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Comparing the efficacy of placental extract & betamethasone with hyaluronidase in stage 2 OSMF patients of Arunachal Pradesh

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Abstract

Objective: To compare the efficacy of Placental Extract vs. Betamethasone with Hyaluronidase in improving mouth opening among Stage 2 Oral Submucous Fibrosis (OSMF) patients from Arunachal Pradesh.

Study Design: Twenty patients were divided into two equal groups and received biweekly intralesional injections of either Placental extract or Betamethasone with Hyaluronidase for a total of 24 sessions.

Results: Significant increase in mouth opening, evaluated at baseline and after each injection, with statistical analysis showing significant improvement in both groups but no statistically significant difference between them.

Conclusion: Both the Placental extract and Betamethasone with Hyaluronidase are safe and effective options for Stage 2 OSMF management in this population

Keywords: Oral submucous fibrosis, placental extract, betamethasone, hyaluronidase, mouth opening, therapy

1. Introduction

In 1952, Schwartz described Oral Submucous fibrosis (OSMF) among five Indian females living in Kenya ^[1]. OSMF is a chronic, insidious disease ^[2] that is strongly associated with the consumption of areca nut ^[3]. When it comes to the consumption of areca nuts, Indians are placed among the world's largest populations ^[4]. Various parts of India have areca nut as the centre of centuries-old traditions and, are found with many different identities such as gutka, sweet supari, paan masala, mawa, and khara ^[5].

In Arunachal Pradesh (AP) areca nut is commonly known as "Tamul", and it is widely cultivated for business and consumption alike ^[6]. There are a lot of reports of Oral cancer studies from various regions of India, but the search engine on the literature for AP showed only one study that revealed a low level of awareness about the disease. A Hospital-based Retrospective study of oral cancers in Itanagar capital region AP (2018-2022), conducted on 135 patients of AP reported that chewing tobacco and betel nut have been associated with the development of buccal mucosa cancer in AP ^[7].

OSMF is uniquely characterised by its widespread involvement in any part of the oral cavity that results in tissue scarring, difficulty in swallowing, and reduced mouth opening. In older literature, OSMF was classified as a Precancerous condition ^[8]. Later in 2007, it was categorised into 'Oral Potentially Malignant Disorders (OPMD)' ^[9].

Various studies have reported patients with OSMF to show a higher risk of developing carcinoma, with some studies showing a 7.6% transformation into Oral Squamous Cell carcinoma ^[10] while more recent studies showing malignant transformation up to 9% ^[11, 12].

2. Materials and Methods

Patients attending the OPD at a private clinic were recruited in this randomised, double blind, controlled clinical trial. All the patients that were allocated, attended the entire process without any dropouts.

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Patients with the presence of Stomatitis and/or blanching of the oral mucosa, palpable fibrous bands in the buccal mucosa and/or oropharynx, with/without stomatitis or in any other parts of the oral cavity with/without stomatitis, with a baseline mouth opening of 18 to 19 mm were included in this study.

Patients with systemic medical problems, a history of drug allergy or hypersensitivity to hyaluronidase, betamethasone, those who had been treated for OSMF or malignancy, those who were unwilling to participate, pregnant patients, and patients with TMJ disorders or pericoronitis of the mandibular third molars were excluded from the trial. Patients were informed about their condition, its cause, and its Malignant potential. All patients underwent informed consent in a language they understood, following the guidelines of Helsinki's declaration-2002.

The selected patients were divided into two groups, each of 10 patients by a simple block randomization method. Both groups 1 and 2 received 24 intralesional injections in total, given as biweekly injections. Group 1 was given intralesional injections of Placental extracts 2 mL with 1 mL LA (each mL is derived from 0.1 g of fresh Human Placenta. Total nitrogen not more than 0.08% w/v, benzyl alcohol IP 1.5% v/v as preservative) and Group 2 was given Hyaluronidase intralesional injections with Betamethasone with 1 mL of LA (1mL of Betamethasone sodium phosphate 4mg/mL with 1500 IU Hyaluronidase).

Patients were followed up for three months after completion of treatment.

The principal investigator confirmed and enrolled patients and also prepared injections. OSMF was confirmed when there was chronic limited mouth opening, burning sensation in the oral cavity either on eating regular or spicy food, blanching of oral mucosa, palpable fibrous bands on buccal mucosa or labial mucosa and an associated areca nut or tobacco habit. Assessment of parameters and performing the injections was done by two separate investigators. These investigators, along with the patient, were blinded to the content of the injections. Most fibrosed areas on both buccal mucosae were selected, and injections were given bilaterally using 30 30-gauge insulin needles (Dispovan). OSMF staging was carried out at baseline based on the clinical staging as described by More CB *et al.*(13) Maximum interincisal opening was assessed both at baseline and at the end of treatment. Mouth opening was assessed in millimetres (mm) at the maximum opening from the edge of the right maxillary CI to the right mandibular CI using a vernier calliper. None of the patients were edentulous in the upper and/ or the lower anterior regions. A change in the measurement on the scale of mouth opening from baseline to the final visit was considered as either improvement or deterioration. Improvement in mouth opening showed synergistic improvement in the burning sensation.

