

## Comparison of intralesional hydrocortisone and hyaluronidase injection to surgical repair in manging the oral submucous fibrosis: A prospective clinical study

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Received: 20-05-2021 / Revised: 15-06-2021 / Accepted: 28-06-2021

### Abstract

**Background:** One of the most prevalent and common premalignant disorders having high potential to turn into malignancy is Oral submucous fibrosis (OSMF). OSMF is associated with the chewing of betel quid and is commonly seen in India with a mean prevalence of 13% and a range of 0-4% based on the geographical areas. **Objective:** The present study was conducted to compare and assess the effectiveness of two treatment methods to treat OSMF of different grades to assess signs and symptoms and improvement of mouth opening. Also, the study compared intralesional hyaluronidase with Dexamethasone to Z-plasty surgery concerning efficacy and mouth opening improvement. **Material and Method:** The study included a total of 88 subjects with OSMF with varied grades. The study subjects were within the age range of 20-40 years and the mean age of 27.6±4.68 years. The subjects were divided into two groups where subjects of Group I were treated with iron and nutritional supplements in addition to Hyaluronidase and Dexamethasone as an intralesional injection, topical Triamcinolone Acetonide 0.1%, and Placentex, whereas, Group II subjects were treated with nasolabial flap repair and Z-plasty. At preoperative assessment and the postoperative follow-up of 1 and 3 months, pallor, oral mucosal blanching, painful ulcerations, burning sensation, and mouth opening were assessed and compared. **Result:** Systemic as well as local therapy including iron and nutritional supplements with the injection of Dexamethasone, Hyaluronidase, and topical Triamcinolone Acetonide 0.1% caused significant improvement in subjects with OSMF. In Grade III subjects, where non-surgical treatment was not effective, surgical therapy showed acceptable results with highly significant mouth opening. Significant reduction in discomfort and severity was seen with pallor, mucosal blanching, painful ulcers, and burning sensation seen in few subjects. **Conclusion:** The present study concludes that surgical as well as conservative management therapy helps in reducing the intensity and grading of OSMF. Also, counseling to break habits in students can decrease OSMF prevalence.

**Keywords:** Burning sensation, Hyaluronidase, Intralesional injections, Oral submucous fibrosis (OSMF), Premalignant condition.

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### Introduction

Oral submucous fibrosis is a clinical entity known in humans since very old times, however, it came to existence after Schwartz in 1952 described a fibrotic condition that was inexplicable in the oral cavity of 5 Indian women[1,2]. The prevalence of OSMF is varied between 0-4% differing on geographical areas assessed and the mean prevalence is 13% approximately[2]. In India, OSMF is more prevalent in South India with the prevalence of .36% Ernakulam in Kerala, 0.4% in Srikakulam district in Andhra Pradesh, 0.16% in Bhavnagar in Gujarat, 0.07% in Bihar, and 0.03% in Maharashtra. The local etiologic factors associated are betel nut chewing, chilly (capsicum), Pan and pan masala chewing, tobacco, and alcohol consumption[3,4]. OSMF is a complex and chronic oral premalignant lesion with a high potential to turn into a malignant lesion. It is characterized by progressive submucosal tissue fibrosis and juxta-epithelial inflammation[5].

OSMF is commonly presented as recurrent stomatitis, ulceration, and burning sensation in the oral cavity.

Other common symptoms associated are hypersalivation, dryness of mouth, xerostomia, defective gustatory sensation, and/or Intraoral petechiae. Also, reduced hearing ability and ear pain are seen in subjects where OSMF causes eustachian tube blockage and extension to the pharynx[6]. Initially, the mucosa is leathery and has fibrotic bands that can be palpated. However, mucosal resiliency is lost in the advanced stage making mucosa stiff and blanched. OSMF starts in the posterior oral cavity spreading outwards[7].

Clinical grading of OSMF as described by Gupta et al[8] in 1992 is as follows:

- Grade I: Presence of only blanching of oral mucosa without symptoms.
- Grade II: Presence of blanching and burning sensation, dryness of the mouth, Vesicles, or ulcers in the mouth.
- Grade III: Presence of blanching and burning sensation, dryness of the mouth, vesicles or ulcers in the mouth with restriction of mouth opening, and palpable bands all over the mouth without tongue involvement.
- Grade IV: Presence of blanching and burning sensation, dryness, of the mouth, vesicles, or ulcers in the mouth with restriction of mouth opening and palpable bands all over the mouth with tongue involvement.

