

Evaluating the Efficacy of All-Trans Retinoic Acid (Retranoid) in Oral Submucous Fibrosis: A Pilot Study on Clinical and Histological Outcomes

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Abstract

Aim: This prospective pilot study aimed to evaluate the efficacy of retranoid, containing 10 mg of all-trans retinoic acid, in treating Grade I and Grade II Oral Submucous Fibrosis (OSMF), focusing on improvements in clinical symptoms and histopathological changes. **Methods:** Ten patients meeting Khanna and Andrade classification criteria were treated with retranoid over 3 months. Clinical parameters including maximum mouth opening and burning sensation Visual Analog Scale (VAS) were assessed at monthly intervals. Histopathological changes were evaluated through pre-operative and post-treatment biopsies. Statistical analysis utilized Friedman's analysis of variance with a significance level set at $P \leq 0.05$. **Results:** Significant increases in maximum mouth opening ($P < 0.01$) and decreases in VAS scores ($P < 0.001$) were observed post-treatment. Histopathological analysis showed reduced fibroblast and collagen levels, indicating the therapeutic efficacy of all-trans retinoic acid in OSMF. **Conclusion:** Retranoid, containing all-trans retinoic acid, demonstrated promising results in improving clinical symptoms and histopathological markers in Grades I and II OSMF patients. Further research in larger, multicenter trials is warranted to validate these findings and establish all-trans retinoic acid as a viable therapeutic option for managing OSMF.

Keywords: All-trans retinoic acid, Betel nut, Mouth mucosa, Oral submucous fibrosis.

INTRODUCTION

Oral submucous fibrosis (OSMF) was first described by Schwartz in 1952 as “idiopathic atrophic mucosa oris.” In 1953, Joshi introduced the term “oral submucous fibrosis.” Joshi *et al.* (1966) characterized OSMF as a gradual, persistent condition that impacts any region of the oral cavity and occasionally the pharynx. It may sometimes begin with or be accompanied by vesicle formation. The condition consistently involves a juxta-epithelial inflammatory response, followed by fibroelastic alterations in the lamina propria and epithelial atrophy, leading to stiffening of the oral mucosa, which results in trismus and difficulty in eating.^[1]

OSMF is a potentially malignant disorder of the submucosa caused by arecoline and copper from betel nut, leading to fibroblast dysfunction and the development of fibrous bands, classified as a class 1 carcinogen. It predominantly occurs in India, Southeast Asia, the South Pacific Islands, and South Africa. The prevalence of OSMF in India ranges from 0.2 to

2.3% in males and 1.2–4.6% in females, affecting individuals aged 11–60 years.^[2] The malignant transformation rate of OSMF is estimated at 7–13%.^[3]

Treatment strategies for OSMF include both conservative management and surgical interventions. Conventional treatments involve steroids, enzymes (hyaluronidase, collagenase, trypsin, chymotrypsin), placental extracts administered intralesionally, and oral drugs such as carotenoids, alpha-lipoic acid, lycopene, vitamins, microelements, and tea pigments.^[4,5] Surgical treatments, however, remain controversial due to limitations such as inadequate harvesting of the buccal fat pad, esthetic morbidity, dysphasia, disarticulation, risk of

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postoperative aspiration, limited reach and coverage by the flaps, hair growth on flaps, donor site morbidity, secondary debulking procedures, and postoperative contractures of the flaps.^[6,7]

Several new methodologies have been implemented to efficiently manage OSMF, including gamma interferon, pentoxifylline, and spirulina with retinoic acid. Retranoid, primarily composed of all-trans retinoic acid (a form of vitamin A), is a naturally occurring compound with vitamin A activity.^[8] Retinol and retinoic acid are required to prevent keratin synthesis and act as antioxidants, preventing malignant transformation, and inducing apoptosis. In OSMF, all-trans retinoic acid is believed to enhance epithelial health by reducing fibrosis and inflammation in the subepithelial region.^[9] However, adequate data on its mechanism of action in OSMF patients is lacking.

