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## Research Article

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# Comparison Of Collagen-Curcumin Blend (Collaper Rtu) With Intralesional Steroid Injections in Oral Submucous Fibrosis a Randomized, Open-Label Interventional Study.

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## ABSTRACTS

**Introduction:** Oral Submucous Fibrosis (OSMF) is a precancerous condition characterized by limited mouth opening, burning sensation, stiffness, and blanching of the oral mucosa induced by areca nut eating. With any of the current therapy regimens, complete regression of the illness has not been accomplished in all patients. Curcumin is a yellow pigment found in curry powder that has antioxidant, anti-inflammatory, and pro-apoptotic properties. As a result, interventional research was conducted to determine the efficacy of Collaper RTu a proprietary collagen-curcumin based product in patients with OSMF.

**Setting and design:** Forty patients with clinically and histologically confirmed Oral Submucous Fibrosis participated in a randomized open label interventional research.

**Method & materials:** For the research, forty patients with clinically and histologically verified Oral Submucous Fibrosis were randomly assigned to one of two groups. The first group was given a weekly intralesional injection of 4 mg Dexamethasone and 1500 I.U Hyaluronidase, whereas the second was given two Collagen-Curcumin pills (Collaper Rtu 60mg Collagen with 100 mg Curcumin) every day for three months. On a weekly basis, the improvement of burning sensation, interincisal distance, and tongue protrusion was assessed.

**Results:** From early to late stages, the burning feeling improved in both groups. Collaper Rtu was found to eliminate the burning feeling. In groups 1 and 2, the mean increase in interincisal distance was 3.13 mm and 1.25 mm, respectively. The interincisal distance improved significantly in both groups by the end of the first month. When compared to group 2, group 1's tongue protrusion recovered faster at the conclusion of the first month.

**Conclusion:** Collaper RTu is useful and effective in lowering the burning feeling in people with early OSMF.

**KEY POINT: Blend of Curcumin and Collagen has not been compared to intralesional steroid treatment in OSMF patients in previous research. The blend was found to successfully minimize burning sensations while also improving mouth opening in this investigation.**

## 1. INTRODUCTION

An insidious chronic illness affecting any portion of the oral cavity and occasionally spreading to the pharynx and esophagus, but occasionally preceded by and/or related vesicle development," according to Pindborg. It's invariably linked to a juxta-epithelial inflammatory reaction followed by fibroelastic alterations in the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa, producing trismus, and feeding difficulties<sup>3</sup>. In recent years, the frequency in India has risen to 6.42 percent, with a greater prevalence in the subcontinent's southern regions<sup>4</sup>. OSMF is most frequent in males between the ages of 20 and 40. Labial mucosa, buccal mucosa, retromolar pads, soft palate, and the floor of the mouth are all common locations.

There have been reports of fibrotic alterations in the pharynx, esophagus, and Para tubal muscles of the eustachian tubes. 2 Burning sensations, hypersalivation/ xerostomia, and mucosal blanching with a marble-like appearance are all early signs of OSMF. The mucosa becomes leathery and inelastic with time, with perceptible fibrous bands, limiting mouth opening. OSMF eventually causes tongue restrictions, swallowing difficulties, speech and hearing problems, and a loss of gustatory sense<sup>5</sup>. OSMF's etiopathogenesis is complicated and incompletely understood. Curcumin (diferuloylmethane) was first discovered in 1910 by Lampe and Milobedzka. Curcumin is a pleiotropic chemical that targets inflammatory molecular mediators. It's been used successfully in inflammatory bowel illness, pancreatitis, rheumatoid arthritis, and another conditions<sup>2-6</sup>. Apart from flavonoids, tannins, catechin, and copper, areca nuts include alkaloids such as arecoline, arecaidine, guvacine, and guvacoline. The alkaloids drive fibroblasts to generate more collagen, while catechin and tannins help to keep its structure stable. The copper-