No general adverse effects like vomiting, diarrhoea, or drowsiness were noted. Counselling for habit cessation was offered to the Patients, and they were free to drop out of the study at any point without offering any reason, although there were no dropouts.

2.1. Data analysis

All quantified variables in this study were transferred onto an Excel spreadsheet (Microsoft Inc., USA) and subjected to statistical analysis. The primary endpoint for this study was mouth opening. Differences between the groups were examined at the end of the study using an independent t-test. Variables were summarized with appropriate descriptive

statistics. p-values were set at 0.05, and values less than this value were considered statistically significant.

3. Results

All the patients in the research finished their prescribed courses of medication. The investigator did not see any indications of medication toxicity, and none of the patients displayed any adverse or unexpected reactions.

3.1 Distribution of Mean Age

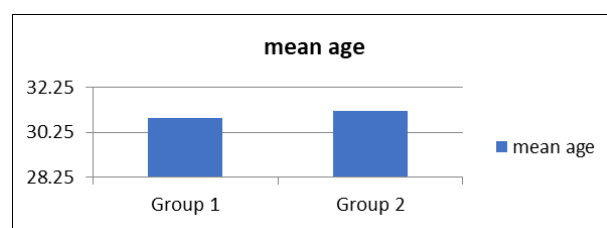
A total of 20 patients were included in this study, 14 were male and 6 were female. The overall age ranged from 20 to 50 years. The patients were divided into two groups. Group 1 was given intralesional injections of Placental extracts and Group 2 was given Hyaluronidase intralesional injections with Betamethasone.

The mean age for Group 1 was 30.90 ± 5.087 years and for Group B it was 32.4 ± 9.8 years. Results were found to be insignificant.

Table 1: Distribution of Mean Age

Group	Mean age	Std. dev	p value
Group 1	30.90	5.087	.90
Group 2	31.20	5.514	

(Test used- independent t-test, $p > 0.05$, insignificant)



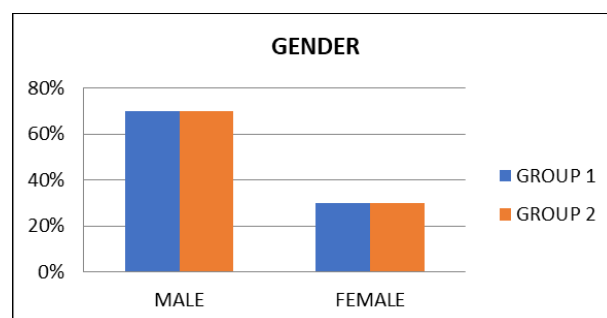
Graph 1: Distribution of Mean Age

3.2. Gender Distribution

Group 1 and Group 2 each had 10 patients in total. There were 7 males and 3 females in each group. From the given Table 2 and Graph 2, it can be noted that Males were 70% in Group 1 and Group 2 and females were 30% in Group 1 and Group 2.

Table 2: Gender distribution of Group 1 and Group 2

Gender	Group		Total
	Group 1	Group 2	
Male	7	7	14
	70.0%	70.0%	70.0%
Female	3	3	6
	30.0%	30.0%	30.0%
Total	10	10	20
	100.0%	100.0%	100.0%



Graph 2: Gender distribution in Group 1 and Group 2.

3.3. Stage distribution

According to the staging proposed by More CB *et al.*, all the patients included in our clinical-trial belonged to Stage 2, with Mean baseline intralesional mouth opening in Group 1 and Group 2 as $18.410 \pm .8399$ and $18.220 \pm .7899$ mm respectively. Patients can be classified as S2M3.

3.4 Comparison of Mouth Opening

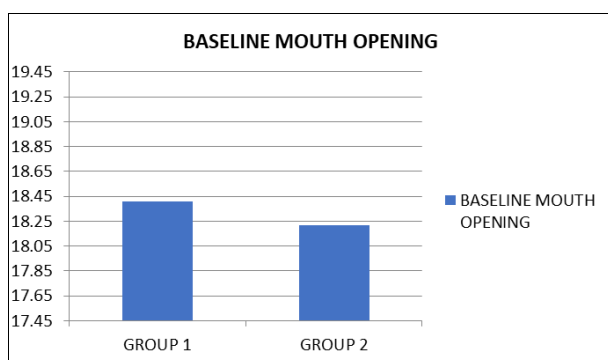
3.4.1. Comparison of Baseline Mouth Opening

Mean baseline intralesional mouth opening in Group 1 and Group 2 was $18.410 \pm .8399$ and $18.220 \pm .7899$ in mm, respectively. Results were found to be insignificant. It is clear from the given Table 3 and Graph 3 that baseline intralesional mouth opening was greater in Group 1.

