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CURCUMIN ORABASE IN THE MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS: A NOVEL APPROACH.

Oral Medicine

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ABSTRACT

Aims and Objectives: The aim of this study was to evaluate the efficacy of 4% curcumin orabase, in oral submucous fibrosis (OSMF).
Materials and Methods: 30 subjects diagnosed with OSMF were included for the study. The patients were administered 4% curcumin orabase (Patent no. 845/CHE/2014) topically three times a day; efficacy of the therapy was evaluated considering the mouth opening and burning sensation of the subjects as parameters. The evaluation was done on a timely basis for a period of three months, and the data was then evaluated.
Results: The improvement in mouth opening and the decrease in burning sensation were statistically significant ($p<0.0001$).
Conclusion: 4% Curcumin orabase can also be considered as a best alternative treatment in OSMF, however, further research is intended on a larger sample size with longer followup.

KEYWORDS:

Oral submucous fibrosis, curcumin, orabase.

Introduction

Oral potentially malignant disorders are one of the most widespread, present worldwide today. They are often neglected by the general population when compared to cancerous lesion. However, they also may be particularly fatal which transforms as cancer if gone untreated at a very initial stage. [1] One such condition 'Oral sub mucous fibrosis' (OSMF) is a chronic insidious disease, associated with significant functional morbidity and risk of malignancy. Betel nut chewing has been implicated as prime etiologic agent with a high incidence of the disease. There is no widely accepted treatment till date. [2] [3]

Indian spice, turmeric (Curcuma longa) is derived from the rhizomes of the perennial plant of zingiberaceae family and has a long history of use in herbal and ayurvedic medicine as a treatment for inflammatory conditions. This plant is cultivated in India and other parts of Southeast Asia. [4] Since ancient times, turmeric has been used in South East Asia as a part of culinary recipes and as traditional medication for ailments.

Curcuminoids, a class of compounds found in turmeric, comprised of curcumin, demethoxy curcumin and bisdemethoxycurcumin. [5] Curcumin is the principal curcuminoid and comprises 2-5% approximately and is responsible for the yellow color of the spice as well as the therapeutic effects of turmeric.

Curcumin exhibits anti-inflammatory, [6] anti-oxidant, [6][7] anti-fibrotic [8] and antineoplastic [9][10] activities. It increases the level of glutathione-S-transferase, thus, up-regulates the synthesis of glutathione, an antioxidant. Other beneficial effects ascribed to curcumin are its wound-healing, antiviral & anti-infectious. Curcumin has been shown to suppress cellular proliferation in breast, colon, oral, and other cancers and is currently being studied for its chemopreventive and anticancer properties. [11] In Indian culture, turmeric (Curcumin) has been consumed as a dietary supplement for centuries and is considered pharmacologically safe.

Considering these properties 4 %(w/v) Curcumin is incorporated in orabase (Patent no. 845/CHE/2014) as a treatment alternative for OSMF.

Advantages of orabase: Orabase paste adheres tenaciously and remains in intimate contact with mucous membranes of the mouth and gums, protecting the afflicted area in the mouth against further irritation from normal oral activity by virtue of its superior adhesive properties. It deliberately dissolves in saliva, increases the effectiveness of the treatment by providing drug for a longer time.

Aims and objectives:

The aim of the study was to evaluate the efficacy of 4% curcumin orabase, in OSMF.

The objective was to check the treatment efficacy of curcumin in terms of alleviating burning sensation on Visual Analog Scale (VAS) and improvement in mouth opening(inter incisal distance).

Materials and Methodology:

This is an in-vivo single arm clinical study, registered for clinical trials of 'Curcumin orabase in Oral Submucous Fibrosis' in the 'US clinical trials registry' (ClinicalTrials.gov; ref no. NCT02645656) in which 30 subjects with clinically diagnosed (based on clinical staging by Haider et al[12]) OSMF were selected from the Department of Oral medicine & Radiology, SVS Institute of Dental Sciences, Mahabubnagar.

