ORIGINAL RESEARCH

A Comparative Study to Evaluate the Efficacy of Curcumin Lozenges (TurmNova®) and Intralesional Corticosteroids with Hyaluronidase in Management of Oral Submucous Fibrosis

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Abstract

Aim and objective: This study aims to compare the efficacy of TurmNova® lozenges and its active ingredient "curcumin" as a low-cost, safe, and noninvasive chemopreventive agent with intralesional corticosteroids (with hyaluronidase) in the management of oral submucous fibrosis (OSMF).

Materials and methods: A total of 80 patients with group III OSMF (Khanna JN and Andrade NN classification) visiting the dental outpatient clinic of the Department of Oral Medicine and Radiology Rama Dental College Hospital and Research Center, Kanpur, were selected for the study. A total of 80 patients were randomly divided into two groups (40 participants each): group A to whom TurmNova® lozenges containing turmeric extract 100 mg along with clove oil 10 mg three times daily for 3 months were given and group B to whom intralesional infiltration of 2 mL dexamethasone (4 mg/mL) + hyaluronidase 1500 IU dissolved in 0.5 mL of 2% lignocaine twice a week for 3 months was given. Data were analyzed using the IBM SPSS Statistics, version 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, version 21.0. Armonk, New York: IBM Corp.)

Results: Statistical analysis revealed that there was significant clinical improvement in mouth opening and subjective symptoms, like burning sensation/pain associated with the lesion and tongue protrusion in the group A as compared to group B.

Conclusion: Curcumin (100 mg) in an innovative delivery system of lozenge results in a higher level of plasma curcumin level. The aforementioned dosages prevent its biotransformation and inactivation by the liver enzymes. Because of these properties, curcumin lozenges are safer, low-cost, and effective alternative treatment in contrast to the present traditional treatment. Further long-term, prospective, large-scale studies need to be done.

Clinical significance: Curcumin has a role in the treatment of oral premalignant conditions and acts as a very effective chemopreventive agent in the prevention of cancer.

Keywords: Corticosteroids, Curcumin lozenges, Oral submucous fibrosis, Turmeric.

The Journal of Contemporary Dental Practice (2021): 10.5005/jp-journals-10024-3144

Introduction

In ancient medicine, Shushrutha described a condition "vidari" under mouth and throat diseases. He noted progressive narrowing of the mouth, depigmentation of oral mucosa, and pain on eating food. These features precisely fit in with the symptomatology of oral submucous fibrosis (OSMF).[1] Schwartz (1952) for the first time reported a case of "atrophica idiopathica tropica mucosae oris" occurring in Indians in East Africa. Lal and Joshi (1953) first described this condition in India. Joshi coined the term "oral submucous fibrosis."[2] Pindborg and Sirsat histologically described the four consecutive stages of the OSMF.[3] Seedat and Van Wyk have reported about the irreversible nature of the disease, i.e., once OSMF is induced by the habit of chewing betel nut, the reversa of the disease after cessation of the habit would not occur.[4] The number of people becoming dependent and/or habitual on such unsafe areca nut products with and without tobacco is increasing day by day, particularly among the younger age-groups. This represents an incredible risk on a long-term basis as a large segment of the society can be afflicted by disorders like OSMF or even oral cancer.[5] Fibrosis is a characteristic feature in the more advanced OSMF, which leads to impairment in mouth opening, speaking, and swallowing. Oral cancer accounts for up to 40% of all malignancies in Asia. The significant risk factors for oral cancer are tobacco smoking and chewing betel quid containing tobacco, whereas betel quid without tobacco significantly increased oral cancer risk in only one study. It is

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How to cite this article: Srivastava R, Kundu A, Pradhan D, *et al.* A Comparative Study to Evaluate the Efficacy of Curcumin Lozenges (TurmNova®) and Intralesional Corticosteroids with Hyaluronidase in Management of Oral Submucous Fibrosis. J Contemp Dent Pract 2021;22(7):751–755.