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- Grade V: Presence of all features of grade IV associated with chronic Ulcer and histopathologically proven carcinoma.
- Grade VI: histopathologically confirmed carcinoma

OSMF is managed with either medical treatment or surgical intervention. The medical treatment includes hydrocortisone and hyaluronidase injection intralesional, triamcinolone acetonide (topical), iron supplements, antioxidants, systemic vitamins, interferon-gamma, and placental extract with the recent inclusion of oral cow milk intake. Other visceral organs involved are the esophagus and nasopharynx and could be associated with systemic disease spectrum with multiple organ involvement[9]. One of the surgical techniques for managing OSMF is Z-plasty, which is a plastic surgery technique that improves cosmetics and function in OSMF subjects without scar formation. In Z-plasty Z-shaped incision is utilized followed by the reflection of triangular flaps on two opposite sites followed by transposition. It has few associated complications including less blood supply, wound tension, flap necrosis, wound infection, and hematoma. Medical, as well as surgical management of the OSMF, have their associated limitations and advantages[10]. However, the data concerning the comparison of the two is limited in the literature. Hence, the present study was conducted to compare and assess the efficacy of the two treatment strategies in managing the OSMF of different stages and grading concerning associated signs, symptoms, and mouth opening.

**Materials and Methods**

The present prospective clinical study was conducted to compare and assess the effectiveness of two treatment methods to treat OSMF of different grades to assess signs and symptoms and improvement of mouth opening. Also, the study compared intralesional hyaluronidase with Dexamethasone to Z- plasty surgery concerning efficacy and mouth opening improvement. The study was conducted at.....from.....to.....after obtaining the clearance from the concerned Ethical committee. The study population was comprised of the subjects visiting the Outpatient Department of Otorhinolaryngology of the Institute with restricted mouth opening due to OSMF.

The study included a total of 88 subjects with OSMF with varied grades. The study subjects were within the age range of 20-40 years and the mean age of 27.6±4.68 years. After explaining the detailed study design, informed consent was taken from all the subjects. After final inclusion, the subjects were divided into two groups where subjects of Group I were treated with iron and nutritional supplements in addition to Hyaluronidase and Dexamethasone as an intralesional injection, topical Triamcinolone Acetonide 0.1%., and Placentrex, whereas, Group II subjects were treated with nasolabial flap repair and Z-plasty.

The detailed history with demographics like address, occupation, sex, and age of all the subjects from both the groups was recorded at the initial visit following inclusion. This was followed by urine and routine blood investigation with general and cardiovascular examination to assess endomyocardial fibrosis. The findings obtained

were recorded on structured proforma. The mouth opening was assessed as the following grade:

- Grade I: Mouth opening 36 mm (or) above
- Grade II: Mouth opening 26 mm to 35 mm
- Grade III: Mouth opening 16 mm to 25 mm
- Grade IV: Mouth opening 6 mm to 15 mm

For different grades, the treatment was as follows:

**Grade I**

- Antioxidants & Multivitamins -1 tab once daily 10 weeks Orally
- Iron Supplements 1 tab once daily 10 weeks Orally
- Topical Ointment Triamcinolone Acetonide 0.10% 4 weeks

**Grade II**

- Antioxidants & Multivitamins (Tablets A to Z) 1 tab once daily 10 weeks Orally
- Iron Supplements (Cap. Hemfer) 1 tab once daily 10 weeks Orally
- Topically Ointment Triamcinolone Acetonide 0.1% for 8 weeks
- Intralesional Inj. Hyaluronidase (Hynidase) 1500 IV + Inj. Dexamethasone 2 ml + Local Anaesthetic 1 ml 2% without adrenaline- Biweekly for 10 weeks

**Grade III**

- Surgical treatment is recommended in cases of progressive fibrosis when inter incisor distance becomes less than 20mm.
- Multiple release incisions deep to mucosa, submucosa, and fibrotic tissue and suturing the gap or dehiscence so created by nasolabial graft.
- Z-plasty- multiple deep z-shaped incisions were made into fibrotic tissue and then sutured in a straighter fashion.

