COMPARE TO INTRALESIONAL THERAPY AND PHYTOCHEMICAL BASED SYSTEMIC DRUG THERAPY IN ORAL SUBMUCOUS FIBROSIS-CLINICO-PHARMACOLOGICAL STUDY

Clinical Research

Dr. Swapnil Srivastava	Assistant Professor, Dept. Of Pharmacology, Hind Institute Of Medical Sciences And Hospital Sitapur Uttar Pradesh
Dr. Krishna Singh	Assistant Professor, Dept. Of Pharmacology, K.D. Medical College & Hospital Mathura Uttar Pradesh
Dr. Dharmendra Gupta	Associate Professor, Dept. Of Pharmacology, Varunarjun Medical College And Hospital Sahajanpur Uttar Pradesh
Dr. Monu Yadav*	Associate Professor, Dept. Of Dentistry, Swaraswati Institute Of Medical Sciences And Hospital Unnao, Uttar Pradesh *Corresponding Author

ABSTRACT

Introduction: Oral sub-mucous fibrosis (OSMF) is characterized by abnormal collagen deposition. It is a precancerous disorder and transforms into a malignant tumor in 1.5–15% of all cases. Symptoms include submucous fibrosis, ulceration, xerostomia, a burning sensation restricted mouth opening and restricted tongue protrusion followed by oral mucosal blanching and uvula deviation. All of these greatly interfere with patient quality of life. Curcuma longa has been used for thousands of years as a remedy in the traditional Indian and folk medicine for the cure of a large variety of illnesses, such as inflammation, infectious diseases, and gastric, hepatic, and blood disorders. Curcumin is a major isolated polyphenol from the rhizome of turmeric (*Curcuma longa*). It has a wide range of pharmacological effects such as antioxidant, anti-inflammatory, antimicrobial, antitumor, and hepatoprotective activities. In our study curcumin used in OSMF as a systemic drug therapy and compare with intralesional therapy that's widely used in OSMF

Aims and objective: To check the efficacy of systemic drug therapy (curcumin longa) in OSMF, and compare with intra-lesional therapy (Dexamethasone with Hyaluronidase) in OSMF.

Material and method: 100 patients with clinically proven Oral Submucous Fibrosis were selected for the study and were randomly divided into 2 groups. The first group was treated with weekly Intralesional injection of 4 mg Dexamethasone & 1500 I.U Hyaluronidase and the second group by oral administration of two Curcumin tablets (Turmix 300 mg) per day for 4 months each. Improvement of burning sensation, interincisal distance, tongue protrusion and ulceration was evaluated on a weekly basis and compare to initial visit to end of treatment duration.

Statistical analysis and Results: Burning sensation improved in both the groups from early to late stages. Complete Resolution of burning sensation was noted with Turmix early compare to intra-lesional therapy. The mean increase in inter-incisal distance or mouth opening was more compare to systemic drug therapy. The inter-incisal distance improved in both the groups gradually, but not more significant results at systemic drug therapy the end of both therapies. Tongue protrusion showed greater recovery at the end of last stmonth in group 1 when compared with group 2.

Conclusion: Turmix is beneficial and effective in reducing burning sensation in early OSMF

Patients so we can concluded on the basis of symptomatic relief systemic drug therapy with phyto-chemical based drug given better results compare to intralesional therapy.

KEYWORDS

Intralesional therapy, Systemic drug therapy, Curcumin longa, Phytochemical

INTRODUCTION:

Precancerous lesions of oral mucosa, known as potentially malignant disorders in recent years, are consists of a group of diseases such as oral sub-mucous fibrosis, oral leukoplakia, oral erythroplakia and oral lichen planus etc, in which oral sub-mucosa is more common in Indian population that can be easily diagnosed clinically. Pindborg has defined Oral Submucous Fibrosis (OSMF) as "an insidious chronic disease affecting any part of the oral cavity and occasionally extending to the pharynx and esophagus, although, occasionally preceded by and/or associated vesicle formation. It is always associated with juxta-epithelial inflammatory reaction followed by fibroelastic changes in the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and difficulty in eating".¹ The prevalence in India had increased in the recent years to 6.42% with a higher predominance in the southern parts of the subcontinent.² Presently phyto-chemicals are used widely for premalignant lesions in oral cavity because Phyto-chemicals have been attracting scientists due to their property in altering cell cycle control, apoptosis evasion, angiogenesis and metastases. They have proved their efficacy in mono treatments or in association with other chemo preventive agents. Phyto-chemicals can be broadly classified into vitamins carotenoids and food polyphenols phenols like flavonoids, phylotaxins, sulfur rich compounds and phenolic acid indoles.³ In our country plants have been widely used as medicinal cure due to their medicinal properties since ancient times, but among all plants, turmeric had always occupied an important place in every house as well as all over due to its unique property.⁴ Turmeric (*Curcuma longa*) is an Indian spice derived from the rhizomes of the plant and is used in Ayurvedic medicine to treat inflammatory conditions. The primary active constituent of turmeric 'Curcumin' (diferuloylmethane), had been identified in 1910 by Lampe, Milobedzka.⁵ Curcumin is a pleiotropic molecule that

targets molecular mediators of inflammation. It had been widely used in inflammatory bowel disease, pancreatitis, rheumatoid arthritis, etc. with good results. The medicinal activity had been attributed to various pharmacological activities, including antioxidant, antimicrobial, pro-apoptotic and anti-inflammatory effects.^{4,5} Zhang SS et al have demonstrated antifibrotic activity of curcumin on human myofibroblasts and suggested that it may be of use in the treatment of OSMF.^{5,6}

AIM AND OBJECTIVE:

To check the efficacy of systemic drug therapy (curcumin longa) in oral submucous fibrosis, and compare with intra-lesional therapy (Dexamethasone with Hyaluronidase) in OSMF.

MATERIAL AND METHOD:

This study was performed on 100 subjects, age group 18 to 45 years considered. All subjects were randomly selected from Department of Dentistry and Department of pharmacology, HIND Institute of Medical Sciences and Hospital, Lucknow. An informed consent was taken from the individual, who participated in the study. The subjects were divided into two groups, such as study group 1 of conventional or intra-lesional therapy and another group 2 has those patients who were taken systemic drug therapy. Group 1, (n = 50) and group 2 (n=50) both group's subjects considered with clinically diagnosed OSMF stage I, II and III along with symptomatic complaints followed by Khanna JN et 1996 classification⁷, patient with a given history of chronic chewing of areca nut with tobacco for at least ≥5 years of duration, subjects with systemic diseases like diabetes mellitus, hypertension and peripheral neuropathies were excluded. Our study plan for 4 month duration in which 4 visits included and each visit clinical changes recorded and data collected on the basis of

symptomatic (Burning, pain sensation and ulceration) and physiological changes (Mouth opening, tongue protrusion) in oral cavity and compare on the bases of clinical and physiological changes at last visit. In our study, the first group was given weekly sub-mucosal intra-lesional injections of Dexamethasone (Inj Decadran 4 mg/ml, marketed by Merck & Co, Inc), 1500 International units of Hyaluronidase (Hynidase 1500 I.U.) along with 0.5 ml of 2% (1:80,000) Lignocaine Hydrochloride. The selection of the sites of injection was based on clinical judgment. Injections were given at multiple sites with a 26 gauge needle, given on alternate sides for a period of four months. The combination of dexamethasone & hyaluronidase is long acting, hence was injected on alternate sides. The second group was given oral administration of tablets of Turmix (Film coated tablet containing C. longa 300 mg, Piperine 5 mg, Sanat Pharma Ltd) given twice daily for a period of four months. No alternative or supplementary forms of therapy were used in any of the study participants, except the study medications. No side effects such as nausea, stomach upsets, diarrhea were reported by any patient. Both groups were treated for a period of 16 weeks. Before started to study we were explained to patients about visual analogue scale (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 & spicy food at the subsequent visits and were asked to mark it again on a VAS scale. Burning sensation was then recorded on a percentage reduction basis. Inter-incisal distance (IID) or mouth opening was measured with vernier callipers 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 baseline, at the end of 1st and 4th months. All measurements were taken by the same examiner to avoid observer variability. After completion of our study data was calculated and performed statistical analysis.