Source of support: Nil

Conflict of interest: None

19.1 times more likely for OSMF to convert into oral cancer.[6] The treatment of OSMF especially medicinal remains an enigma. Corticosteroids have been found to be the medicine of choice by professionals. Turmeric (*Curcuma longa*) is a therapeutic plant broadly utilized in Ayurveda, Unani, and Siddha medication as a home remedy for different diseases. A large number of studies have revealed that curcumin has wide therapeutic activities, like anti-inflammatory, antioxidant, and anticancer properties. Hastak et al., Chainani-Wu et al., Das et al., and Rai et al. have studied the role of curcumin in the treatment of OSMF.[7] A comprehensive review of the scientific literature has shown that restricted ayurvedic preparations were used in OSMF therapy, but their effectiveness needs to be evaluated with appropriate clinical trials. Natural ayurvedic OSMF therapy along with lifestyle modification can assist to reduce OSMF symptoms and help in curing the disease.[8]

Steroids are well-known immunosuppressive agents for the suppression of fibroproductive inflammation found in OSMF. Hyaluronidase degrades the fibrous matrix promoting the lysis of fibrinous coagulum and activating specific plasmatic mechanism.[9] Hyaluronidase is an enzyme that hydrolyses the mucopolysaccharides present in connective tissue, resulting in the increased permeability of the tissue and subsequently enhancing the diffusion of liquids through the subcutaneous space. It is hypothesized to help the tissue to absorb water-based medication more readily. It is believed that combining hyaluronidase with corticosteroids facilitates penetration of the corticosteroids.[10] Combination of corticosteroids with hyaluronidase showed quicker improvement in symptoms, like stiffness in the oral cavity that occurs through softening and diminishing fibrous tissue, and gave better, long-term results.

The objective of this study was to compare the efficacy of TurmNova® lozenges and its active ingredient "curcumin" as a low-cost, safe, and noninvasive chemopreventive agent with intralesional corticosteroids (with hyaluronidase) in the management of OSMF.

Materials and Methods

The present prospective study was conducted in the Department of Oral Medicine and Radiology in Rama Dental College Hospital and Research Center, Kanpur, Uttar Pradesh, India. The study was approved by the Institutional Ethical Committee of Rama Dental College Hospital and Research Centre, Kanpur, Uttar Pradesh, India (Ethical approval no /02/IEC/RDCHRC/2018-19/022 dated 15/1/2019). The purpose of the study was explained and informed consent was taken from the participants. The participants who consented to participate in the study were included. Patients were randomly selected from the department with a clinical diagnosis of group III OSMF (Khanna JN and Andrade NN classification). Patients belonging to group III OSMF (moderately advanced cases, Khanna and Andrade classification) with restricted mouth opening and interincisal distance of 15–25 mm, blanched oral mucosa, palpable fibrous bands at the soft palate, pterygomandibular raphe, anterior faucial pillars, and burning sensation were included in the study. Patients with OSMF who were not willing to take part in the study; group I, group II, and group IV (Khanna and Andrade classification) patients; patients with a known history of systemic diseases where steroids were contraindicated; and pregnant ladies were excluded from the study.

The study population consisting of 80 patients was divided randomly into two groups, viz. group A and group B, with 40 patients in each group. The complete case history was recorded in a predetermined format. Special attention was given to deleterious habits (betel nut, betel quid, tobacco and pan/pan masala chewing, and smoking) along with frequency and duration of habits. A calibrated digital vernier caliper, accurate up to 0.01 mm, was used to record the maximum unaided mouth opening between the upper and lower incisal edge in millimeters. The clinical parameters, such as burning sensation and pain associated with the lesion, were evaluated using a visual analog scale (VAS). The score of 0–1 was considered as absent, a score of 2–6 was considered as reduced, and a score of 7–10 was evaluated as the present. Patients were randomly allocated into two groups:

- Group A: Patients were administered curcumin lozenges (TurmNova®, Gelnova Laboratories Pvt. Ltd, Navi Mumbai, India) containing turmeric extract 100 mg along with clove oil 10 mg three times daily for 3 months. Patients were advised to chew these lozenges slowly followed by swallowing.
- Group B: Patients were given intralesional infiltration of 2 mL dexamethasone (injection Decadran 4 mg/mL, marketed by Merck and Co, Inc) + hyaluronidase 1500 IU (Hynidase 1500 I.U. Shreya Life Sciences Pvt. Ltd) dissolved in 0.5 mL of 2% lignocaine twice a week for 3 months.

