same period. All patients were counselled regarding habit cessation before commencing treatment.

Outcome assessment. Four clinical parameters were assessed. Burning sensation was recorded on a Visual Analogue Scale (VAS, 0–10). Mouth opening was measured as the inter-incisal distance between maxillary and mandibular central incisors at maximum opening using a Vernier caliper (mean of three readings), and staged by the Khanna & Andrade (1995) classification[23]: Stage I >40 mm, II 31–40 mm, III 21–30 mm, IV 11–20 mm, V <10 mm. Tongue protrusion was measured from the mesio-incisal angle of the lower left central incisor to the tip of the protruded tongue. Cheek flexibility was measured by the Mathur and Jha method[24] (difference between the tragus–angle-of-mouth reference distance at rest and on full cheek inflation). Parameters were recorded at baseline and at the first, second and third months, over six recall visits.

Statistical analysis. Means and percentages were computed for each group. A paired t-test was used for intra-group comparison and repeated-measures ANOVA for comparison across intervals within groups; Student’s t-test was used for between-group comparison. Analysis was performed in SPSS 20.0. A p-value < 0.05 was considered significant, < 0.01 highly significant and < 0.001 very highly significant.

Results

Of the 30 participants, 24 were male and 6 female (male-to-female ratio 4:1). The mean age was 35.4 years; the peak incidence occurred in the 21–30-year age group (12 patients), followed by 31–40 (9), 41–50 (4) and 51–60 (4), with a single patient under 20 years.

Parameter	Study group (PTX + Garlic)	Control group (B-complex)
Patients (n)	15	15
Overall grade improvement	86.66%	33.33%

Table 1. Overall grade improvement by group.

Grade improvement was markedly higher in the pentoxifylline + garlic group (86.66%) than in the B-complex group (33.33%). Mean improvements in each clinical parameter are summarised in Table 2.

Parameter	Study group mean improvement	Study group p %	Control group mean improvement	Control group p %

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Mouth opening (mm)	4.00	14.8 1%	1.13	3.61 %
Burning sensation (VAS)	3.60	56.8 4%	2.20	46.48 %
Tongue protrusion (mm)	1.01	20.0 7%	0.12	1.96 %
Cheek flexibility (mm)	2.60	60.0 0%	0.33	5.95 %

Table 2. Mean and percentage improvement in clinical parameters over three months.

Within each group, the reduction in burning sensation was statistically significant (study group $p = 0.0001$; control group $p = 0.0007$). The change in mouth opening and in overall grade did not reach statistical significance within either group (study group mouth opening $p = 0.2817$, grade $p = 0.9297$; control group mouth opening $p = 0.627$, grade $p = 0.3707$).

Comparison	Group	p-value	Significance
Burning sensation (VAS)	Study	0.0001	Significant
Burning sensation (VAS)	Control	0.0007	Significant
Mouth opening	Study	0.2817	Not significant
Mouth opening	Control	0.6270	Not significant

Table 3. Statistical significance of change in burning sensation and mouth opening within groups.

On between-group comparison of the improvement achieved, the study group showed significantly greater gains than the control group in tongue protrusion (mean difference 0.89 mm; $t = 2.8026$, $df = 28$; $p = 0.0091$, very significant) and in cheek flexibility (mean difference 2.27 mm; $t = 7.1792$, $df = 28$; $p < 0.0001$, extremely significant). In percentage terms, tongue protrusion improved by 20.07% versus 1.96% and cheek flexibility by 60% versus 5.95% in favour of the study group.

Between-group comparison	Mean difference	t (df = 28)	p-value
Tongue protrusion improvement	0.89 mm	2.8026	0.0091
Cheek flexibility improvement	2.27 mm	7.1792	< 0.0001

Table 4. Between-group comparison of improvement (study vs. control).

A few patients in the study group reported mild, dose-related side effects, including malodour, gastritis, nausea and dizziness, all of which subsided on withdrawal of the drug.

