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Original Research

Intralesional Steroid plus Hyaluronidase and Oral Physiotherapy in the management of Oral submucous fibrosis: Clinicians Experience

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***ABSTRACT*:**
Background: Various treatment strategies have been proposed in the literature for the management of oral submucous fibrosis (OSMF) but most of these modalities have been associated with relapse. This prospective clinical trial evaluated the efficacy of intralesional injection of Triamcinolone acetonide (40mg/ml) and hyaluronidase (1500IU) with regular oral physiotherapy exercises in 30 subjects of clinically diagnosed Oral submucous fibrosis patients. **Material & Method:** 30 subjects of clinically diagnosed grade II OSMF following informed consent and total habit counselling and cessation, were given biweekly injection (18 injections) of Triamcinolone Acetonide and hyaluronidase for a total period of 9 weeks and followed up for 16 weeks. All subjects were advised adjunctive oral physiotherapy exercise for mouth opening and cheek flexibility. Clinical improvement was evaluated by visual analog scale for pain/burning sensation, interincisal mouth opening, cheek flexibility and tongue protrusion in mm. **Results:** 24 out of 30 subjects completed the protocol with clinical improvement in burning sensation as, 7.98±2.55 ($p=0.000$, $t = 11.071$) and mean interincisal mouth opening, 0.4583±0.83297 mm($p=0.000$, $t=-5.324$). Cheek flexibility 0.2 mm left and 0.41 mm right side improvement ($p= \geq 0.05$)and tongue protrusion 1.37 mm improvement ($p=\geq 0.05$) , did not show any improvement in all subjects. **Conclusion:** Intralesional Triamcinolone Acetonide and hyaluronidase biweekly injections with oral physiotherapy shows promising result in symptomatic relief of burning sensation and increase in interincisal mouth opening in OSMF subjects.
Keywords: Oral submucous fibrosis, trismus, triamcinolone acetonide, hyaluronidase, oral physiotherapy

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INTRODUCTION

Oral Submucous fibrosis (OSMF) is a chronic disease of oral mucosa characterized by inflammation and progressive fibrosis of lamina propria and deeper connective tissues, followed by stiffening of an otherwise yielding mucosa resulting in difficulty in opening the mouth.[1] OSMF was first described by Schwartz in 1952 among five East African women of Indian origin under the term atropica idiopathica (tropica) mucosae oris. OSMF has multifactorial aetiology but is commonly associated with areca nut chewing habitually, and several other factors such as chilli consumption, nutritional deficiency states, genetic susceptibility, autoimmunity & collagen disorders leading to decreased collagen degradation have been suggested to be involved in the pathogenesis of the condition.[2]Arecoline , an alkaloid in areca nut leads to fibrosis in OSMF patients by increase in fibroblast proliferation, hence collagen formation and decrease in collagen degradation occurs. Moreover, lysyl oxidase, copper containing enzyme is upregulated in these patients, which has a key role in collagen synthesis and linkage of collagen fibres.[3,4]

The prevalence of OSMF in India has been found to be 0.4 % due to increase in the consumption of areca nut (component of betel quid) preparations, pan masala and mawa especially by young people.[5]It has also been estimated that approximately 5 million of Indians are victims of this potentially malignant disorder. [6] OSMF is more common in males than females with male to female ratio 4.9:1 and is seen in the individuals less than 30years of age.[5] Malignant rate of OSMF has been reported to be 7-13 % with long term follow up studies reporting a rate of 7.6%.[2]

