

Comparative Study of the Efficacy of Curcumin and Turmeric Oil as Chemopreventive Agents in Oral Submucous Fibrosis: A Clinical and Histopathological Evaluation

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Abstract

Background and Objectives: Oral submucous fibrosis (OSMF), A chronic disease characterized by fibrosis of oral mucosa is a premalignant condition carrying a high-risk of malignant transformation. So far none of the treatment modalities have proved curative. Turmeric and its active ingredient "curcumin" are being studied upon as chemopreventive agents in various diseases. This study was carried-out to evaluate the efficacy of turmeric dispensed in two forms, namely curcumin capsules and turmeric oil in patients with OSMF both clinically and histopathologically and to compare them with conventional chemopreventive treatment.

Materials and Methods: Forty eight patients who were clinically and histopathologically confirmed as having OSMF were selected for the study and were randomly divided into three groups. Group I patients were given curcumin capsules, Group II turmeric oil and Group III; the control group were provided with multinal tablets. The patients were called upon every 15 days for 3 months of treatment and then followed up, every month for 6 months. The results were analyzed with Anova Technique and Students' test.

Results: After treatment and follow-up statistically significant improvement was observed in the clinical signs and symptoms of patients treated with curcumin and turmeric oil when compared to those with multinal. Positive changes were also observed in the histopathological examination after treatment with curcumin and turmeric oil.

Conclusion: The therapy with curcumin and turmeric oil is beneficial, affordable and noninvasive form of treatment in patients with OSMF.

Keywords: Curcumin, turmeric oil, oral submucous fibrosis.

INTRODUCTION

Oral submucous fibrosis (OSMF) has been mentioned in the Indian medical literature, since the time of Sushruta. Epidemiological studies show a unique prevalence of this premalignant condition in India and Southeast Asia. Though chewing betel quid is considered an important risk factor for OSMF, the exact etiology and pathogenesis is still obscure. Pindborg has summed up the clinical and histopathological features in his definition for OSMF as "an insidious chronic disease affecting the mucosa or any part of the oral cavity and occasionally extending into the pharynx and esophagus. Although, occasionally preceded by and/or associated with vesicle formation, it is always associated with a juxtaepithelial inflammatory reaction followed by a fibroelastic change in the lamina propria with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat".¹ A wide range of treatment modalities both medical and surgical have been proposed for OSMF, but none have proved curative or reduced the morbidity significantly. Hence, the search for an effective treatment modality still continues.

Plants have been a major source of medicine since the time immemorial. Turmeric, has been attributed a number of medicinal properties in the traditional systems of medicine. Turmeric and its active ingredient, "curcumin" are being studied upon as chemopreventive agents in India and abroad. 'Chemo-prevention' is the use of pharmacologic or natural agents that inhibit the development of cancer. Curcumin and the essential oil of turmeric have been found to inhibit many disease processes through their anti-inflammatory, antioxidant and anticancer properties.²

Preliminary studies by Hastak et al³ have found turmeric to be effective in the amelioration of clinical signs and symptoms in patients with OSMF. But a histopathological evaluation was not conducted. The present study was taken up to evaluate the efficacy of curcumin and turmeric oil in patients with OSMF both clinically and histopathologically and to compare them with conventional chemopreventive treatment.

MATERIALS AND METHODS

The study was conducted in the department of oral medicine and radiology, government dental college, Trivandrum for a

period of 9 months. 48 patients who were clinically and histopathologically confirmed as having OSMF were selected for the study. Patients who had signed the informed consent on an approved format were included in the study. Clearance to conduct the study was obtained from the ethical committee. Curcumin capsules were obtained from a pharmacologist, Dr SB Rao and turmeric oil from kancor flavor extracts, angamaly. Each capsule contained 250 mg of curcumin and they were sealed in polythene covers containing 60 each. Turmeric oil was dispensed in bottles provided with droppers which dispensed 25 mg drops and each bottle contained 9 gm of the oil.

The patients selected for the study were randomly divided into three groups of 16 patients each. Group I patients were given curcumin capsules and instructed to take two capsules twice daily making a daily dose of 1 gm. Group II patients were given turmeric oil and were instructed to hold 12 drops of the oil in mouth for sometime and swallow it twice daily making a daily dose of 600 mg. Group III patients were taken as the control group and provided multinal tablets, one tablet of 500 mg to be taken twice daily, the daily dose of which was 1 gm.