All participants were informed about the condition and its precancerous potential, were instructed to discontinue the use of areca nut with tobacco, and were advised to perform physical exercises with the help of ice-cream sticks to increase the mouth opening and cheek blowing exercise for 10 minutes minimum two times a day. Clinical evaluation was done during their subsequent visits through the assessment of improvement of subjective symptoms, like burning sensation, objective signs like interincisal distance, and tongue protrusion. Patients were explained about the VAS and were asked to mark the severity of burning sensation on it. The patients were enquired for the improvement of burning sensation or the inability to take hot and spicy food at the subsequent visits and were asked to mark it again on a VAS. The burning sensation was then recorded on a percentage reduction basis. The interincisal distance was measured with vernier calipers between the right maxillary and mandibular central incisors on maximum opening. If these teeth were missing, they were measured on the corresponding teeth of the left arches. The measurements at subsequent visits were done at the previously recorded sites only, to avoid misinterpretation. Tongue protrusion was measured with a scale as the distance of movement of the tongue beyond the incisal tips of the lower incisors. These parameters were analyzed at the baseline and at the end of 1st, 2nd, and 3rd months. All measurements were taken by the same examiner (M.Y.) to avoid observer variability.

Data were analyzed using IBM SPSS Statistics, version 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, version 21.0. Armonk, New York: IBM Corp.) Descriptive statistics included the calculation of percentages, mean, and standard deviation (SD). Data distribution was assessed for normality using the Shapiro–Wilk test. The Student's unpaired t-test was applied for comparing the continuous type of parametric data among unrelated groups. All values were considered statistically significant for a value of $p<0.05$.

Results

Table 1 shows that out of the total 80 OSMF patients, 71 (88.75%) were men and 09 (11.25%) were women with an age range of 31–40 in years and mean ± S.D of 33.5 ± 9.5. Table 2 shows the effect of TurmNova® lozenges and intralesional injection [2 mL dexamethasone (4 mg/mL) + hyaluronidase 1500 IU] in burning sensation/pain associated with lesion. Both group A and group B patients revealed a significant reduction in burning sensation/pain associated with lesion after 1 month of treatment with mean ± S.D of 3.80 ± 0.853 and 2.95 ± 0.846. After 2 months of treatment, both groups (group A and group B) revealed a significant reduction in burning sensation/pain associated with lesion with mean ± S.D of 3.65 ± 1.703 and 3.13 ± 0.335 as compared to after 1 month of treatment. After 3 months of treatment, both groups (group A and group B) revealed the absence of burning sensation/pain associated with mean ± S.D of 0.48 ± 0.506 and 0.38 ± 0.401. Clinical improvement in burning sensation/pain associated with lesion was significant in both group A and group B (p <0.001). Table 3 shows the effect of TurmNova® lozenges and intralesional injection [2 mL dexamethasone (4 mg/mL) + hyaluronidase 1500 IU] and the change of mouth opening. Group A patients revealed a significant difference in mouth opening after 1 month of treatment with mean ± S.D of 2.0 ± 0.66 than group B patients with mean ± S.D of 1.93 ± 0.267. After 2 months of treatment, group A patients revealed a significant difference in mouth opening with mean ± S.D of 2.78 ± 0.423 than group B patients with mean ± S.D of 2.73 ± 0.452. After 3 months of treatment, group A patients revealed a significant difference in mouth opening with mean ± S.D of 4.0 ± 0.981 than group B patients with mean ± S.D of 3.28 ± 0.552. Clinical improvements in mouth opening were significant in group A (p <0.001). Table 4 shows the effect of TurmNova® lozenges and intralesional injection (2 mL dexamethasone (4 mg/mL) + hyaluronidase 1500 IU) and the improvement of tongue protrusion. There was no significant improvement observed in the tongue protrusion in both groups (group A and group B) with mean ± S.D of 2.0 ± 0.66. After 2 months of treatment, group A revealed significant improvement of tongue protrusion as compare to group B with mean ± S.D of 3.00 ± 0.14 and 2.48 ± 0.506. In the same way, after 3 months of follow-up, significant improvement of tongue protrusion was seen in group A patients as compared to group B with mean ± S.D of 3.85 ± 0.362 and 3.00 ± 0.14. Clinical improvement in tongue protrusion was significant in both group A and group B (p <0.001). However, few patients reported pain at the site of injection in the early visits, which was well-tolerated. None of the patients withdrew during the study.