At preoperative assessment and the postoperative follow-up of 1 and 3 months, pallor, oral mucosal blanching, painful ulcerations, burning sensation, and mouth opening were assessed and compared. The collected data were subjected to the statistical evaluation using SPSS software version 21 (Chicago, IL, USA) and one-way ANOVA for results formulation. The data were expressed in percentage and number, and mean and standard deviation. The level of significance was kept at p<0.05.

**Results**

The present prospective clinical study was conducted to compare and assess the effectiveness of two treatment methods to treat OSMF of different grades to assess signs and symptoms and improvement of mouth opening. Also, the study compared intralesional hyaluronidase with Dexamethasone to Z- plasty surgery concerning efficacy and mouth opening improvement. The study included a total of 88 subjects with OSMF with varied grades from both genders. The study subjects were within the age range of 20-40 years and the mean age of 27.6±4.68 years. After final inclusion, the subjects were divided into two groups where subjects of Group I had 64 subjects and Group II had 24 subjects that had undergone surgery (Z-plasty). The gender-wise distribution of the study subjects is described in Table 1.

**Table 1: Demographic characteristics of the study subjects**

S. No	Study Group	OSMF Grade	Females	Males	Total
1.	Group I	I	17	21	38 (43.18)
2.		II	9	17	26 (29.54)
3.	Group II	III	10	14	24 (27.27)
4.		Total	36 (40.90)	52 (59.09)	88

In Group I, there was 17 females and 21 males having Grade I OSMF making a total of 43.18% (n=38) subjects, whereas, in Grade II there were 9 females and 17 males, and a total of 29.54% (n=26) subjects. In Group II, there were 10 females and 14 males having Grade III OSMF, making a total of 27.27% (n=24) subjects.

On assessing the postoperative findings in the study subjects at 1 month, the results are interpreted in Table 2.

**Table 2: Assessment of the postoperative symptoms in the study subjects after 1 month**

S. No	Symptoms	Group I		Group II	p-value
		Grade I	Grade II	Grade III	
1.	Pallor	7	9	13	0.003

2.	<b>Oral Mucosal Blanching</b>	9	11	12	0.001
3.	<b>Painful Ulcers</b>	8	13	17	0.01
4.	<b>Burning sensation</b>	13	11	15	0.05
5.	<b>Mouth opening (Limited) in mm</b>	31.4	26.8	38.8	0.003

It was seen that pallor was seen in Group I in 7 subjects having Grade I OSMF and 9 subjects having Grade II OSMF, whereas, in Group II and Grade III OSMF, it was seen in 13 subjects. Oral mucosal blanching was seen in 9 and 11 Grade I and Grade II OSMF subjects of Group I, and in 12 subjects with Grade III OSMF in Group II. Painful ulcers were seen in 8 and 13 subjects of Group I with Grade I and Grade II OSMF respectively and in 15 subjects of Group II and Grade III OSMF. Limited mouth opening was 31.4mm and 26.8mm in Grade I and Grade II OSMF subjects respectively in Group I, and was 38.8mm in Group II Grade III OSMF subjects. All these differences were statistically significant with  $p=0.003$ ,  $0.001$ ,  $0.01$ ,  $0.05$ , and  $0.003$  respectively in two groups concerning pallor, oral mucosal blanching, painful ulcers, burning sensation, and mouth opening.

The present study also assessed these findings at 3 months post-treatment. Pallor was seen in 7 (3 in Grade I and 4 in Grade II subjects) subjects with a non-surgical intervention group and in 7 subjects who underwent surgical intervention. This was statistically significant ( $p=0.005$ ) Oral mucosal blanching was seen in 4, 7, and 7 subjects with Grade I, II, and III OSMF respectively, which was statistically significant ( $p=0.002$ ). Painful ulcers were seen at 3 months in 3, 5, and 6 subjects respectively with Grade I, II, and III OSMF. This was also statistically significant ( $p=0.003$ ). The burning sensation was also statistically significant between Group I and II and in Grade I, II, and III OSMF with 8, 7, and 8 subjects respectively ( $p=0.01$ ). Mouth opening was 37.4, 32.8, and 40.6 respectively in Grade I, II, and III OSMF subjects. This was statistically significant ( $p=0.001$ ) as shown in Table 3.