The patients were instructed to report every 15 days for clinical evaluation and to collect the medication. Informed consent was taken from the patients before the study. Patients were clinically categorized into mild, moderate and severe, before the treatment based on the criteria proposed in various studies.⁴⁻⁷

Biopsies were taken before the treatment and after 3 months of treatment and based on the histopathological reports, the

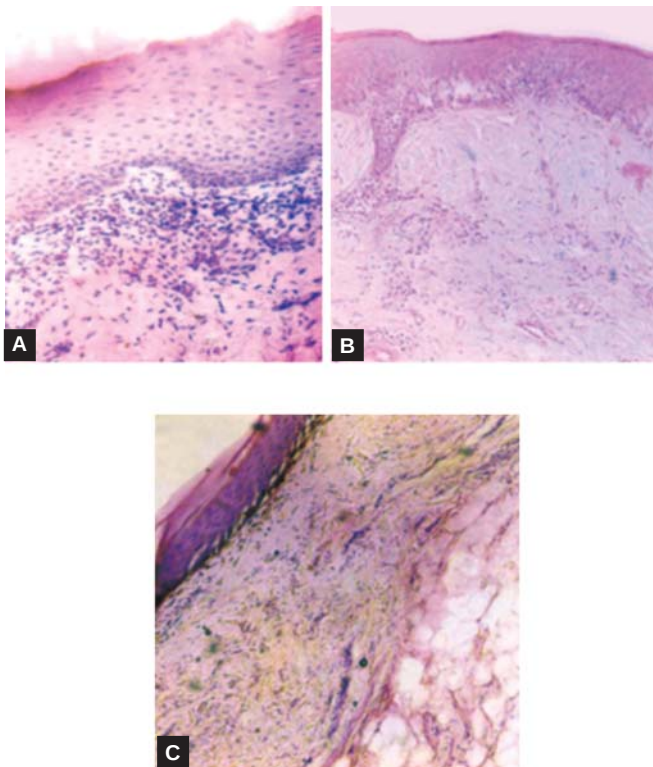
patients were grouped into three grades namely early, moderately advanced, advanced according to the criteria proposed by Abrol,⁸ Sirsat and Pindborg⁹ (Figs 1A to C).

The patients were called upon every 15 days for 3 months of treatment and then followed up, every month for 6 months. The severity of clinical signs and symptoms were entered as scores in the proforma. The data collected were tabulated and analyzed. The equality of mean scores of the three groups was tested statistically using anova technique. The differences in the scores at 15 days, 1 month, 3 months and 6 months were compared between Groups I and II, Groups II and III, and Groups I and III by using the student's 't' test.

RESULTS AND DISCUSSION

All the patients in the study tolerated the treatment regimens well. None of the patients reported any allergic or abnormal reaction nor did we elicit signs or symptoms of toxicity to the treatment modalities. The cdc_{ri}, as well as various studies have reported turmeric to be nontoxic.¹⁰

Patients in Groups I and II presented with statistically significant reduction in burning sensation and intolerance to spicy food after 3 months of treatment and follow-up, when compared to those in Group III (Figs 2 and 3). While curcumin



Figs 1A to C: Photomicrographs showing histopathological grading of OSMF: (A) Early (B) Moderately advanced (C) Advanced