dependent enzyme lysyl oxidase is upregulated, resulting in enhanced collagen crosslinking<sup>6,7</sup>. Because of its cytotoxic, apoptotic, and proliferative actions, documented data suggests that areca nut is the principal etiological agent. In addition to the production of free radical-induced mutations, the cytotoxic effects of the areca nut cause genotypic and phenotypic changes, which are important in the pathogenesis of OSMF<sup>8</sup>. Apart from areca nut, commercial items such as gutkha, mawa, and pan masala have been demonstrated to develop OSMF quickly due to higher levels of areca nut in these processed products and/or the synergistic effect of nicotine over arecoline<sup>8,9,10</sup>. The optimum aims of therapy for this potentially malignant ailment include not just symptom relief (burning sensation, mouth opening limitation), but also halting disease development and malignant transformation. Despite the number of medications or therapies tested, no complete regression of this mucosal condition has been shown in any of the case studies described to far, hence the search for a lasting cure continues<sup>8,11,12</sup>. Curcumin is a pleiotropic chemical that targets inflammatory molecular mediators. It's been used successfully in inflammatory bowel illness, pancreatitis, rheumatoid arthritis, and other conditions. Various pharmacological actions, including antioxidant, antibacterial, pro-apoptotic, and anti-inflammatory properties, have been linked to the therapeutic activity<sup>14,15</sup>. Curcumin has antifibrotic effect in human myofibroblasts, according to Zhang SS et al, and may be useful in the treatment of OSMF<sup>15</sup>. As a result, it's possible that curcumin's anti-inflammatory, antioxidant, and antifibrotic qualities, all of which function concurrently, might stymie OSMF progression at different phases of the disease's etiology. We decided to do this study because of the useful qualities of a frequently available, well tolerated, household component with a non-invasive mode of administration. Intralesional steroid treatment has been thoroughly studied and approved for its positive benefits in the management<sup>14,15</sup>. Tilakartane W et al, on the other hand, report that treating OSMF with different surgical and intralesional injections leads to scarring and fibrosis in the long run<sup>8</sup>. As a result, the current study was designed to compare the efficacy of curcumin and collagen-based blend (Collaper) in OSMF to the most widely used medication, intralesional steroid injections.

## 2. MATERIAL AND METHODS

### 2.1. Study Design

In forty patients with clinically and histologically established Oral Submucous Fibrosis, a randomized open label interventional research was done.

### 2.2. Subjects

The final research comprised forty OSMF patients who attended Career Dental College's Department of Oral Medicine and Radiology over an 8-month period, as illustrated in Fig. 1. The study received ethical approval from the institution. All study participants gave their informed permission. The Khanna and Andrade classification was used to diagnose and stage OSMF<sup>1</sup>.

### 2.3. Inclusion and exclusion criteria

The research comprised patients between the ages of 20 years to 50 years who had a histopathological diagnosis of OSMF. Patients with coexisting malignancy/white lesions, known medication allergies, or who had previously been treated for OSMF and were unwilling to have a biopsy were excluded from the research.

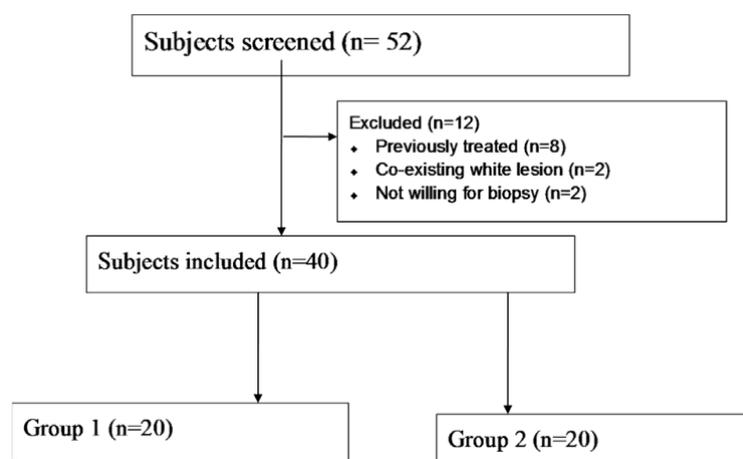


Figure 1 Flow diagram of the study.