Of the randomly diagnosed 30 subjects, majority were male with only 4 females. Mean age of the patients is 32 years. 4% curcumin orabase is advised to these patients and recalled after 15 days to evaluate burning sensation & mouth opening.

Inclusion Criteria: 30 subjects clinically diagnosed with OSMF.
Exclusion Criteria:

1. Patients underwent/undergoing treatment for OSMF.
2. Patients allergic to turmeric.

Method of application-

- All the patients were counseled about adverse effects of quid/gutkha chewing and malignant potential of OSMF, & thereby advised to quit the habit.
- They are advised to apply 4% curcumin orabase three times daily after meals.

Clinical evaluation: Reviewed for every 15 days to a period of 3 months, to evaluate the effectiveness of treatment in terms of increase in mouth opening (by measuring the inter incisal distance in 'millimeters' using a digital Vernier callipers) as well as alleviation of burning sensation (using VAS scale with score range of 1-10)

Statistical analysis: The data was analyzed by using statistical package for social sciences software (SPSS software, version 22.0). It is summarized by mean ± SD, for continuous data and percentages for categorical data. Difference between before and after or continuous data was done by students paired't' test. All the 'p' values <0.05 were considered as statistically significant.

Results: A total of 30 patients with age range of 16-52 were included in the study. Favoring the epidemiology, male predilection is seen.

Economic status didn't seem to affect choice of the beetle nut product used. Majority had the habit of gutkha chewing (commercially available forms), 3 subjects with habit of paan chewing. Duration of the habit is 4.65 years on an average with a mean frequency of 4.5/day. One patient discontinued the treatment and was excluded from the study. None of the subjects showed adverse reactions due to curcumin. four of the subjects had adequate mouth opening but with burning sensation and palpable fibrous bands. Hence only VAS score was determined during follow up in these patients (Figure-1 & 2).

Figure 1: Series of pictures showing improvement in mouth opening.

First visit Third visit Sixth visit

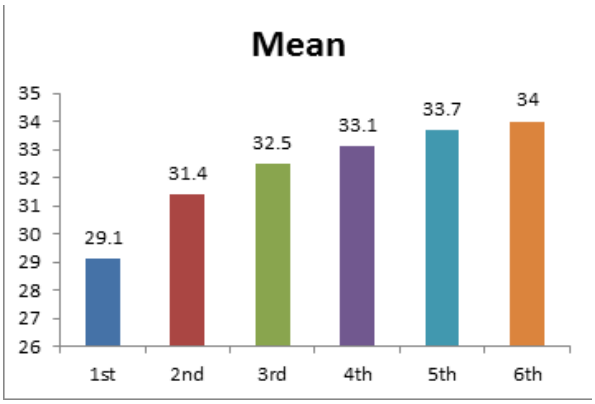
Figure 2: Series of intra oral pictures depicting the efficacy of treatment.

The mean mouth opening measured as inter incisal distance is 29.13 mm (n=25). The mean interincisal distance in first visit (15 days) is 31.44 mm with improvement in mouth opening of 2.31 mm. By the end of 6th visit it increased to 34.03 mm (table 1) with 14.4% mean improvement in mouth opening. 4.9 mm was the average improvement in the mouth opening, with 15.4mm being the maximum. One way ANOVA showed statistical significance with P<0.0001. Mean progressive improvement in mouth opening through follow up is documented in graph-1.

Table 1: Depicts the progression in mouth opening (in mm) through follow-up visits.

Visits	N	Range	Mean	SD	P-Value
1st	25	9.0 to 46.5	29.1	10.6	<0.0001
2nd	25	10.6 to 54.0	31.4	11.4	
3rd	25	11.5 to 54.0	32.5	11.3	
4th	25	11.5 to 54.0	33.1	11.4	
5th	25	11.5 to 54.0	33.7	11.8	
6th	25	11.5 to 54.0	34	11.8	

Graph 1: Shows mean improvement of mouth opening (in mm).