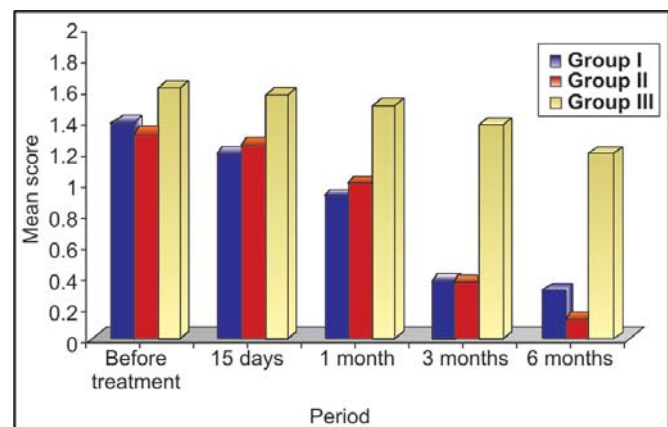


Fig. 2: Burning sensation according to time of assessment

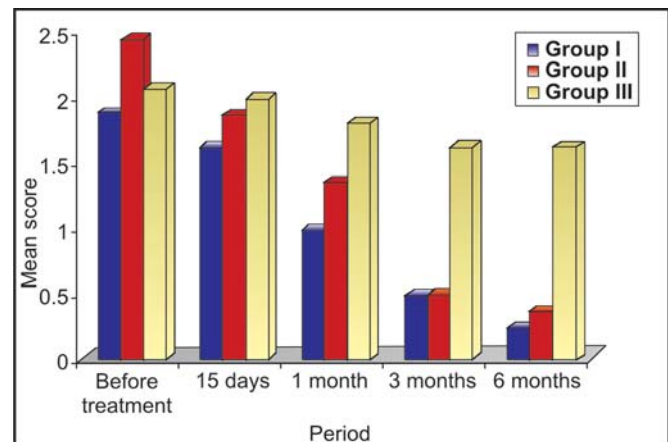


Fig. 3: Intolerance to spicy food according to time of assessment

produced quicker improvement than the other medications during treatment, turmeric oil was found to have a long-term effect on follow-up evaluation. Patients in Group III showed only minimal improvement, when compared to the other groups. Curcumin and turmeric oil have been reported to reduce burning sensation in precancerous lesions.¹¹

Complete relief from pain was reported by patients in Groups I and II within one month of treatment while pain persisted in 5 patients in Group III. But many studies¹²⁻¹⁴ have demonstrated curcumin to be a weak inhibitor of cyclooxygenase enzyme and lacks analgesic properties. The amelioration of the above symptoms could be attributed to the anti-inflammatory property of curcumin¹⁵⁻²⁰ and turmeric oil.²¹⁻²³ Pindborg and Sirsat have defined OSMF as juxtaepithelial inflammatory reaction followed by fibroelastic change of the lamina propria.¹ So inflammation is definitely a component in OSMF and the anti-inflammatory action of turmeric oil and curcumin might have brought about the regression of symptoms. Turmeric has been described as a dual inhibitor of arachidonic acid metabolism, as it inhibits both cyclooxygenase and lipoxygenase pathways of inflammation, thus inhibiting the products of inflammation such as prostaglandins, leukotrienes.¹²⁻¹⁴ Rao et al²⁴ has demonstrated the scavenging effect of curcumin on superoxide radicals, hydroxyl radicals and lipid per oxidation. So the effects brought about by the treatment regimen using turmeric oil and curcumin could be a synergism of their anti-inflammatory and antioxidant properties.

There was statistically significant and equal increase in the mouth opening of patients in Groups I and II after one month and 3 months of treatment and also after the follow-up period (Fig. 4). The mean increase was 0.87 cm in both the groups. Patients in Group III presented only a slight increase of 0.18 cm, which was insignificant when compared with the other groups. Patients treated with turmeric oil (group II) showed better increase in tongue protrusion when compared to those in Group I, followed by patients in Group III. The increase in mouth opening and tongue protrusion brought about by the treatment could be a result of the anti-inflammatory, antioxidant and fibrinolytic properties of curcumin and turmeric oil. Curcumin has been reported to possess fibrinolytic action in liver and lung fibrosis in studies conducted by Kuttan et al.²⁵ Turmeric and curcumin are regarded as fibrinolytic agents in chinese medicine.²⁶ Li et al²⁷ has attributed the fibrinolytic action of curcumin to its three properties namely inhibition of lipid per oxidation, checking cellular proliferation and inhibition of collagen synthesis. Above findings in this study also suggest turmeric to have a fibrinolytic action in OSMF, which needs to be investigated further. The same action of turmeric and curcumin would be responsible for the statistically significant and equal reduction of palpable fibrotic bands in patients of Groups I and II and their persistence in patients of Group III.

Also observed in patients treated with turmeric oil was a change of color of the oral mucosa from blanched to erythematous, which might be due to the increase in vascularity brought about by the treatment regimen. Leukoplakic lesions in 3 patients of Group II disappeared after treatment with turmeric oil. Topical along with systemic action of turmeric oil can be attributed to the above effects which were not observed in patients of Groups I or III.

