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Evaluation of efficacy of intralesional Xantinol Nicotinate in the treatment of OSMF

[1]Dr. Somi Fatima, [2]Dr.Nitin Agarwal, [3]Dr. Neha Agarwal, [4]Dr. K.K. Chaudhary, [5]Dr. Nadia Irshad, [6]Dr. Soni

[1]Assistant Professor, [2]Professor and Head, [3,4]Associate Professor, [5,6]Post Graduate student
Department of Oral Medicine and Radiology, Career Post Graduate Institute of Dental Sciences and Hospital, Lucknow, U.P., India

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ABSTRACT: Oral Sub mucous fibrosis is well-recognised potentially malignant disorder affecting oral cavity and pharynx. It is most commonly seen in south east asian population. There have been many researches held in the field of management of OSMF which still remains a challenge for clinicians to treat. In the present study we are evaluating the efficacy of intralesional injections of a peripheral vasodialator Xantinol Nicotinate in the treatment of Oral sub mucous fibrosis. In this clinical study we have included 20 patients aged between 20-40 years, clinically diagnosed with OSMF. Intralesional Xantinol nicotinate injection were given biweekly for a period of 10 weeks. All the patients were instructed to perform mouth opening physiotherapy exercises. At each visit parameters like increase in inter-incisal distance, tongue protrusion, cheek flexibility and relief in burning sensation were evaluated and any side effects were measured and recorded. The result showed promising outcome with statistically significant improvement in inter-incisal distance, cheek flexibility, tongue protrusion and decrease in burning sensation after 10 weeks of treatment and 6 months of follow up. Xantinol nicotinate , a peripheral vasodilator when injected biweekly for a period of 10 weeks is probably a good treatment option for OSMF although sample size and time period of study is small. So, it can be further tried for a longer period of time on a larger population of OSMF patients

KEYWORDS: Xantinol nicotinate, OSMF, Intralesional injection, burning sensation, cheek flexibility, tongue protrusion.

I. INTRODUCTION

[1]0ral submucous fibrosis is a chronic disease affecting the oral mucosa, as well as the pharynx and the upper two-thirds of the esophagus. There is substantial evidence that lends support to a critical role of areca nuts in the etiology behind oral submucous fibrosis .[2] Oral Submucous Fibrosis (OSMF) is a potentially malignant disorder which was described by Schwartz in 1952 as "Atropica idiopathica mucosae oris" and later by Jens J. Pindborg in 1966 as "an insidious, chronic disease that affects any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by, or associated with, the formation of vesicles, it is always associated with a juxtaepithelial inflammatory reaction followed by fibroelastic change of the lamina propria and epithelial atrophy that leads to stiffness of the oral mucosa and causes trismus and an inability to eat" . This disease is predominantly seen in the south east asian population, the reason being frequent and random use of areca nut and tobacco in this region. The pathogenesis of the disease is not well established, but the cause of oral submucous fibrosis is believed to be multifactorial. Factors include areca nut chewing, ingestion of red chilies, genetic and immunologic processes, nutritional deficiencies, and other factors. Areca nut–derived products are commonly used by several hundred million individuals in the southern parts of Asia. Oral complications are most commonly observed on the lips, buccal mucosa, retromolar area, and soft palatal mucosa. The habit of chewing betel quid, containing fresh, dried, or cured areca nut, and flavouring ingredients is widespread in India, Pakistan, Bangladesh, and Sri Lanka and in immigrants coming from these regions. Tobacco is often used in conjunction with betel quid. The disease starts with burning sensation in the oral cavity with changes in the colour of oral mucosa which is mainly blanching or depigmentation, gradually restricted mouth opening and reduced tongue protrusion is noticed by the patient. Sometimes loss of papilla, pain while mastication, difficulty in eating and phonation arises. Later stages are more severe and difficult for patient where overall lifestyle is disturbed due to affected nourishment. OSMF has tendency to convert into squamous cell carcinoma. OSMF is well known for

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its resistant to various treatment modalities that are available to treat this condition which includes medicinal approach, surgical management and physiotherapy. Medical management includes Antioxidants, Micronutrients, Intralesional injection, Corticosteroids, Hyaluronidase, Placental extracts, IFN- γ, Physiotherapy and surgical treatments are also done in later stages of the disease, although till date, no definitive and widely excepted treatment is available.