Table 3: Mean baseline interincisal mouth opening

Group	Mean baseline interincisal mouth opening	Std. dev	p value
Group 1	18.410	.8399	.60
Group 2	18.220	.7899	

(Test used- independent t-test, $p > 0.05$, insignificant)



Graph 3: Baseline mouth opening

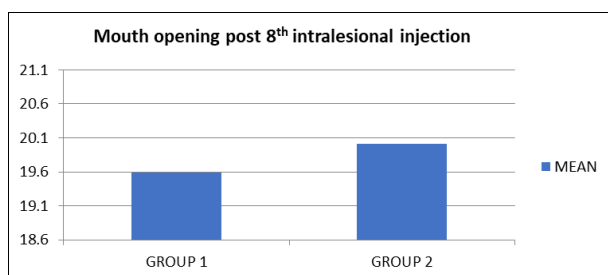
3.4.2. Comparison of Mouth opening post-8th intralesional injection

Mean 8th intralesional mouth opening in Group 1 and Group 2 was 19.590 ± 3.5837 and $20.010 \pm .8875$ in mm, respectively. Results were found to be insignificant. It is clear from Table 4 and Graph 4 that the 8th intralesional mouth opening was greater in Group 2.

Table 4: Mouth opening post 8th intralesional injection

Group	Mouth opening post 8 th intralesional injection	Std. dev	p value
Group 1	19.590	3.5837	.72
Group 2	20.010	.8875	

(Test used- independent t-test, $p > 0.05$, insignificant)



Graph 4: Mouth opening post 8th intralesional injection

3.4.3. Comparison of Mouth opening post-14th intralesional injection

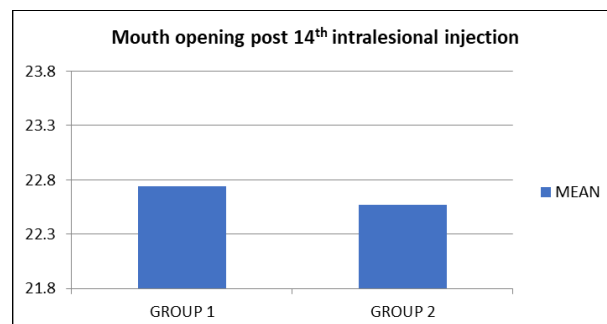
Mean 14th intralesional mouth opening in Group 1 and Group

2 was $22.740 \pm .4742$ and $22.570 \pm .7227$ in mm, respectively. Results were found to be insignificant. It is clear from Table 5 and Graph 5 that the 14th intralesional mouth opening was greater in Group 1.

Table 5: Mouth opening post-14th intralesional injection

Group	Mouth opening post 14 th intralesional injection	Std. dev	p value
Group 1	22.740	.4742	.54
Group 2	22.570	.7227	

(Test used- independent t-test, $p > 0.05$, insignificant)



Graph 5: Mouth opening post 14th intralesional injection

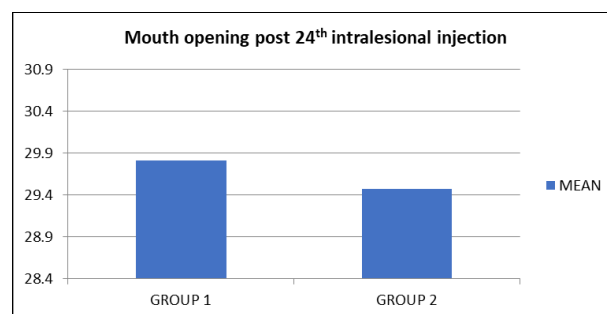
3.4.4. Comparison of Mouth opening post-24th intralesional injection

Mean 24th intralesional mouth opening in Group 1 and Group 2 was 29.810 ± 1.7572 and 29.470 ± 1.6892 in mm, respectively. Results were found to be insignificant. It is clear from Table 6 and Graph 6 that the 24th intralesional mouth opening was greater in Group 1.