STATISTICAL ANALYSIS & RESULTS

The baseline profile between the groups was compared using Students t test. The improvement observed within the group by the end of 1st month, 2nd and 3rd months was tabulated and analyzed. The clinical improvement of a particular regimen (within the same group) before and after treatment was analyzed using paired t test. The improvement observed serially within the same group was evaluated using repeated measures ANOVA. Comparison between the two groups was done using unpaired t test.

In this study participants (100) consisted of 81 males and 19 females, with a mean age of 31.3 yrs. 26.5% of them were college students, 15.67% were unemployed/housewives, 35.67% were daily wage labourers and the rest 22.16% were holding desk jobs. 77.67% of the patients used commercially available gutkha products, while the rest 12.93% used either areca nut or gutkha depending on the availability. Only 9.4% patients reported the concomitant use of betel leaves along with areca nut occasionally.

The quid was placed in the right or left lower buccal vestibule for more than half an hour by 79.5%, while the rest used it for duration of 4 to 15 min. None of them had a habit of swallowing the contents. The average frequency per day and total duration of gutkha/areca nut chewing were 4.5 times and 5.4 years respectively. None of them had reported the concomitant use of smoking or alcohol. The clinical sites of involvement were labial mucosa, buccal mucosa, soft palate, floor of the mouth, retro-molar area and tongue. All the study participants had multiple areas of involvement. Buccal mucosa was involved in all the cases, followed by soft palate in 60%, tongue & floor of the mouth in 20% of the cases, retro-molar area in 55% of cases. Eighteen patients had clinical grading of Grade II (early cases) and 22 had Grade III (moderately advanced). Fibrous bands were palpable in the buccal mucosa, labial mucosa in all patients respectively. In our study 81% male and 19% female participated. So we can say male more effected compare to female.

Table 1: Pre and post treatment of conventional and systemic drug therapy in OSMF (Average value)

Visits	Intra-lesional therapy				Systemic drug therapy			
	Burning sensation	Mouth opening (IID)	Tongue protrusion	Ulcer	Burning sensation	Mouth opening (IID)	Tongue protrusion	Ulcer
1 st	5.8	26.84	28.46	0.54	6.9	26.84	29.08	0.6
2 nd	4.28	28.2	20.18	0.38	1.08	27.14	29.7	0.26
3 rd	3.16	29.42	30.5	0.16	0.2	27.92	29.94	0.14
4 th	0.94	31.02	32.72	0.04	0	28.24	30.58	0

In table 1 showing increasing average value of mouth opening and tongue protrusion in intra-lesional therapy compare to systemic drug therapy so we can say intra-lesional therapy is better than systemic drug therapy but burning sensation and ulceration has given significant decreasing value showing systemic drug therapy is better for symptomatic relief as showing in graph 1 and 2.

Graph 1: showing Intra-lesional therapy at 1st, 2nd, 3rd and 4th visit along with progression average value.

Graph 2: showing Systemic drug therapy at 1st, 2nd, 3rd and 4th visit along with progression average value.

Graph 3: Showing progressive result between ILT & SDT

Graph 3 showing decreasing value of burning sensation and ulceration in systemic drug therapy (SDT) that's suggestive as systemic relief more comfortable compare to intra-lesional therapy and mouth opening and tongue protrusion has good results by intra-lesional therapy so can prove it for physiological improvement better by intra-lesion therapy.

Table 2 Comparison between intra-lesional and systemic drug therapy in oral sub-mucous fibrosis at 4th visit

	BS		MO (IID)		TP		Ulceration	
	ILT	SDT	ILT	SDT	ILT	SDT	ILT	SDT
N	50	50	50	50	50	50	50	50
M	0.94	0	31.02	28.24	32.72	30.58	0.04	0
SD	0.8345	0	1.9645	3.4557	3.2682	3.9703	0.1959	0
T value	7.8849		4.8953		2.9129		1.4288	
P value	0.00001		0.00001		0.002217		0.07811	

In our study after completion of statistical analysis, significant value obtained among burning sensation (0.00001), mouth opening (0.00001) and tongue protrusion (except to ulceration. In case of intralesional therapy multiple puncture of oral mucosa with needle so some time ulcer and burning sensation re-occurs but systemic drug therapy (curcumin longa) has no any site complications.