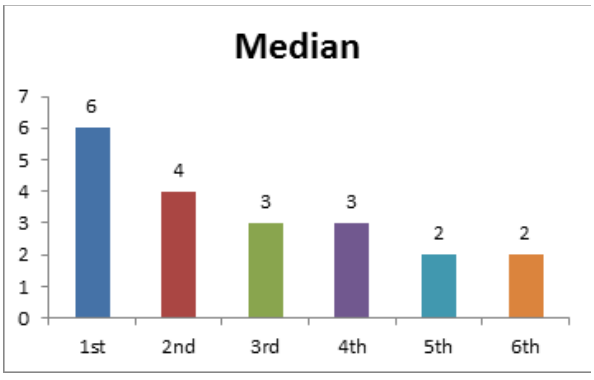


The median of VAS score, in the initial visit was 6 with the range of 4-8 (n=29). VAS score by the end of 15 days of using curcumin in orabase was reduced to 4 (range of 2-7). By 3rd visit it decreased to the median of 3, to median of 2 by 5th visit presenting statistical significance with P<0.0001 (table 2). Graph -2 depicts decreasing VAS score in 3 month follow up.

Table 2: Depicts the alleviation of burning sensation (VAS) through follow-up visits.

Visits	N	Range	Median	IQR	P-Value
1st	29	4 to 8	6	5 to 7	<0.0001
2nd	29	2 to 7	4	3 to 5	
3rd	29	2 to 7	3	2 to 4	
4th	29	2 to 7	3	2 to 4	
5th	29	2 to 7	2	2 to 4	
6th	29	2 to 7	2	2 to 4	

Graph 2: Shows median of decreasing burning sensation (VAS score).



Discussion

OSMF, a chronic disease is well known to oral and maxillofacial physicians of 'Asian subcontinent' and the 'Far East', owing to its utmost incidence in this area. [13] First described in the early 1950s, is having an estimated malignant transformation rate of 7-13%. [14] It is characterized by the inflammation and progressive fibrosis of lamina propria the upsurge of constricting bands of collagen. [15] The buccal mucosa is the most commonly involved site, may also involve the other parts of the oral cavity including pharynx. [16]

The etiology of OSMF is considered to be multifactorial: betel quid chewing, excessive use of spices, poor nutrition and iron and vitamin deficiency has been suggested as causative agents. [7]

The wide range of treatment modalities currently used for OSMF is ample evidence that there is no simple answer to how it should be managed. Many practitioners preference in treating this disorder is corticosteroids, either topical or Intralesional, used alone or in combination with other medication. They even presented better results compared to various other modalities. 17,18 Steroids though beneficial, had adverse effects like candidal infection and are contraindicated in some of the common medical conditions like hypertension, diabetes.

Various other treatment options have been tried to treat OSMF, none of which could cure this condition completely. In prevention strategies, secondary prevention is about treating the potentially malignant condition with use of natural, synthetic or biologic chemical agents to suppress, reverse or prevent carcinogenic progression, known as chemoprevention. Various chemo-preventive agents are employed, in which use of curcumin, an herbal extract is one of the modality. [19]

Turmeric as a traditional remedy in "Ayurveda" and ancient Indian medicinal system that dates back greater than 5,000 years, it has been used through the ages as an "herbal aspirin" and "herbal cortisone" to alleviate discomfort and inflammation allied with an extraordinary spectrum of communicable and autoimmune diseases. [20] It's been widely used in Ayurvedic, sidda medicine and unani for its antiseptic, anti-oxidant, anti-inflammatory, anti-aging, analgesic, antibacterial, antifungal, antimalarial, antiprotozoal, antiviral, anticoagulant, antifertility, hypotensive, anti-diabetic, hypocholesteremic, antivenom, anti-fibrotic, antiulcer, anti-carcinogenic and anti-mutagenic activities. [6]

Curcumin is considered to be of low toxicity in human and animals. There are no reports of adverse effects of either curcumin or its analogues except for rare cases of contact dermatitis, one of which occurred as an occupational. [21]

M Yadav et.al conducted a comparative study in 40 patients with clinically and histologically proven OSMF, were randomly divided into 2 groups. The first group was treated with 4 mg Dexamethasone & 1500 I.U Hyaluronidase intralesional injections weekly and the second group with two Curcumin tablets (Turmix 300 mg) per day for 3 months each. [22] Burning sensation improved in both the groups from early to late stages. With curcumin complete resolution of burning sensation was noted. The mean enhancement in interincisal distance was 3.13 mm and 1.25 mm respectively in groups 1 & 2. The results of this study are analogous to present trial with curcumin.