[3]In OSMF excessive deposition of collagen leads to surrounding blood vessels occlusion and hyper coagulation of blood. Both these acts as an obstacle for the nutrients to reach to the surrounding tissue and failure of drug treatment in cases of OSMF. Xantinol is a very potent water soluble derivative of niacin found in diet supplements,.also known as xantinol nicotinate it is also a potent vasodilator that can easily pass through the cell membrane and once inside the cell it causes an increase in glucose metabolism resulting in an increased energy. It reduces cholesterol and elevates blood flow in the region. After absorption, xantinol nicotinate rapidly degrades into negatively charged nicotinic acid and positively charged xantinol ion. It is available as oral tablets (eg. Complamina 150mg, 300mg) or in the form of injections to be used through intravenous or intralesional routes.We presume xantinol to be effective in the treatment of various stages of OSMF. Thus, the aim of this study is to check the efficacy of intralesional injection of xantinol nicotinate in cases of OSMF.

II. MATERIAL AND METHOD

This randomised clinical study was conducted in the department of Oral medicine and radiology of Career Post graduate institute of dental sciences and hospital, lucknow (U.P.) INDIA. This study was conducted from October 2020 to October 2021. In this study 20 patients were included who were clinically diagnosed with OSMF. Patients with any underlying medical condition or who were hypersensitive to xantinol nicotinate or pregnant women were all excluded from this study. Before proceeding with the treatment, blood pressure monitoring, pulse recording, hypersensitivity test (for xantinol nicotinate) and blood test(total leucocyte count, differential leucocyte count, bleeding time, clotting time, hemoglobin percentage and platelet count) were carried out.

An informed written consent was taken from every participant of this study. Detailed case history was taken from each patient then they were clinically examined, diagnosed and divided according to their stages of OSMF. [4]This staging was done according to the criteria proposed by More CB et al., in 2012 which are as follow.

CLINICAL
STAGE I (S1): Stomatitis and or blanching of oral mucosa.
STAGE II (S2): Presence of palpable fibrous bands in buccal mucosa and/or oropharynx with or without stomatitis.
STAGE III (S3): Presence of palpable fibrous bands in buccal mucosa and/or oropharynx and in any other part of oral cavity with or without stomatitis.
STAGE IV (S4)
a. Any one of the above stage with premalignant lesions like leukoplakia, oral erythroplakia etc.
b. Any of the above stages with oral carcinoma.
FUNCT IONAL
M1: Interincisal mouth opening is up to or more than 35mm.
M2: Interincisal mouth opening is between 25mm-35mm.
M3: Interincisal mouth opening is between 15mm-25mm.
M4: Interincisal mouth opening is less than 15mm.

Patients were called twice weekly for 10 weeks and they were followed up for next 6 months. All the patients were asked to perform mouth opening physiotherapy exercises at home during the entire treatment procedure. the assessment of the patients were done which included four parameters. i.e.

1.Inter incisal distance: Inter-incisal distance is the distance between the mesio-incisal angle of maxillary central incisor and mandibular central incisor at maximum mouth opening . The inter-incisal distance is measured by keeping vernier calliper and asking the patient to open the mouth to the maximum and the reading is noted.
2.Cheek flexibility: Cheek flexibility is measured as the distance between two point marked on the ala tragus line, when ala tragus line is divided in three equal halves, then V2 is the point marked at 1st one-third from angle of mouth and V1 is the same point when the patient instructed to below his cheeks, cheek flexibility is measured as (V2-V1).
3.Burning sensation: burning sensation was measured as subjective assessment of patient's pain. It is measured by using visual analog scale on the rating of 0 to 10. Where 0 means no pain and 10 means maximum pain.
4.Tongue protrusion: tongue protrusion is the distance between the mesio-incisal angles of

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mandibular central incisor to the tip of the tongue when maximally extended with mouth wide openend.

The patient were given Intra-lesional injection of Xantinol Nicotinate (Trade name complamina, manufactured by German remedies, division of cadila Health care limited. 20 patients, aged between 20 – 60 year of both the sex were injected with intralesional injection of xantinol nicotinate. At each follow up visit improvement in mouth opening , tongue protrusion , relief in burning sensation and cheek flexibility was measured and recorded in proforma. Careful monitoring of patients was done by investigator during and after the injection of drug, patients were also observed for any side effects with xantinol nicotinate intralesional injections. If any side effects were noted it was written in proforma and appropriate treatment was given.