DISCUSSION AND CONCLUSION:

In our study, 81 were males and 19 were females. This male preponderance was in accordance with various studies. The higher male preponderance probably reflects their easier access to the abusive habits or less social restrictions.^{8, 9} The majority of the study participants had used commercially available tobacco products probably due to the attractiveness of the multi-colour packets, ease of availability or the influence of advertising campaigns of gutkha companies.^{10,11} Economic status or employability did not seem to affect the choice of product in our series as 85% of them used commercial products, even when 40% of them were either students or unemployed. The average duration of chewing was around 5.4 years, with a frequency of 4.5 per day. Turmeric is non toxic phyto-chemical, easily availability and is extremely safe even at higher doses.^{12,13} This is in agreement with our study since none of the participants in our study reported with any side effects. Our study showed early, rapid and complete improvement of burning sensation and ulceration with turmix (curcumin longa). These findings are similar to those reported by Das DA et al¹² and M. Yadav et al.¹⁴

The maximum and minimum reduction in burning sensation with conventional as well as intralesional therapy was 5.8, 4.28, 3.16 and 0.94 at 1st, 2nd, 3rd and 4th visit respectively, with a mean value as above mentioned residual burning sensation at the end of therapy. This could have been due to the improper diffusion of the drug to all sites of affected mucosa due to the local drug delivery system and multiple points and multiple time puncher of mucosa. The complete resolution of burning sensation in the systemic drug therapy group (Turmixon) could be due to its anti-inflammatory properties at the end of therapy. Curcumin modulates the inflammatory response by down-regulating the activity of cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS) enzymes and inhibits the production of the inflammatory cytokines, tumor necrosis factor- α (TNF- α), interleukin (IL) -1, -2, -6, -8, and -12, monocyte chemoattractant protein (MCP), and migration inhibitory protein.¹⁵ In our study, group 2 (Turmixon) participants showed mild gradual improvement of interincisal distance and tongue protrusion towards the end of 4th month. Turmix could cause improvement of inter-incisal distance or mouth opening & Tongue protrusion when given for longer duration. Improvement in interincisal distance and tongue protrusion were higher with conventional therapy when compared with turmix. This difference could be due to the potent anti-inflammatory properties of steroid when compared with that of curcumin or the poor bioavailability of turmix with the existing dose and formulation. Previous studies have indicated poor absorption of curcumin leading to low systemic availability. The systemic availability can be improved by complexing curcumin to a phospholipid, since curcumin is lipid soluble.^{13, 15} Manufacturing curcumin as a phospholipid preparation may improve its bioavailability. The exact reasons for better improvement of tongue protrusion in group 1, despite no injections given in the floor of the mouth or base of the tongue are unknown but may be at least partly attributed to increase in mouth opening in these patients. Das DA et al reported a mean increase of 0.87 cm of mouth opening with turmeric oil and turmeric capsules in contrast to our finding with turmix. These differences could be attributed to the variation in the formulations, dosages or clinical profile of the patients included. Jurenka JS in his review, reported that same dose of different formulations may give rise to different mean serum curcumin concentrations, the reason being unclear. They had also reported that low doses resulted in lesser concentrations in serum.¹³ With turmix, the interincisal distance improved not better than tongue protrusion in our study in our study tongue protrusion is lesser higher comparatively inter-incisal distance with turmix therapy probably due to the anti-inflammatory and anti-fibrinolytic activity of turmix.^{13,5}