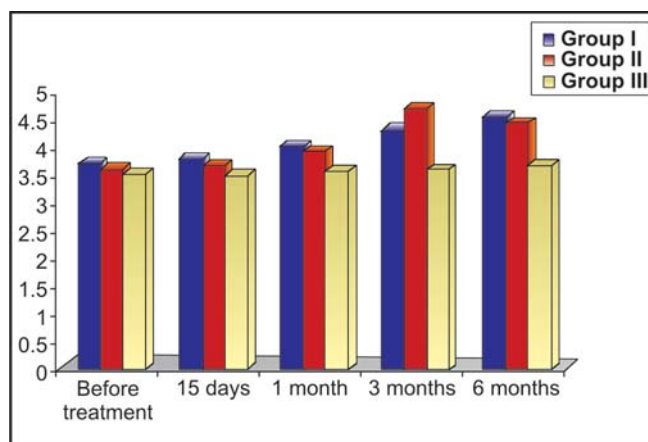


Fig. 4: Extent of mouth opening according to time of assessment

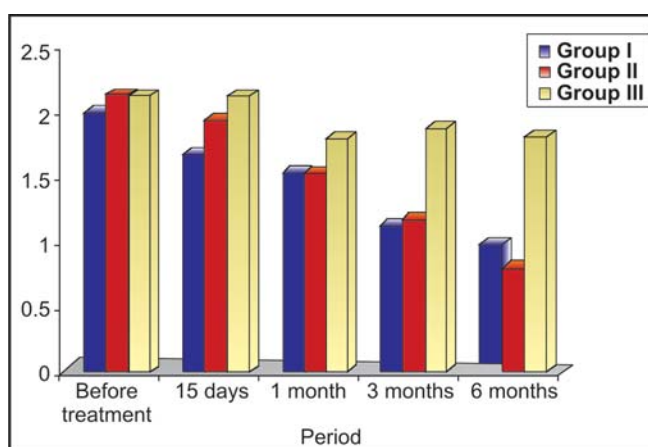


Fig. 5: Clinical scoring according to time of assessment

It is of interest to note that, none of the patients in Groups I and II presented a deterioration of their signs and symptoms nor a malignant transformation. Krishnaswamy²⁸ reported that turmeric inhibits carcinogenesis by polycyclic aromatic hydrocarbons and hence, a prospective chemopreventive agent against oral cancer. Earlier studies have reported turmeric and curcumin to be potent antioxidants and coupled with their anti-initiating and detoxifying effects, they have proven to be effective in the chemoprevention of cancer.²⁹ Along with the inhibition of arachidonic acid metabolism, they also inhibit superoxide generation, and thus prevent tumor promotion.^{30,31} Kerry bone has stated that curcumin alters the metabolism of carcinogens in liver and increases the activity of carcinogen detoxifying enzyme glutathione-s-transferase, thus preventing oncogenesis.²⁹

The clinical scores of OSMF in patients of the three groups were noted before treatment and at every visit during treatment and follow-up. There was remarkable reduction in the clinical scoring of patients in Groups I and II after the first 15 days of treatment. After 3 months of treatment and 6 months of follow-up, patients in Groups I and II showed statistically significant down grading of clinical scores, when compared with those in Group III, (Fig. 5). But after the follow-up period, patients in Group II showed better reduction in clinical scores than those