Table 1: Age- and gender-wise distribution

Sl. No.	*Males n (%)*	*Females n (%)*	*Age range (in years)*	*Age in years (mean ± S.D)*
1	71 (88.75%)	09 (11.25%)	31–40	33.5 ± 9.5

Table 2: Effect of TurmNova® lozenges intralesional injection and in burning sensation/pain associated with any lesion

Sl. No.	*Timelines*	*TurmNova® Lozenges (Mean ± S.D)*	*Intralesional injection (Mean ± S.D)*	*p value*
1	After 1 month	3.80 ± 0.853	2.95 ± 0.846	
2	After 2 months	3.65 ± 1.703	3.13 ± 0.335	p <0.001
3	After 3 months	0.48 ± 0.506	0.38 ± 0.401	S

S: p <0.05, statistically significant

Table 3: Effect of TurmNova® lozenges and intralesional injection and in the change of mouth opening

Sl. No.	*Timelines*	*TurmNova® lozenges (mean ± S.D)*	*Intralesional injection (mean ± S.D)*	*p value*
1	After 1 month	2.0 ± 0.66	1.93 ± 0.267	
2	After 2 months	2.78 ± 0.423	2.73 ± 0.452	p <0.001
3	After 3 months	4.0 ± 0.981	3.28 ± 0.552	S

S: p <0.05, statistically significant

Table 4: Effect of TurmNova® lozenges intralesional injection and in improving tongue protrusion

Sl. No.	*Timelines*	*TurmNova® lozenges (Mean ± S.D)*	*Intralesional injection (Mean ± S.D)*	*p value*
1	After 1 month	2.0 ± 0.66	2.0 ± 0.66	
2	After 2 months	3.00 ± 0.14	2.48 ± 0.506	p <0.001
3	After 3 months	3.85 ± 0.362	3.00 ± 0.14	S

S: p <0.05, statistically significant

Discussion

OSMF is a potentially malignant, precancerous condition of the oral cavity and oropharynx, which is predominantly seen in the Indian subcontinent and Southeast Asian countries and is now globally considered an Indian disease.[11]

Despite the various treatment modalities available researched for OSMF, in each case, not a single one is absolutely effective. However, it has been discovered that numerous pharmaceutical drugs have side effects and recurrences in the treatment of OSMF. There has recently been an expansion of enthusiasm for herbal medicines, and various researches are being done to explore the clinical effectiveness of such compound preparations. Considering the disadvantage of traditional OSMF therapy, turmeric was tried. Turmeric constituents include three curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Curcumin (diferuloylmethane), an anti-inflammatory agent, was used in traditional medicine. They have been shown to suppress cellular transformation, proliferation, invasion, angiogenesis, and metastasis. Curcumin suppresses tumor necrosis factor (TNF)-induced NF-κB activation and NF-κB-dependent reporter gene expression. Such products which are involved in cellular proliferation (COX-2, cyclin D1, and c-myc), anti-apoptosis (IAP1, IAP2, XIAP, Bcl-2, Bcl-xL, Bfl-1/A1, TRAF1, and cellular cFLIP), and metastasis (VEGF, MMP-9, ICAM-1) were downregulated by curcumin.[8] In OSMF, hyaluronidase acts by breaking down hyaluronic acid (the ground substance in connective tissue) and lowers the viscosity of intercellular cement substance, while corticosteroid acts as an immune suppressive agent by its antagonistic activity on the soluble factors released by the sensitized lymphocytes succeeding the activation by nonspecific antigens. It additionally muzzles the inflammatory reaction. Thus, fibrosis is prevented by a decrease in fibroblastic proliferation and deposition of collagen.[12] Das et al. evaluated the efficacy of