III. STATISTICAL ANALYSIS

All the data collected were statistically analysed. Data were summarized as Mean ± SD (standard deviation). Groups were compared by paired t test. A two-tailed $p<0.05$ was considered statistically significant. Analysis was performed on SPSS software (Windows version 17.0).

IV. RESULTS

The present study evaluates efficacy of intralesional injection (Xantinol Nicotinate) in treatment of oral sub mucous fibrosis (OSMF). Total 20 symptomatic patients were recruited. The outcome measures of the study were inter-incisal distance, tongue protrusion, cheek flexibility and burning sensation assessed for 10 weeks duration of treatment and 6 months post treatment for follow up. The outcome measures viz. inter-incisal distance, tongue protrusion and cheek flexibility measured in millimeter (mm) whereas burning sensation was assessed in visual analogue scale (VAS). The objective of the study was to evaluate the efficacy of treatment (Xantinol Nicotinate Injection) on outcome measures.

The pre and post outcome measures of OSMF patients is summarized in Table 1 and also depicted in Fig. 1 to Fig. 4. The pre inter-incisal distance (mm) of patients ranged from 15 to 36 with mean (± SD) 27.20 ± 7.16 and median 28 while at post it ranged from 18 to 40 with mean (± SD) 30.40 ± 7.25 and median 31. Table 1 and Fig. 1 showed marked increase in mean intra-incisal distance at post as compared to pre. Comparing the mean intra-incisal distance at two periods, paired t test showed significant increase (10.5%) in intra-incisal distance at post as compared to pre (27.20 ± 7.16 vs. 30.40 ± 7.25, $t=17.17$, $p<0.001$) (Table 1 and Fig. 1).

Similarly, the pre tongue protrusion (mm) of patients ranged from 13 to 28 with mean (± SD) 19.90 ± 3.71 and median 20 while at post it ranged from 15 to 31 with mean (± SD) 22.40 ± 4.17 and median 22. Like, intra-incisal distance, mean tongue protrusion also increased comparatively at post as compared to pre. Comparing the mean tongue protrusion at two periods, paired t test showed significant increase (11.2%) in tongue protrusion at post as compared to pre (19.90 ± 3.71 vs. 22.40 ± 4.17, $t=14.69$, $p<0.001$) (Table 1 and Fig. 2).

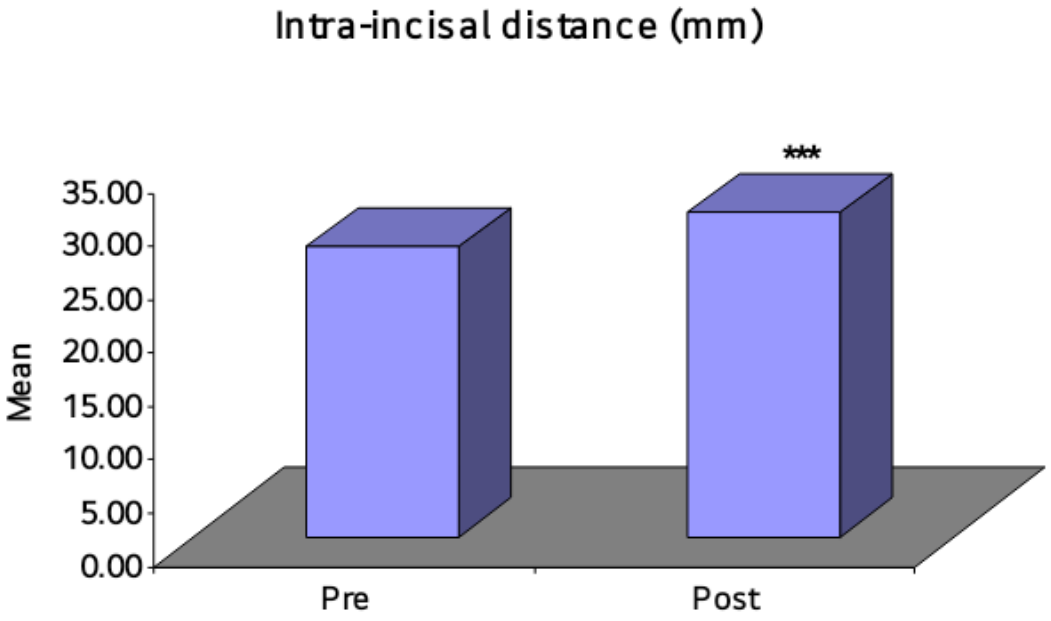
Further, the pre cheek flexibility (mm) of patients ranged from 0.10 to 0.50 with mean (± SD) 0.26 ± 0.11 and median 0.25 while at post it ranged from 0.20 to 0.80 with mean (± SD) 0.48 ± 0.18 and median 0.50. Like, intra-incisal distance and tongue protrusion, mean cheek flexibility also increased comparatively at post as compared to pre. Comparing the mean cheek flexibility at two periods, paired t test showed significant increase (46.9%) in cheek flexibility at post as compared to pre (0.26 ± 0.11 vs. 0.48 ± 0.18, $t=11.05$, $p<0.001$) (Table 1 and Fig. 3).