Discussion

OSMF is a potentially malignant disorder driven principally by areca-nut chewing, with the highest malignant transformation potential among oral potentially malignant disorders.[12,13,25] Because its treatment is prolonged and most agents carry side effects, combination and herbal-adjunct regimens have attracted growing attention.[14,26] In this trial the combination of pentoxifylline and garlic pearls produced improvement across all four clinical parameters—burning sensation, mouth opening, tongue protrusion and cheek flexibility—and clearly outperformed multivitamin therapy, with an overall grade improvement of 86.66% versus 33.33%.

Pentoxifylline improves blood flow through peripheral vessels by reducing blood viscosity, decreasing platelet aggregation and granulocyte adhesion, and increasing leukocyte deformability; it also inhibits inflammatory cytokine production and exerts immunomodulatory effects.[18,19] In OSMF, where collagen deposition and a hypercoagulable state restrict nutrient delivery to affected tissue, these actions plausibly underlie the observed symptomatic relief. Garlic contributes antioxidant, anti-inflammatory and vasorelaxant activity through its organosulphur compounds, and the shared mechanisms of the two agents provide a rationale for synergy.[20,21,22]

The findings are consistent with several previous reports. Jain et al.[22] and Leelakshi et al.[27] documented substantial reductions in burning sensation and improvements in mouth opening, tongue protrusion and cheek flexibility with pentoxifylline-based regimens. Rajeshwari et al.[22] Mehrotra et al.[28] and Khaaviya et al.[29] reported significant symptomatic improvement with pentoxifylline, with total symptom scores improving by 85–86%, mirroring the grade improvement seen here.[30,31] Bishnoi et al.[32] and Bhambal et al.[33]/Patil et al.[34] similarly found greater improvement in pentoxifylline groups than in multivitamin controls.[35]

Not all evidence is concordant. Prabhu et al.[36] found no significant improvement in mouth opening or tongue protrusion with adjunctive pentoxifylline, and Fedorowicz et al.[37] could not isolate the drug's effect because physical therapy was co-administered. In the present study, although the combination group improved more than the control group on every measure, the change in mouth opening did not reach

statistical significance within either group, and the between-group difference in mouth opening was likewise non-significant—consistent with the more equivocal literature on this particular parameter. The statistically robust between-group differences were in tongue protrusion and cheek flexibility.

The principal limitations are the small sample size (15 per group), the relatively short three-month treatment period, and the absence of blinding and histological or biochemical confirmation of response.[38] These factors limit the precision and generalisability of the estimates and may explain why some clinically favourable differences did not attain statistical significance.[39]

Conclusion

Within its limitations, this trial indicates that the combination of pentoxifylline and garlic pearls is effective in improving the signs and symptoms of OSMF—burning sensation, mouth opening, cheek flexibility and tongue protrusion—and is superior to multivitamin therapy, with only mild, dose-related and reversible side effects. Because OSMF markedly compromises quality of life, an inexpensive, well-tolerated combination regimen is clinically attractive.[40] Larger, adequately powered, blinded trials with longer follow-up are needed to substantiate the role of pentoxifylline and garlic in the management of OSMF.