**Table 3: Assessment of the postoperative symptoms in the study subjects after 3 months**

S. No	Symptoms	Group			p-value
		Group I	Grade II	Grade III	
1.	<b>Pallor</b>	3	4	7	0.005
2.	<b>Oral Mucosal Blanching</b>	4	7	7	0.002
3.	<b>Painful Ulcers</b>	3	5	6	0.003
4.	<b>Burning sensation</b>	8	7	8	0.01
5.	<b>Mouth opening (Limited) in mm</b>	37.4	32.8	40.6	0.001

## Discussion

The present prospective clinical study was conducted to compare and assess the effectiveness of two treatment methods to treat OSMF of different grades to assess signs and symptoms and improvement of mouth opening. Also, the study compared intralesional hyaluronidase with Dexamethasone to Z-plasty surgery concerning efficacy and mouth opening improvement. The study included a total of 88 subjects with OSMF with varied grades from both genders. The study subjects were within the age range of 20-40 years and the mean age of  $27.6 \pm 4.68$  years. After final inclusion, the subjects were divided into two groups where subjects of Group I had 64 subjects and Group II had 24 subjects that had undergone surgery (Z-plasty). In Group I, there was 17 females and 21 males having Grade I OSMF making a total of 43.18% ( $n=38$ ) subjects, whereas, in Grade II there were 9 females and 17 males, and a total of 29.54% ( $n=26$ ) subjects. In Group II, there were 10 females and 14 males having Grade III OSMF, making a total of 27.27% ( $n=24$ ) subjects. The demographics were comparable to the studies of Mithani S.K et al[11] in 2007 and Hove C et al[12] in 2001 where authors assessed subjects with comparable characteristics.

Concerning postoperative findings in the study subjects at 1 month, it was seen that pallor was seen in Group I in 7 subjects having Grade I OSMF and 9 subjects having Grade II OSMF, whereas, in Group II and Grade III OSMF, it was seen in 13 subjects. Oral mucosal blanching was seen in 9 and 11 Grade I and Grade II OSMF subjects of Group I, and in 12 subjects with Grade III OSMF in Group II. Painful ulcers were seen in 8 and 13 subjects of Group I with Grade I and Grade II OSMF respectively and in 15 subjects of Group II and Grade III OSMF. Limited mouth opening was 31.4mm and 26.8mm in Grade I and Grade II OSMF subjects respectively in Group I, and was 38.8mm in Group II Grade III OSMF subjects. All these differences were statistically significant with  $p=0.003$ ,  $0.001$ ,  $0.01$ ,  $0.05$ , and  $0.003$  respectively in two groups concerning pallor, oral mucosal blanching, painful ulcers, burning sensation, and mouth opening. These results were in agreement with the findings of Nair U et al[13] in 2004 and Reddy V et al[14] in 2011 where comparable mouth opening and other findings were seen as in the present study.

The present study also assessed these findings at 3 months post-treatment. Pallor was seen in 7 (3 in Grade I and 4 in Grade II

subjects) subjects with a non-surgical intervention group and in 7 subjects who underwent surgical intervention. This was statistically significant ( $p=0.005$ ) Oral mucosal blanching was seen in 4, 7, and 7 subjects with Grade I, II, and III OSMF respectively, which was statistically significant ( $p=0.002$ ). Painful ulcers were seen at 3 months in 3, 5, and 6 subjects respectively with Grade I, II, and III OSMF. This was also statistically significant ( $p=0.003$ ). The burning sensation was also statistically significant between Group I and II and in Grade I, II, and III OSMF with 8, 7, and 8 subjects respectively ( $p=0.01$ ). Mouth opening was 37.4, 32.8, and 40.6 in Grade I, II, and III OSMF subjects respectively. This was statistically significant ( $p=0.001$ ). These results were consistent with the studies of Hazarey V.K et al[15] in 2015 and Balaji S.M[16] in 2016 where pallor, oral mucosal blanching, ulcerations, and mouth opening were similar as in the present study.

## Conclusion

Within its limitations, the present study concludes that surgical as well as conservative management therapy helps in reducing the intensity and grading of OSMF. Also, counseling to break habits in students can decrease OSMF prevalence. However, the present study had few limitations including a smaller sample size, geographical area biases, shorter monitoring period, and single-institution nature. Hence, further longitudinal studies with a larger sample size and longer monitoring period are required to reach a definitive conclusion.

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**Conflict of Interest: Nil Source of support: Nil**