Table 6: Mouth opening post 24th intralesional injection

Group	Mouth opening post 24 th intralesional injection	Std. dev	p value
Group 1	29.810	1.7572	.66
Group 2	29.470	1.6892	

(Test used- independent t-test, $p > 0.05$, insignificant)



Graph 6: Mouth opening post 24th intralesional injection

4. Discussion

Areca nut (AN) is a popular psychoactive drug consumed by millions of people worldwide. According to 2002 research, there are 600 million AN users worldwide, with Asia-Pacific accounting for the majority of usage.⁵ It is the major causative factor for OSMF, which is a collagen-related disorder characterised by the deposition of excessive abnormal collagen in the submucosa, leading to tissue fibrosis, hyalinization, and degenerative changes in the muscles^[14].

At present, OSMF is considered to be one of the common OPMDs leading to high morbidity. Early diagnosis and

management are necessary to prevent further complications. Early stages may improve with treatment, but moderately advanced stages show a worse prognosis [15]. OSMF may be followed by various complications such as malnutrition, speech and hearing defects, airway problems, masticatory difficulty, and deafness [16]. It shows a 9.13% malignant transformation rate and a 29.26 times higher risk of developing cancer than those who do not [17].

Numerous therapy methods, including corticosteroids, antioxidants, nutritional supplements, and vasodilators, have been tried in studies with varying degrees of success. Corticosteroids continue to be among the most widely recognised methods of treating OSMF, mostly due to their anti-inflammatory properties. Betamethasone's likely mode of action is that it inhibits the rate of protein synthesis, decreases the number of neutrophils and fibroblasts, reverses capillary permeability, and stabilises lysosomes at the cellular level to avoid or manage inflammation [18].

India is a nation with a high prevalence of OSMF, the efficacy of Placenta and the combination of betamethasone and hyaluronidase (a common therapy method) has never been evaluated in a randomised setting for a controlled trial (RCT) in AP. In addition, there is no standardisation regarding the quantity of injections, single or multiple site injections, and the exact location of injections [19]. Since the clinical symptoms of OSMF are so clear that histological confirmation is not required for diagnosis, histopathological confirmation was not one of the study's primary inclusion criteria. In addition, a biopsy leads to further scarring and worsening of the symptoms.

Our study is a randomised controlled trial comparing the efficacy of Placental Extract & Betamethasone with Hyaluronidase in Stage 2 OSMF patients of Arunachal Pradesh. The statistical data showed no significant difference in the improvement of mouth opening between the two groups, suggesting that both Placental extract and Betamethasone with Hyaluronidase show no significant difference in their efficacy. However, there was marked improvement in the mouth opening from the baseline record in all the patients, along with synergistic improvement in the burning of the mouth.

Reports from previous studies conducted more than 25 years ago indicate that intra-lesional injections of steroids do not provide results that are equivalent to those of conservative approaches [20]. The current study made use of Dispovan, a 30-gauge insulin needle, which is thought to result in little mechanical harm. For the injections, the treating physician determined the most fibrosed areas by gently palpating along the buccal mucosa and the retromolar region.

The study included 20 patients in total, 70% were male, and 30% were female. This is in concurrence with earlier studies, which also showed male predominance. Study of Kumar *et al.* showed 100% male predominance [21], and Lai *et al.*, 96.67% male predominance [22]. This male predominance could be explained by males dominating the habit of consumption of areca nut and females not coming forward for treatment of OSMF. The mean age of the patients in the current study was around thirty years old, which is in line with previous research by Kumar *et al.*, 70.69%20 and 70%. Maher *et al* [23].

4.1. Mouth Opening

A recent study found that the mouth opening of the hyaluronidase group improved the most, while the combination of dexamethasone and hyaluronidase group improved the least [24]. In the present study, both the groups, the mean baseline intralesional mouth opening in group 1 and

group 2 was 18.410 ± 8.399 and 18.220 ± 7.899 in mm, respectively, while after 24th intralesional injection, the mean mouth opening in group 1 and group 2 was 29.810 ± 1.7572 and 29.470 ± 1.6892 in mm, respectively. Both Placental Extract and Betamethasone with Hyaluronidase showed improvement in mouth opening without any statistical difference among receivers.

The pathophysiology of OSMF can be broadly classified into two stages: the early inflammatory phase and the late fibrotic stage [25]. At the time of presentation, both stages may overlap. Concerns regarding its safety would arise from repeated injections, betamethasone's extended half-life, and the possible inhibition of the hypothalamic-pituitary-adrenal axis. Lack of adverse effects, both widespread & local, suggests that OSMF patients may safely receive both Placental extract and Betamethasone with hyaluronidase up to 24 injections. Professional counselling for habit may be included in future research.

5. Conclusion

Placental extract and Betamethasone with hyaluronidase intralesional injections both seems to be feasible treatment options to increase mouth opening with reduction in burning sensation in OSMF patients.

Conflict of Interest

Not available

Financial Support

Not available

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