To address this, we investigate the use of retranoid in OSMF patients. This study aims to establish the mechanism of action of retranoid in eliciting the aforementioned changes.

MATERIALS AND METHODS

A prospective pilot study was conducted to evaluate the mechanism of action of retranoid 10 mg (a supplement of Vitamin A) in patients with Grade I and Grade II OSMF. The study aimed to assess the effect of all-trans retinoic acid in the treatment of OSMF. The research was carried out in the Department of Oral and Maxillofacial Surgery at the Dental College and Hospital, following approval from the Institutional Ethics Committee.

Ten patients with Grade I and Grade II OSMF were included in the study. These patients received the test drug retranoid, which contains 10 mg of all-trans retinoic acid.

Inclusion criteria

Patients were selected based on the Khanna and Andrade classification system (1995) for the surgical management of OSMF. Included patients were categorized as Group I (very early cases), Group II (early cases), or Group III (moderately advanced cases). The age range was 20–55 years.

Exclusion criteria

Patients were excluded if they were classified under Group IVA or Group IVB of the Khanna and Andrade system, were on anticoagulant or antiplatelet drugs, had high triglyceride levels, had compromised hepatic or renal function, or had any cardiovascular disease.

Parameters assessed

The study assessed maximum mouth opening (measured between the maxillary and mandibular central incisors with a vernier caliper or metallic scale), burning sensation (using a Visual Analog Scale [VAS]), development of pain and soreness, ulceration, difficulty in mastication, stratum basale condition, and subepithelial fibroblast and collagen levels, as well as blood vessel congestion.

Study population and intervention

Ten patients with OSMF (Grades I, II, III) according to the Khanna and Andrade classification^[10] were enrolled. They received all-trans retinoic acid (Retranoid, Hrikan Biotech, Guwahati, Assam, India). Patients were reviewed at 30-day intervals over 3 months, marked as T0, T1, T2, and T3, with assessments conducted before, during, and after therapy, concluding with a final biopsy.

Statistical analysis

Data were tabulated using Microsoft Excel 2021 and analyzed with IBM Statistical Package for the Social Sciences Statistics for Windows, Version 27.0 (IBM Corp). Shapiro-Wilk's test and visual inspections indicated skewed data. The Friedman's analysis of variance test assessed baseline and post-test values, with significance set at $P \leq 0.05$.

RESULTS

All the study subjects were males and the mean age of the study participants was 29 ± 7.76 years in with an age range of 18–42 years.

Table 1 and Figure 1 represent the interincisal distance (in mm) at different time points during the study, reporting means with standard deviations and medians with interquartile ranges (IQR). At the initial assessment, the median interincisal distance was 21.50 mm (IQR: 15–32.5 mm), showing a significant increase over subsequent months ($P < 0.01$).

The VAS scores showed a significant decrease over time: initially, the median score was 9 (IQR: 8–10), which reduced to 7 (IQR 4.5–8) at 1 month, 3.5 (IQR 2–5) at 2 months, and 0.5 (IQR 0–2) at 3 months ($P < 0.001$) (Table 2 and Figure 2).

Initial histopathological analysis revealed that five of 10 patients exhibited a moderate amount of fibroblasts, while the remaining showed extensive fibroblastic proliferation. Dense, thickened collagen bundles were observed in six patients, separate thickened collagen bundles in three patients, and fine, fibrillar collagen in one patient. Conversely, after drug therapy, the final histopathological analysis of 10 patients indicated reduced fibroblasts in seven patients and their absence in three patients. Few patients showed fine, fibrillar

Table 1: Descriptive statistics and comparisons of interincisal distance of the study participants across follow-up points (in mm)

Time points	Mean $\pm$ SD	Median (Q1–Q3)	Mean ranks	P-value ^a
T0	23.90 $\pm$ 10.75	21.50 (15–32.5)	10 ^a	<0.001*
T1	27.8 $\pm$ 10.32	25.50 (21.75–38.00)	22.50 ^{a, b}	
T2	29.10 $\pm$ 9.92	25.50 (22.75–38.75)	29.50 ^{b, c}	
T3	30.40 $\pm$ 10.29	26.50 (25.00–40.75)	38.00 ^c	