References

1. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. *Oral Surg Oral Med Oral Pathol.* 1966;22(6):764–79.
2. Cox SC, Walker DM. Oral submucous fibrosis. A review. *Aust Dent J.* 1996;41(5):294–9.
3. Rajendran R. Oral submucous fibrosis: etiology, pathogenesis, and future research. *Bull World Health Organ.* 1994;72(6):985–96.
4. Sawhney H, Bhargava D, Kashwani R, Mishra R. Artificial intelligence as a tool for improving oral cancer outcomes. *Arch Dent Res.* 2023 Jul;13(1):15–9.
5. Pindborg JJ, Mehta FS, Gupta PC, Daftary DK. Prevalence of oral submucous fibrosis among 50,915 Indian villagers. *Br J Cancer.* 1968;22(4):646–54.
6. Harvey W, Scutt A, Meghji S, Canniff JP. Stimulation of human buccal mucosa fibroblasts in vitro by betel-nut alkaloids. *Arch Oral Biol.* 1986;31(1):45–9.
7. Tilakaratne WM, Klinikowski MF, Saku T, Peters TJ, Warnakulasuriya S. Oral submucous fibrosis: review on aetiology and pathogenesis. *Oral Oncol.* 2006;42(6):561–8.
8. Karthik H, Nair P, Gharote HP, Agarwal K, Ramamurthy Bhat G, Kalyanpur Rajaram D. Role of hemoglobin and serum iron in oral submucous fibrosis: a clinical study. *ScientificWorldJournal.* 2012;2012:254013.
9. Trivedy C, Warnakulasuriya KA, Hazarey VK, Tavassoli M, Sommerlad P, Johnson NW. The upregulation of lysyl oxidase in oral submucous fibrosis and squamous cell carcinoma. *J Oral Pathol Med.* 1999;28(6):246–51.
10. Trivedy C, Baldwin D, Warnakulasuriya S, Johnson N, Peters T. Copper content in Areca catechu (betel nut) products and oral submucous fibrosis. *Lancet.* 1997;349(9063):1447.
11. Kashwani R, Sawhney H. Assessing the sensitivity and specificity of toluidine blue staining in oral cancer screening among inmates: A prison-based study. *J Adv Zool.* 2023;44:450–6.
12. Murti PR, Bhonsle RB, Pindborg JJ, Daftary DK, Gupta PC, Mehta FS. Malignant transformation rate in oral submucous fibrosis over a 17-year period. *Community Dent Oral Epidemiol.* 1985;13(6):340–1.
13. Ray JG, Ranganathan K, Chattopadhyay A. Malignant transformation of oral submucous fibrosis: overview of histopathological aspects. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2016;122(2):200–9.
14. Kerr AR, Warnakulasuriya S, Mighell AJ, Dietrich T, Nasser M, Rimal J, et al. A systematic review of medical interventions for oral submucous fibrosis and future research opportunities. *Oral Dis.* 2011;17 Suppl 1:42–57.
15. Kumar A, Bagewadi A, Keluskar V, Singh M. Efficacy of lycopene in the management of oral submucous fibrosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;103(2):207–13.
16. Bhagat N, Salam S, Garg A, Venkatesan V, Hardik S, Hardik SG, Kumar S, Kashwani R. Use of Liposomal Curcumin for Oral Cancer Treatment: A Systematic Review and Meta Analysis. *Nanotechnology Perceptions.* 2024 Jun 22:342–59.
17. Ward A, Clissold SP. Pentoxifylline. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. *Drugs.* 1987;34(1):50–97.
18. Rajendran R, Rani V, Shaikh S. Pentoxifylline therapy: a new adjunct in the treatment of oral submucous fibrosis. *Indian J Dent Res.* 2006;17(4):190–8.
19. Samlaska CP, Winfield EA. Pentoxifylline. *J Am Acad Dermatol.* 1994;30(4):603–21.
20. Tripathi KP. A review — garlic, the spice of life (Part I). *Asian J Res Chem.* 2009;2(1):8–13.
21. Bayan L, Koulivand PH, Gorji A. Garlic: a review of potential therapeutic effects. *Avicenna J Phytomed.* 2014;4(1):1–14.