### 2.4. Procedure

A detailed history was taken, with specific attention paid to the kind, frequency in a day, and length of habit (areca nut, gutkha, or a mix of both), as well as whether they swallowed or spit out the product. Clinical examination findings were documented on a specifically created proforma, which was supplemented with clinical pictures. Patients were advised to quit smoking and given oral prophylaxis to help them stay away from it. Khanna and Andrade classification was used for clinical grading<sup>1</sup>. The usual hematological and blood sugar tests were carried out. Under local anesthetic, an incisional biopsy was collected from the buccal/labial mucosa, depending on the severity, and histological investigation was performed.

Using a table of random numbers, the individuals with verified histological diagnosis were separated into two groups of 20 each. The first group received weekly submucosal intralesional injections of Dexamethasone (Inj Decadran 4 mg/ml, Merck & Co, Inc), 1500 international units of Hyaluronidase (Hynidase 1500 I.U. ), and 0.5 ml of 2 percent (1:80,000) Lignocaine Hydrochloride. The injection locations were chosen based on clinical judgement. For a three-month period, injections were delivered at different locations with a 26-gauge needle on alternating sides. Because the combination of dexamethasone and hyaluronidase has a lengthy half-life, it was given on both sides. For the second group, two Collaper RTu tablets (Film coated tablet containing Rose Hip Extract (275mg), Chondroitin sulphate (200mg), Curcumin (100mg), Collagen Peptide(60mg), Sodium Hyaluronate(30mg), L-Arginine(13.28mg), Piperine(2mcg), Vitamin K2-7(22.5mcg), Conceptive Farmacia Pvt Ltd) were administered once daily for three months.

Except for the research drugs, no alternative or extra forms of therapy were taken by any of the study participants. No patients reported any negative effects such as nausea, stomach problems, or diarrhea. Both groups were given 12 weeks of treatment.

## 2.5. Follow Up

During their future visits, clinical evaluation was conducted by assessing subjective symptoms such as burning sensations, as well as objective markers such as inter-incisal distance (IID) and tongue protrusion (TP). Patients were instructed to use a visual analogue scale (VAS) to rate the degree of their burning feeling. At following visits, the patients were asked if the burning sensation or incapacity to eat hot and spicy food had improved, and they were asked to rate it on a VAS scale again. The % reduction in burning feeling was then reported. On maximal opening, the interincisal distance (IID) between the right maxillary and mandibular central incisors was measured with vernier calipers. These teeth were measured on the equivalent teeth of the left arches if they were absent. To minimize misunderstanding, measurements were taken only at the previously reported places during future trips. Tongue protrusion was measured using a scale as the distance between the incisal points of the lower incisors and the tip of the tongue. These variables were examined at the start of the study, as well as at the conclusion of the first, second, and third months. To eliminate observer variability, all measures were collected by the same examiner (MY).

## 2.6. Statistical Analysis

Students t test was used to compare the baseline profiles of the two groups. The group's progress was tallied and examined at the conclusion of the first, second, and third months. A paired t test was used to compare the clinical improvement of a certain regimen (within the same group) before and after treatment. Using repeated measures ANOVA, the improvement exhibited serially within the same group was examined. The researchers used an unpaired t test to compare the two groups.

## 3. RESULTS

The participants in the research were 32 men and 8 women, with an average age of 32 years. Twenty percent were students, twenty percent were unemployed/housewives, twenty percent were daily wage laborers, and the rest worked at desk jobs. Eighty-seven percent of the patients utilized commercially accessible gutkha products, while the remaining 12.5% used areca nut or gutkha depending on availability.

Only three patients said they have used betel leaves and areca nut together on occasion. The quid was put in the right or left lower buccal vestibule for more than half an hour by 86 percent of the participants, while the others utilized it for 5-10 minutes. They were not in the habit of ingesting the contents. The average frequency of gutkha/areca nut chewing per day and total length of chewing were 4.8 times and 5.9 years, respectively. None of them had said that they smoked or drank at the same time.