Deepa DA et al (2010) evaluated the efficacy of curcumin and turmeric oil as chemopreventive agents in a comparative study with 48 patients, clinically and histopathologically confirmed as having OSMF. [23] The subjects were randomly divided into three groups. Group I patients were given curcumin capsules (250 mg), Group II turmeric oil and Group III, the control group 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. 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.
Agarwal N et al. (2014) conducted a study to check the efficacy of turmeric in 30 OSMF patients. The subjects were administered with commercially available turmeric followed by periodic evaluation of mouth opening and burning sensation on VAS scale and then the data was compared. Unlike the present study, the improvement in mouth opening was not statistically significant ($P = 0.109$), with the improvement in mouth opening being 0.69 cm. However, the alleviaton of burning sensation was significant ($P < 0.001$) which is in agreement with results of the present study. [24]

Hazarey VK (2015) treated 30 clinically diagnosed OSMF patients dividing them into two groups, one with Longvida (curcumin) lozenges and other group using tenovate ointment (clobetasol propionate 0.05 mg) were given for 3 months duration and follow-up was done for 6 months. Both the groups were advised for physiotherapy exercises by mouth exercise device. [25]

The curcumin group showed 5.93 (±2.37) mm improvement in mouth opening compared to 2.66 (±1.76) mm of the control group. In relation to VAS scale with spicy and normal food the average reduction was 64 (42-73) and 77 (70.5-82) as compared to 34 (14.5-64.5) and 64 (46-75.5) respectively in control group. The test group results achieved in the treatment span was sustained in the follow-up ($P < 0.05$) compared to control group which showed statistically significant ($P < 0.05$) relapse. This outcome with curcumin group supports the present study (4.9 mm increased IIO, 50% reduction in VAS score).

Adit S et al in 2015 [26] conducted a prospective observational study on 45 patients diagnosed with OSMF. Patients were involved irrespective of age, gender, occupation, social status, ethnicity, and stages of OSMF. The patients were advised to mix 1 gm of turmeric powder and 1 gm of tulsi powder in glycerine to make a paste, instructed to apply this all over the oral mucosa 4-5 times per day. The mean burning sensation was 6.07 ± 1.75 before treatment and 2.22 ± 1.41 after the treatment ($t = 15.52$; $P < 0.001$). Mean mouth opening was 24.46 ± 4.0 mm before the treatment and 27.85 ± 3.39 mm after the treatment ($t = 9.06$; $P < 0.001$). The current study too produced similar results.

The clinical trials mentioned in the literature as well as the present study proves efficacy of the curcumin as a potent remedy in OSMF, which is in comparison with other traditional treatments of choice. The evidence shows the potency of curcumin sharing similar platform as achieved with steroids in the treatment of OSMF without any untoward complications.

Conclusion:

An extensive array of treatment modalities has been anticipated for OSMF, but none of them were proven remedial, with potent therapeutic side effects (as with the continuous administration of steroids which still remains a main stay) on the sideline, consequently the investigation for efficient treatment modality still continues. Herbs have been a major resource of medicine since the time immemorial. Various studies have been conducted worldwide to show the therapeutic effect of curcumin on OSMF. Orabase with its superior adhesive properties provides the drug locally for longer periods, extending the effect. As per the outcome of this study, we conclude that 'curcumin in orabase' has a therapeutic effect in patients diagnosed with OSMF. Turmeric is considered a safe, nontoxic, and effective alternative for many conventional drugs due to its distinguished therapeutic properties and multiple effects on various systems of the body. As this was a short-term study, further research is needed with a larger sample size over long term to achieve more definite results.

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