Moreover, the pre burning sensation (VAS) of patients ranged from 0 to 8 with mean (± SD) 5.75 ± 2.10 and median 6 while at post it ranged from 0 to 6 with mean (± SD) 2.85 ± 2.03 and median 2. In contrast to inter-incisal distance, tongue protrusion and cheek flexibility, mean burning sensation decreased comparatively at post as compared to pre. Comparing the mean burning sensation between two periods, paired t test showed significant decrease (50.4%) in burning sensation at post as compared to pre (5.75 ± 2.10 vs. 2.85 ± 2.03, $t=9.27$, $p<0.001$) (Table 1 and Fig. 4).

Table 1: Pre and post outcome measure level (Mean ± SD, n=20) of patients

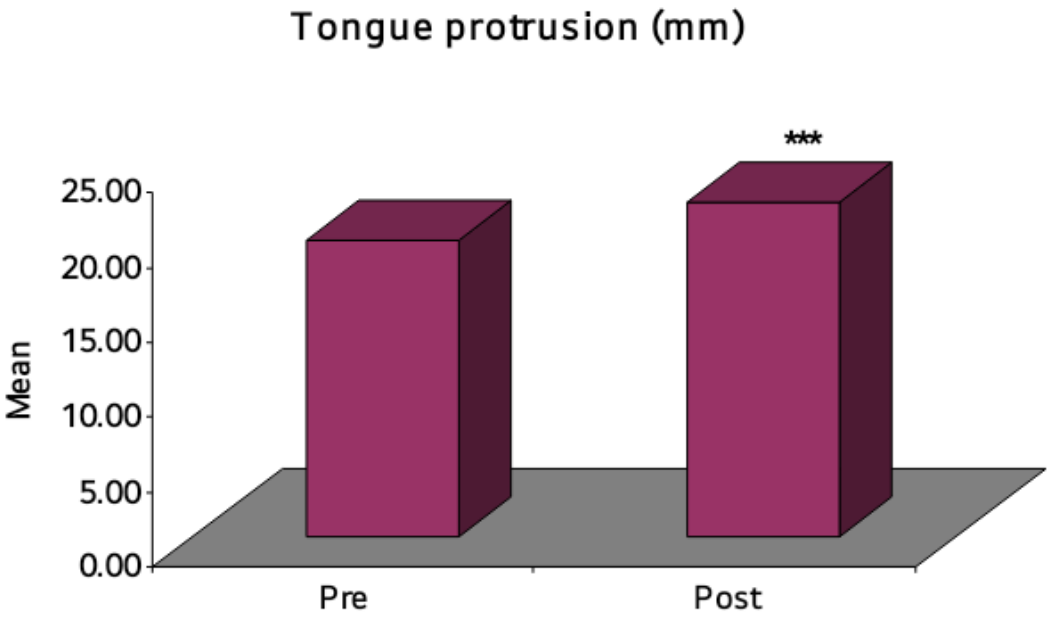
Outcome measure	Pre (n=20)	Post (n=20)	Mean difference	t value	p value
Intra-incisal distance (mm)	27.20 ± 7.16	30.40 ± 7.25	3.20 ± 0.83	17.17	<0.001
Tongue protrusion (mm)	19.90 ± 3.71	22.40 ± 4.17	2.50 ± 0.76	14.69	<0.001

Cheek flexibility (mm)	0.26 ± 0.11	0.48 ± 0.18	0.23 ± 0.09	11.05	<0.001
Burning sensation (VAS)	5.75 ± 2.10	2.85 ± 2.03	2.90 ± 1.33	9.27	<0.001



***p<0.001- as compared to Pre

Fig. 1. Pre and post mean intra-incisal distance of patients.