The labial mucosa, buccal mucosa, soft palate, floor of the mouth, retromolar region, and tongue were all clinically involved. All the research participants were involved in a variety of activities. Buccal mucosa was implicated in every instance, followed by soft palate in 65% of cases, tongue and floor of mouth in 22% of cases, and retromolar region in 58% of cases. Grade II (early cases) was assigned to 19 patients, while Grade III was assigned to 21 others (moderately advanced). In 25 and 9 patients, fibrous bands were perceptible in the buccal and labial mucosae, respectively.

*Table 1 Comparison between the clinical profile of two groups.*

Parameter	Units	Group 1(Conventional) <sup>a</sup>	Group 2 (Collaper RTU) <sup>a</sup>	P value
Age	years	40.8 (14.9)	37.9 (10.5)	0.4811
Sex M:F		16:04	16:04	0.999
Burning sensation improvement baseline		0	0	–
IID baseline	mm	23.4 (5.3)	25.5 (4.3)	0.1769
Tongue protrusion baseline	mm	19.7 (2.5)	19.7 (2.5)	0.9999
<sup>a</sup> Mean (SD).				

Burning sensation, interincisal distance, and tongue protrusion were all measured at 100 percent, 23.4 mm, and 19.7 mm, respectively. Table 1 shows that the comparison of baseline profiles between the groups is not statistically significant. This shows that the clinical characteristics of the individuals in both groups were identical.

The therapy regimens were well tolerated by all research participants, with no adverse effects. With both therapies, all the measured metrics improved. Burning sensation improved in both groups from the end of the first month (mean values of 23.4 & 65.5 in group 1 & 2 respectively) to the end of the third month (mean values of 23.4 & 65.5 in group 1 & 2 respectively) (16.6 & 0 in groups 1 & 2 respectively). Collaper RTu was found to eliminate the burning feeling. When Collaper RTu was compared to conventional treatment, the reduction in burning sensation was statistically significant (P 0.001).

In groups 1 and 2, the mean increase in IID was 4.13 mm and 2.25 mm, respectively. Table 2 shows that the IID improved in both groups, with substantial improvements at the end of the first month. Tongue protrusion recovered more quickly in group 1 than in group 2 at the end of the first month (P = 0.003). At the end of the trial period, the mean increase in TP was 3.56mm and 1.48mm in groups 1 and 2, respectively.

When the clinical improvement in groups 1 and 2 was assessed serially, it was discovered that group 2 had improved totally and swiftly in comparison to group 1 (p < 0.0001). Both modalities showed similar sequential improvements in IID, as indicated in Table 2. With Collaper Rtu, there was no significant improvement in TP, whereas it was at its peak at the end of the first month with conventional treatment (P = 0.0006).

Table 2 Comparison between clinical improvement of the 2 groups.

Stage	Burning sensation			Interincisal distance			Tongue protrusion		
	Group 1	Group 2	P value	Group 1	Group 1	P value	Group 1	Group 2	P value
1st month	23.4 (9.7) <sup>a</sup>	64.5 (25.7)	<0.0001	0.68 (0.89)	0 (0)	0.0015	1.62 (1.48)	0.21 (0.6)	0.0003
2nd month	19.5 (11.4)	37.5 (25.7)	0.0001	2.1 (0.9)	0.33 (0.76)	<0.0001	0 (0)	0 (0)	–
3rd month	16.6 (12.2)	0 (0)	<0.0001	2.5 (2)	0.92 (2.1)	0.0916	0.9 (0.9)	0.23 (0.66)	0.0107
P*	0.2416	<0.0001		0.0265	0.0276		0.0005	0.3728	

<sup>a</sup> Mean (SD); P\* - Repeated measures ANOVA.

## 4. DISCUSSION

There were 32 males and 8 females in our research. According to numerous research, there was a male preponderance. The larger male prevalence is likely due to their better acceptance of harmful practices or a lack of societal constraints<sup>8,15</sup>. Because of the beauty of the colorful packets, convenience of availability, or the influence of gutkha firms' advertising efforts, most of the survey participants had used commercially accessible tobacco products<sup>6,7</sup>. Even though 40% of them were either students or jobless, economic position or employability did not appear to influence product choice in our series, since 85 percent of them utilized commercial items. Chewing lasted an average of 5.4 years, at a frequency of 4.5 times each day.