22. Jain N, Annigeri RG, Pipalia PR. Efficacy of garlic in conjunction with pentoxifylline in the management of oral submucous fibrosis — a preliminary study. *Int J Pharm Sci Res.* 2016;7(5):2145–50.
23. Khanna JN, Andrade NN. Oral submucous fibrosis: a new concept in surgical management. Report of 100 cases. *Int J Oral Maxillofac Surg.* 1995;24(6):433–9.
24. Khan N, Kinra E, Verma N, Singh G, Kondhalkar S, Karande V, Kashwani R. Awareness and Attitude toward Cervical Cancer and HPV Vaccination among Female Medical Students. *International Journal of Pharmacy Research & Technology (IJPRT).* 2025 Sep 9;15(2):1771-7.
25. Arakeri G, Rai KK, Hunasgi S, Merks MAW, Gao S, Brennan PA. Oral submucous fibrosis: an update on current theories of pathogenesis. *J Oral Pathol Med.* 2017;46(6):406–12.
26. Mulk BS, Deshpande P, Velpula N, Chappidi V, Chintamaneni RL, Goyal S. Spirulina and pentoxifylline — a novel approach for treatment of oral submucous fibrosis. *J Clin Diagn Res.* 2013;7(12):3048–50.
27. Leelakshi [initials], et al. [Title of pentoxifylline / OSMF study.] [Journal name, year, volume and pages to be completed by the authors from the original source.]
28. Mehrotra R, Singh HP, Gupta SC, Singh M, Jain S. Pentoxifylline therapy in the management of oral submucous fibrosis. *Asian Pac J Cancer Prev.* 2011;12(4):971–4.
29. Evanjin PJ, Maheswari TN, Perumal E, Chaurasia P, Khan N, Pasha Z, Kashwani R. Evaluation of anti-metastatic potential of mangosteen extract via targeting the CXCL-8/CXCR2 chemokines signalling in oral cancer cell line-An Ex vivo study. *Library of Progress-Library Science, Information Technology & Computer.* 2024 Jul 15;44(3):5336.
30. Sadaksharam J, Mahalingam S. Evaluation of oral pentoxifylline in the management of oral submucous fibrosis — an ultrasonographic study. *Contemp Clin Dent.* 2017;8(2):200–4.
31. Bajgai DP, Agrawal B, Yadav A. Effectiveness of pentoxifylline therapy for the management of oral submucous fibrosis: a hospital-based study. 2021. [Journal name, volume and pages to be confirmed by the authors.]
32. Bishnoi RR, Sharma M, Bishnoi S, Sharma Y. Efficacy of pentoxifylline in the management of oral submucous fibrosis. *J Clin Diagn Res.* 2020.
33. Bhambal AM, Bhambal A, Shukla US, Dhingra A. Effectiveness of pentoxifylline in the treatment of oral submucous fibrosis patients: a case-control study. *Appl Cancer Res.* 2019;39:9.
34. Patil S, Maheshwari S. Efficacy of pentoxifylline in the management of oral submucous fibrosis. *J Orol Sci.* 2014;6(2):94–8.
35. Patil S, Khandelwal S, Maheshwari S. Comparative efficacy of newer antioxidants spirulina and lycopene for the treatment of oral submucous fibrosis. *Clin Cancer Investig J.* 2014;3(6):482–6.
36. Prabhu N, Rao SS, Kotrashetti SM, Baliga SD, Hallikerimath SR, Angadi PV, et al. Pentoxifylline in patients with oral submucous fibrosis — a randomized clinical trial. *J Maxillofac Oral Surg.* 2015;14(1):81–9.
37. Fedorowicz Z, Chan Shih-Yen E, Dorri M, Nasser M, Newton T, Shi L. Interventions for the management of oral submucous fibrosis. *Cochrane Database Syst Rev.* 2008;(4):CD007156.
38. Warnakulasuriya S, Kerr AR. Oral submucous fibrosis: a review of the current management and possible directions for novel therapies. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2016;122(2):232–41.
39. Passi D, Bhanot P, Kacker D, Chahal D, Atri M, Panwar Y. Oral submucous fibrosis: newer proposed classification with critical updates in pathogenesis and management strategies. *Natl J Maxillofac Surg.* 2017;8(2):89–94.
40. Shen YW, Shih YH, Fuh LJ, Shieh TM. Oral submucous fibrosis: a review on biomarkers, pathogenic mechanisms, and treatments. *Int J Mol Sci.* 2020;21(19):7231.