***p<0.001- as compared to Pre

Fig. 2. Pre and post mean tongue protrusion of patients.

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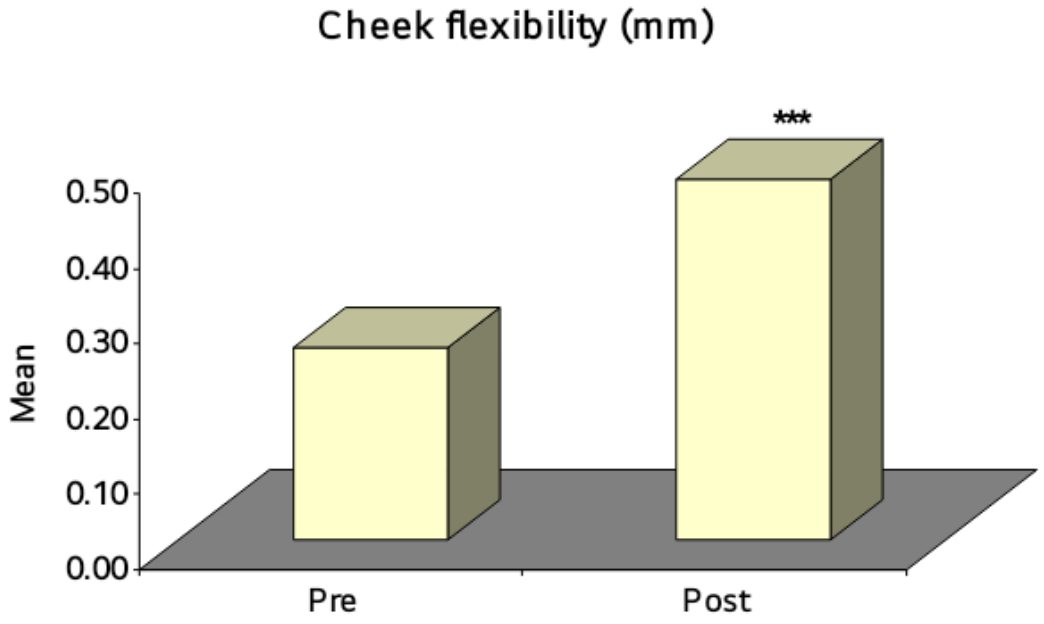
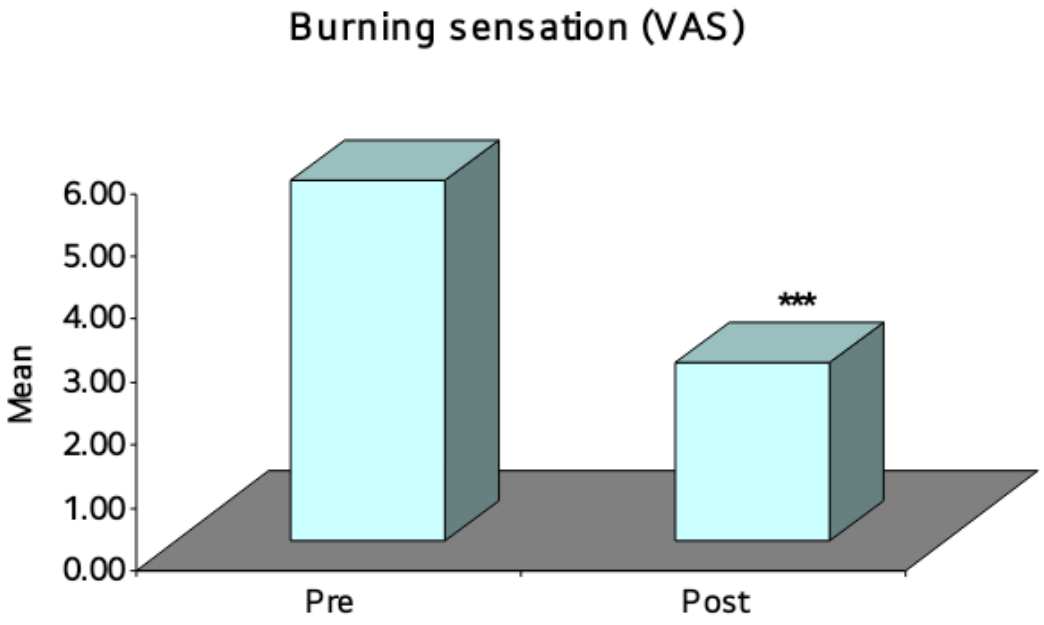


***p<0.001- as compared to Pre

Fig. 3. Pre and post mean cheek flexibility of patients.