SD: Standard deviation, Q1: First quartile, Q3: Third quartile, Q1-Q3: Inter-quartile range. ^a: Analyzed by Friedman's analysis of variance different lowercase letters imply statistically significant differences between them. *: Statistically significant ($P \leq 0.05$)

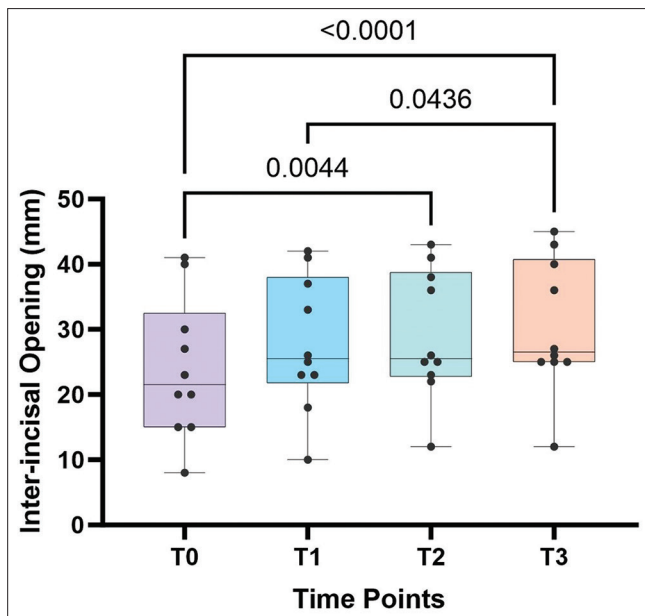


Figure 1: Box and Whisker Plot depicting the Interincisal Distance of study participants across follow-up periods. The lines above boxes denote statistically significant pairwise differences

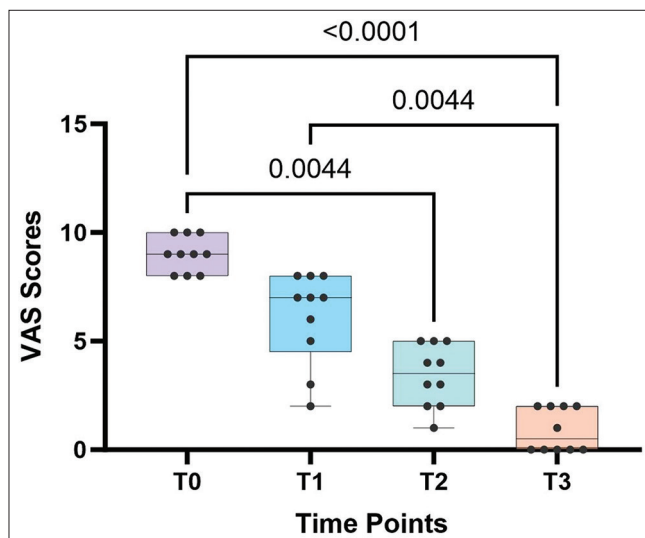


Figure 2: Box and Whisker Plot showing the Visual Analog Scale scores to assess mucosal burning of the study participants across the follow-up periods. The lines above boxes denote statistically significant pairwise differences

collagen ($n = 6$), while collagen was absent in four patients. This comparative analysis demonstrates a decrease in fibroblast numbers and collagenization following treatment (Figure 3).

DISCUSSION

The management of OSMF aims to alleviate symptoms and improve mouth opening through various medicinal and surgical interventions. Medicinal treatments typically involve steroids, hyaluronidase, pentoxifylline, antioxidants, collagenase, colchicine, and nutrient supplements such as vitamin A.