turmeric (curcumin capsules and turmeric oil) in patients with OSMF both clinically and histopathologically and compared them with conventional chemopreventive treatment. He found early, rapid, and complete improvement of burning sensation with turmeric in OSMF cases, and curcumin was well-tolerated without any toxic manifestations or degradation of their condition.[13] Srikanth et al. published a case report to highlight the unusual complication of intralesional steroid in the form of abscess formation in a patient with OSMF, which may be due to the inoculation of the oral flora to the deep tissues during the injections.[14] In the present study, none of the participants reported with any side effects with TurmNova® lozenges although few patients reported pain at the site of injection in the early visits, which was well-tolerated. Hazarey et al. conducted a study to determine the efficacy of curcumin in the treatment of OSMF. The curcumin group showed a significant increase in mouth opening compared to the control group. In relation to VAS, with spicy and normal food, there was an average reduction as compared to the control group. He concluded that curcumin holds good promise in the management of OSMF in the future.[7] James et al. conducted a study to evaluate the efficacy of dexamethasone and hyaluronidase in the treatment of grade III OSMF. Improvement in the patient's mouth opening and a definite reduction in burning sensation, painful ulceration, and blanching of oral mucosa was found.[12] In the present study, both groups showed improvement in patient's mouth opening and reduction in burning sensation and pain associated with lesions. However, group A (TurmNova® lozenges) showed significant improvement in mouth opening and reduction in burning sensation and pain associated with lesions as compared to group B (intralesional injection). This could have been due to submucosal injections that attributed to repeated needlestick injury to the soft tissues at multiple sites, clinical irritation from drugs being injected, and the progressive nature of the disease that leads to the aggravated fibrosis and pronounced trismus. Menon et al. evaluated the bioavailability of lozenge with 100 mg turmeric extract as compared with the conventional hard gelatin capsule containing 475 mg curcumin. He stated that the buccal absorption of curcumin with an innovative delivery system of lozenge results in a higher level of plasma curcumin level with 100 mg dose compared to the 475 mg of curcumin dosed through hard gelatin capsules. The absorption curve demonstrates that higher bioavailability is achieved with buccal lozenge, when the gastrointestinal tract is bypassed.[15] In the present study, group A (TurmNova® lozenges) participants showed significant improvement of tongue protrusion as compare to group B (intralesional injection). This difference could be due to potent anti-inflammatory properties and good bioavailability of TurmNova® lozenges with prescribed dose and formulation. None of the patients of groups A and B have deteriorated in their clinical condition. This may be due to the successful pharmacological activity of the medications utilized in both the groups. The strength of the present study is the randomization of patients into the two groups, similar clinical profile in both the groups, and 100% follow-up for 3 months.The present study has certain implications that incorporate the early administration of TurmNova® lozenges in OSMF patients to provide rapid symptomatic relief. Turmeric has anti-inflammatory and antifibrinolytic properties with amazing antioxidant properties. Also, the noninvasive nature of this treatment makes it attractive.

Curcumin (diferuloylmethane) found in turmeric, a natural yellow pigment, exhibits antioxidant, anti-inflammatory, and anticancer properties. Turmeric oil and turmeric oleoresin together offer defense against DNA damage. As such, it may fulfill two roles in the putative treatment of OSMF, both as an anti-inflammatory agent and as a chemopreventive agent. It also provides a base for a simple, safe, acceptable, and cost-effective interference for earlier stages of OSMF.[16] Rai et al. conducted a study using curcumin in the treatment of oral precancers including 25 patients with OSMF. This study reported that OSMF was "cured by curcumin" due to increasing local and systemic antioxidative status.[17]

Conclusion

Curcumin is an anti-inflammatory and antioxidant compound possessing antirheumatic and anti-arthritic properties. It provides health benefits mainly through anti-inflammatory and antioxidant mechanisms. It has been reported that inhibiting the AKT/MTOR pathway with curcumin may also be useful as an oral chemopreventive agent. Curcumin with an innovative delivery system of lozenge results in a higher level of plasma curcumin level with 100 mg dose and prevents its biotransformation and its inactivation by the liver enzymes. Because of this property, curcumin lozenges are fast-acting, safer, noninvasive, low-cost, and effective alternative treatment in contrast to the present traditional treatment. Further long-term, prospective, and large-scale studies need to be done.

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