***p<0.001- as compared to Pre

Fig. 4. Pre and post mean burning sensation of patients.

V. DISCUSSION

OSMF is a premalignant condition affecting oral cavity and pharynx, causing stiffness due to fibrosis of oral mucosa. It has a high rate of malignant potential. In south east asia a large number of population is in the habit of consuming tobacco products which is responsible for causing OSMF. Patients don't even notice the changes in early phase due to negligence or due to poor oral hygiene. [5]The global incidence of oral

submucous fibrosis is estimated at 2.5 million individuals. [8,11,12]In our study most affected age group was 21-30 years with male predominance which is similar to the findings of other study like Anuradha P. and Mishra G (2011), Afroz N and his colleagues (2006) - 4:1 . [10]Another study done by srivastav R. et al., shows result in which most affected age group was 21 – 30 years, amongst them males in 2nd decade of their life were mainly affected where 38.80% males and 5.97% females were affected. [9]In a study done by Yang et al., where 97.33% males were affected against 2.33% females due to easy accessibility for males to use areca nut and its products more frequently than females. Men had a significantly higher OSMF prevalence than women. Proper treatment begins with education of the patient regarding the ill effects of arecanut and related chewing products. The patient should be informed about the irreversible nature of the disease despite quitting the habit and possibilities of developing oral cancer.

A number of treatment modalities have been tried and still being searched for curing this disease So, we have conducted this study to check the efficacy of intralesional xantinol nicotinate on OSMF patients. In our knowledge not enough work has been done on the use of intralesional xantinol nicotinate on OSMF patients. [6]Xantinol nicotinate or nicotinyl xanthinate is a compound of xanthine and nicotinic acid. Both of which are vasodilators. It increases blood flow in vascular beds. In this study we have tried to take advantage of this property of xantinol nicotinate as in OSMF surrounding blood vessels occludes and hypercoagulation of blood occurs in the tissue of oral mucosa. So, we injected intralesional injection of xantinol nicotinate for peripheral vascular dilatation. Nutritive microcirculation is enhanced by increasing erythrocyte elasticity, improving the properties of blood and reducing peripheral resistance.

In this study we have tried to investigate the efficacy and potency of intralesional xantinol nicotinate for the management of OSMF patients. A total of 20 patients were taken into the study and were injected with 1ml of xantinol injection on each buccal mucosa. (150mg/ml) biweekly for 10 weeks with follow up for 6 months. After the complete course of treatment it was observed that inter incisal distance and cheek flexibility increased which was statistically significant, this can be attributed to the property of xantinol as Xantinol nicotinate was found to be fibrinolytic by two mechanism: reduction of fibrinogen levels and increase in tissue plasminogen activators which disolve clot. [7] Similar result of xantinol was seen in the study done by Dr.Udita Singh in 2016 in which inter incisal opening, cheek flexibility and relief from burning sensation significantly improved in OSMF patients but no significant difference was seen in tongue protrusion which was contrary to the result of our study wherein tongue protrusion also increased. Although not enough literature is available for comparison with this study as not much work has been done on this subject yet major limitation of this study is lack of histopathological confirmation of OSMF cases and less number of patients. Thus, larger clinical trials for longer period of time is required.

VI. CONCLUSION

In this study we propose intralesional Xantinol nicotinate as an efficacious cost effective and safe drug for patients of OSMF . Intra lesional Xantinol nicotinate, a peripheral vasodilator has given the promising results. It has relieved the burning sensation and improved cheek flexibility, tongue protrusion and also increased inter-incisal distance. The potency and accuracy of Xantinol nicotinate is satisfactory in OSMF patients. This drug is not very widely used, as more studies are required to be done to show promising results on bigger sample size and longer follow up.

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