Turmeric is non-toxic and highly safe in large dosages<sup>13,14</sup>. This is consistent with our findings, as none of the individuals in our trial experienced any negative side effects. With Collaper Rtu, we saw an early, quick, and total relief in burning sensation. Das DA et al. published findings that are comparable to these<sup>13</sup>. With conventional therapy, the highest and minimal reductions in burning sensation were 80 percent and 40%, respectively, with a mean 15.6 percent residual burning sensation at the conclusion of therapy. This might be owing to the local drug delivery system's ineffective diffusion of the medicine to all locations of impacted mucosa. The anti-inflammatory characteristics of Collaper Rtu may have contributed to the full relief of burning feeling in the Collaper rtu group. Curcumin inhibits the inflammatory response by inhibiting the production of prostaglandins.

- 1) The enzymes cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS) are all downregulated.
- 2) Inhibits the inflammatory cytokines tumor necrosis factor-alpha (TNF-alpha), interleukin (IL) 1, 2, 6, 8, and 12, monocyte chemoattractant protein (MCP), and migration inhibitory protein synthesis<sup>14</sup>.

Group 2 (Collaper RTu) individuals in our study demonstrated a slight improvement in interincisal distance and tongue protrusion by the end of the third month. This suggests that when administered for IID and TP, Collaper rtu might help, when given for longer durations. When compared to Collaper rtu, conventional treatment improved interincisal distance and tongue protrusion more than Collaper rtu. This disparity might be related to steroid's stronger anti-inflammatory activities as compared to curcumin, or to Collaper rtu's low absorption at the current dose and formulation. Curcumin- Collagen blend has been shown to have limited absorption, resulting in low systemic availability in previous investigations. Because curcumin is lipid soluble, it can be made more systemically available by combining it with a phospholipid<sup>14,2</sup>. Curcumin's bioavailability may be improved by manufacturing it as a phospholipid formulation. The specific reasons for improved tongue protrusion improvement in group 1 despite no injections in the floor of the mouth or the base of the tongue are unknown, however it might be at least partly linked to the patients' increased mouth opening. In contrast to our finding of 2.25 mm with Collaper Rtu, Das DA et al observed a mean increase of 0.87 cm in mouth openness with turmeric oil and turmeric pills. These discrepancies might be due to variances in the formulations, doses, or clinical profiles of the individuals studied. In his review, Jurenka JS said that the same dose of various formulations might result in varied mean serum curcumin concentrations for unknown reasons. They also claimed that modest dosages resulted in lower serum concentrations. In our investigation, Collaper RTu improved the interincisal distance more than tongue protrusion, which is likely related to Collaper rtu's anti-inflammatory and antifibrinolytic properties<sup>14,15</sup>. Turmeric oil had a greater response in tongue protrusion than turmeric systemic injection, according to Das DA et al.

None of the patients in groups 1 and 2 had had their clinical status worsen. This might be owing to the medications' good pharmacological activity in both groups. Curcumin based blends has even been linked to the reduction or stability of malignancies in several studies. Curcumin's antioxidative and scavenger characteristics make it an excellent chemo preventive agent in cancer prevention<sup>14,2</sup>. Our study's strengths include randomization of subjects into two groups, a similar clinical profile in both groups, and a three-month follow-up. The limited sample size, data from a single center, and lack of histological proof of improvement at the conclusion of the research period are all limitations of our investigation. The early use of Collaper RTu in OSMF patients to give immediate symptomatic relief is one of the consequences of our research. It has great antioxidant capabilities in addition to anti-inflammatory and anti-fibro lytic properties. Furthermore, the non-invasive aspect of this treatment makes it appealing<sup>13</sup>. To corroborate the conclusions of this preliminary investigation, more long-term, prospective, large-scale trials with greater dosages are needed.

## 4. CONCLUSION

To summarize, Collaper RTu is successful and useful in the treatment of early OSMF.

## 5. CONFLICTS OF INTREST

There are no conflicts of interest for any of the authors.

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