Das DA et al reported better response in tongue protrusion with turmeric oil than with systemic administration of turmeric. None of the patients of groups 1 & 2 have deteriorated in their clinical condition. This in both groups could be due to the effective pharmacological action of the drugs used. Some trials have even reported the regression

or stabilization of malignancies with the use of curcumin. The antioxidative and scavenger properties of curcumin, make it a very effective chemopreventive agent in the prevention of cancer.^{13, 15} The strengths of our study include randomization of subjects into the 2 groups, similar clinical profile in both the groups, 100% follow-up for 4 months. The limitations of our study include small sample size, data from a single centre and lack of histopathological confirmation of improvement at the end of the study period. Our study has certain implications which include the early use of turmix in OSMF patients to provide rapid symptomatic relief. In addition to its anti-inflammatory and anti-fibrolytic properties, it possesses excellent anti oxidant properties.

Moreover, the non invasive nature of this therapy makes it attractive.¹² Further long term, prospective, large scale studies with higher doses are required to confirm the findings of this preliminary report. After completion of study we concluded, turmix or curcumin is beneficial and effective in the management of early OSMF with symptomatic conditions.

REFERENCES

1. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. *Oral Surg Oral Med Oral Path.* 1966;22:764-779.
2. Hazarey VK, Erlewad DM, Mundhe KA, Ughade SN. Oral submucous fibrosis: a study of 1000 cases from central India. *J Oral Pathol Med.* 2007;36:12e17.
3. Das DA, Balan A, SreeLatha KT. Comparative study of the efficacy of curcumin and turmeric oil as chemopreventive agents in oral submucous fibrosis: a clinical and histopathological evaluation. *JIAOMR.* 2010;22:88e92
4. Jurenka JS. Anti-inflammatory properties of curcumin, a Major constituent of curcuma longa: a review of preclinical and clinical research. *Altern Med Rev.* 2009;14:141e153.
5. Zhang SS, Gong ZJ, Li WH, Wang X, Ling TY. Antifibrotic effect of curcumin in TGF- β 1-induced myofibroblasts from human oral mucosa. *Asian Pac J Cancer Prev.* 2012;13:289e294.
6. Surh YJ. Cancer chemoprevention with dietary phytochemicals. *Nat Rev Cancer.* 2003;3(10):768-80.
7. Khanna JN, Andrade NN. Oral submucous fibrosis: a new concept in surgical management. Report of 100 cases. *Int J Oral Maxillofac Surg.* 1995;24:433e439.
8. N, Keluskar V, Bagewadi A, Shetti A. Effectiveness of micronutrients and physiotherapy in the management of oral submucous fibrosis. *IJCD; 12(2):101e105.*
9. Babu S, Bhat RV, Kumar PU, et al. A comparative clinicopathological study of oral submucous fibrosis in habitual chewers of pan masala and betel quid. *Clin Toxicol.* 1996;34:317e322.
10. Nigam NK, Aravinda K, Dhillon Manu, Gupta Siddharth, Reddy Satheesha, Srinivas Raju M. Prevalence of oral submucous fibrosis among habitual gutkha and areca nut chewers in Moradabad district. *J Oral Biol Craniofac Res.* 2014;4(1):8e13. <http://dx.doi.org/10.1016/j.jobcr.2013.10.005>.
11. Shahid RA. Coming to America: betel nut and oral submucous fibrosis. *JADA.* 2010;141:423e428.
12. Das DA, Balan A, SreeLatha KT. Comparative study of the efficacy of curcumin and turmeric oil as chemopreventive agents in oral submucous fibrosis: a clinical and histopathological evaluation. *JIAOMR.* 2010;22:88e92.
13. Jurenka JS. Anti-inflammatory properties of curcumin, a Major constituent of curcuma longa: a review of preclinical and clinical research. *Altern Med Rev.* 2009;14:141e153.
14. Monu Yadav, K. Aravinda. Comparison of curcumin with intralesional steroid injections in Oral Submucous Fibrosis -A randomized, open-label interventional study. *J. Of oral biology and craniofacial fresearch* 4(2014) 169-173.
15. Tuba AK, Gulcin I. Antioxidant and radical scavenging properties of curcumin. *Chem Biol Interact.* 2008;174:21e31.