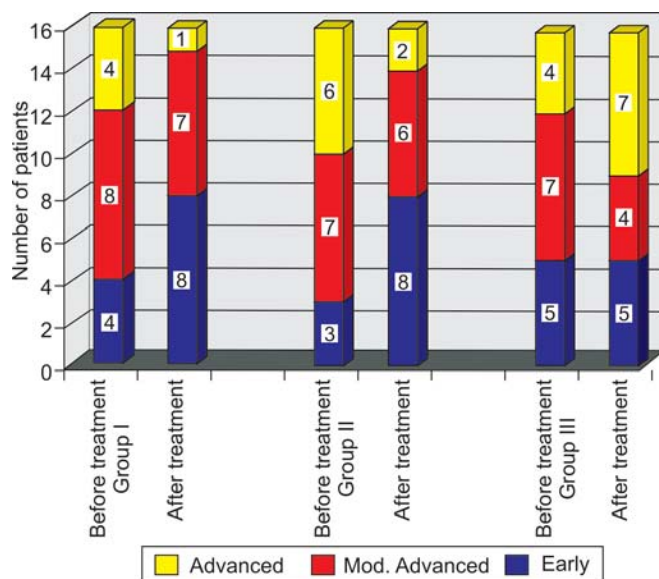
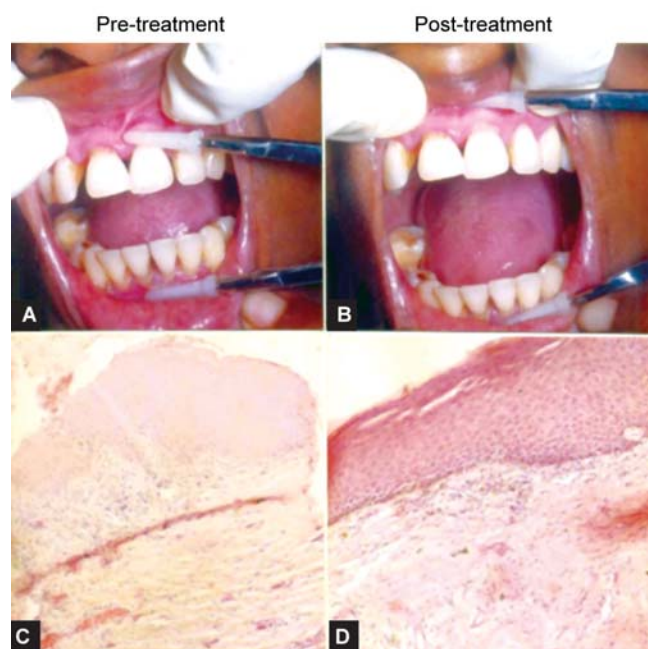


Fig. 6: Histopathological grading of patients in the three groups before and after treatment



Figs 7A to D: Photographs/Photomicrographs showing clinical and histopathological changes after treatment with curcumin

in Group I. Therefore turmeric oil was found to have a long-term effect than curcumin in improving the signs and symptoms of OSMF. Patients treated with multinal presented with only minimal reduction from their original scores.

Histopathological findings of biopsies conducted before and after 3 months of treatment were graded and compared. Histopathological reports after treatment showed 7 patients in Group I and 9 patients in Group II improved a stage better, while 3 patients in Group III deteriorated into the advanced stage (Fig. 6).

Histopathologic changes such as hyperplasia of epithelium and reduction in inflammatory cells were observed after treatment in patients of Groups I and II (Figs 7A to D) these findings correlate with the clinical reduction in burning sensation and intolerance to spicy foods in patients treated with curcumin and turmeric oil respectively. A marked reduction in the hyalinization of connective tissue was observed in patients of Groups I and II, and along with a decrease in inflammatory cells would have improved the extent of mouth opening and tongue protrusion after treatment. The above findings support the anti-inflammatory and fibrinolytic actions of turmeric. Conversely, the increase in the hyalinization of connective tissue and number of inflammatory cells along with a reduction in blood vessels, which was observed in a few patients in Group III would have aggravated their signs and symptoms. There was an increase in number of blood vessels in the post-treatment histopathologic picture of patients in Group II, who had presented with a significant improvement in the color of oral mucosa from blanched to erythematous. The topical action of turmeric oil on oral mucosa along with its systemic effect could have brought about this change after treatment.

A significant reduction in the number of mitotic figures was observed in the histopathologic examination of patients in Groups I and II after treatment. This supports the antioxidant property of turmeric. But in patients of Group III who were treated with multinal, an increase in mitotic figures was observed which points out the fact that turmeric is a better antioxidant than multinal. Rao et al has reported curcumin to be a better antioxidant than beta carotene.²⁴

CONCLUSION

Statistically significant improvement was observed in the clinical signs and symptoms of patients treated with curcumin and turmeric oil, when compared to those treated with multinal after treatment and follow-up evaluation. Positive changes were also observed in the histopathological examination after treatment with curcumin and turmeric oil. However, those treated with multinal did not present any significant improvement from their presenting signs and symptoms or histopathologic picture. Rather, there was a deterioration of the condition in few of the patients. Above all, curcumin and turmeric oil were well-tolerated without any toxic manifestations or degradation of their condition, making them potential chemopreventive agents. Thus, the choice of therapy is beneficial, affordable and noninvasive to those affected with OSMF. Extensive studies with a larger population and longer follow-up evaluation are required to arrive at a definite conclusion. Since only limited actions of turmeric are known, further investigations with scientific proofs and long-term detailed *in vivo* studies need to be carried out so as to pinpoint the exact mechanism of action.

It is evident from the study that curcumin and turmeric oil holds good promise in the treatment of OSMF in future.

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