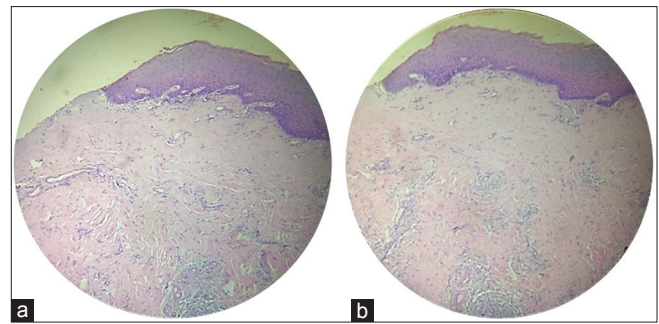


Figure 3: Histopathological images comparing (a) Pre-operative state with dense collagen bundles in fibroblastic tissue and (b) Post-drug therapy showing reduced fibroblast presence and collagenization. Stained with Hematoxylin and Eosin (H&E), magnification $\times 40$

Table 2: Descriptive statistics and comparisons of VAS scores to assess mucosal burning of the study participants across follow-up points (in mm)

Time points	Mean $\pm$ SD	Median (Q1-Q3)	Mean ranks	P-value ^a
T0	9 $\pm$ 0.82	9 (8–10)	40 ^a	<0.001*
T1	6.1 $\pm$ 2.13	7 (4.5–8)	29.50 ^{a, b}	
T2	3.4 $\pm$ 1.43	3.5 (2–5)	20.50 ^{b, c}	
T3	0.9 $\pm$ 0.99	0.5 (0–2)	10 ^c	

SD: Standard deviation, Q1: First quartile, Q3: Third quartile, Q1-Q3: Inter-quartile range. ^a: Analyzed by Friedman's analysis of variance different lowercase letters imply statistically significant differences between them. *: Statistically significant ($P \leq 0.05$). VAS: Visual Analog Scale

Surgical options include band excision and grafting to address trismus and enhance overall oral function.

A randomized controlled trial by Rajendran *et al.* demonstrated the efficacy of pentoxifylline in improving mouth opening and tongue protrusion and alleviating symptoms such as spice intolerance, burning sensation, tinnitus, and difficulties in speech and swallowing.^[11] This study underscores the therapeutic benefits of medicinal interventions in managing OSMF.

In addition, Krishnamoorthy and Khan conducted a comparative study exploring two drug regimens for OSMF treatment. One group received oral colchicine and intralesional hyaluronidase, while another group was treated with intralesional hydrocortisone acetate and hyaluronidase alternately. The findings indicated superior improvement in mouth opening and histological parameters among patients treated with colchicine and hyaluronidase.^[12]

Furthermore, a study evaluating the effects of tretinoin (10 mg daily for 30 days) observed significant improvements in mouth opening, subjective symptoms like oral mucosa burning sensation, and histopathological changes in basement membrane integrity, subepithelial collagen levels, fibroblast count, and vascular congestion. Monthly follow-ups over 3 months revealed progressive improvement in the interincisal distance, indicating therapeutic efficacy. Similarly, there was

a reduction in VAS scores over time, reflecting decreased symptom severity.^[5]

Histopathological analysis of biopsy samples before and after treatment revealed a notable reduction in subepithelial collagen and fibroblast levels, along with decreased vascular congestion, highlighting the therapeutic impact on tissue morphology.

This evidence supports the efficacy of various therapeutic modalities in managing OSMF, emphasizing the importance of tailored treatment strategies to improve patient outcomes and quality of life.

Strength and limitations

The study rigorously evaluates all-trans retinoic acid (Retranoid) in Grades I and II OSMF, employing robust statistical analysis and monthly assessments over 3 months to observe clinical and histological improvements, although limited by a small sample size, single-center design, exclusion criteria, and short-term follow-up, highlighting the potential for broader application with larger, multicenter trials.

CONCLUSION

The encouraging results of the study prompt clinical trials on more patients. This baseline study provides opportunities for additional research on the use of all-trans-retinoic acid for treating OSMF and controlling this potentially malignant disorder in its initial stages thereby preventing its further progress.

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