Various treatment modalities proposed to manage the OSMF include nutritional support, immunomodulatory drugs, physiotherapy, microwave diathermy, local drug delivery, combined therapy and surgical excision of fibrotic bands.[3,5] Some conservative therapies and surgical treatment may lead to improvement, but there is not complete regression of the lesion and the results are short lived with patient getting only symptomatic relief. Studies have demonstrated that intralesional steroid injections in combination with hyaluronidase are effective in relieving signs and symptoms of OSMF giving better and long term results than either agent used alone.[6-8] Steroids act as immunosuppressive agents, slow down the proliferation of fibroblasts, liberate cellular proteases in the connective tissue which in turn activates the collagenase and zymogen that consume insoluble collagen. Hyaluronidase degrades the hyaluronic acid matrix, breaks the collagen fibres and lowers the thickness of intracellular cemental substances rapidly in OSMF patients than normal subjects.[3] So, the study was undertaken with an aim to evaluate the clinical efficacy of a combination of intralesional Triamcinolone acetonide and Hyaluronidase in oral submucous fibrosis.

MATERIALS AND METHODS

Study Settings and cases

An open clinical trial to evaluate the clinical efficacy of a combination of intralesional Triamcinolone acetonide and Hyaluronidase in oral submucous fibrosis was conducted in the Department of Oral Medicine and Radiology, New Horizon Dental College and Research Institute, Bilaspur, Chhattisgarh, over a period of three years. Ethical Clearance was obtained from the institutional ethical clearance committee. 50subjectswith age ranging from 15to 40 years, presenting with signs and symptoms of Grade II OSMF according to the criteria given by Nagesh and Bailoor (1993)[9]were selected from the Dental Outpatient Department. The treatment plan was explained to all study subjects and informed consent was taken from all patients. 30 patients gave written informed consent and were clinically evaluated. Complete haemogram and radiographs were taken to exclude any diseases or pathology. The following participants were excluded: i) subjects with infections, specially tuberculosis, kidney or liver disease, hypothyroidism, hypertension, diabetes mellitus, ii)subjects with oral fibrosis other than OSMF , iii) subjects suffering from bleeding and clotting disorders, iv)subjects with a prior history of intralesional therapy for the OSMF, v)Subjects who showed clinical evidence of dysplastic changes and neoplastic transformation of OSMF vi) Subjects with severe restriction of mouth opening where access to intralesional therapy was limited.

After informed consent, detailed case history was recorded for all the patients on a specially designed proforma. A detailed personal history with special reference to betel quid chewing habit was obtained and all the patients gave positive habit history. For clinical examination, variables assessed in the study were as follows: i) Mouth opening ii) Burning sensation iii) Cheek Flexibility and iv) Tongue Protrusion.The interincisal mouth opening was measured using vernier calliper in millimeters (mm) by measuring the distance between incisal edge of upper and lower incisor tooth (11 & 41) after maximum opened mouth [Figure 1].Clinical evaluation for burning sensation was done by visual analog scale (VAS) which is a numeric rating scale of 0-10 scores, where 0 means no symptoms and 10 means severe symptoms as perceived by the individual. Cheek Flexibility (CF) was measured using inch tape which is a difference between (V1-V2) two points measured, point V2 is marked at 1/3rd the distance from the angle of the mouth on a line joining the tragus of the ear and the angle of the mouth and point V1 is marked by asking the subject to blow his

cheeks fully and the distance measured between the two points marked on the cheek [Figure 2].[5]Tongue protrusion was measured using divider and scale from the incisal-most point of the labial surface ofthe upper incisor to the tip of the dorsal surface of the tongue on maximal protrusion[Figure 3].

Management
Habit counselling was done for all the subjects, and they were sent for oral prophylaxis. Any co-existing factors causing trauma like sharp teeth, cusp tip was also eliminated. All the subjects were advised to perform oral physiotherapy exercises such as balloon blowing exercise, water holding in mouth exercise, incremental ice cream sticks exercise on regular basis for improving cheek flexibility and mouth opening.

Medicinal Treatment
Patients planned for medicinal treatment were given intralesional injections of Triamcinolone Acetonide (40 mg/ml) and Hyaluronidase (2ml) diluted with 1ml of 2%Lignocaine with adrenaline (1:80000).Injections were given where the maximum fibrosis was felt on palpation, by dividing the mucosa arbitrarily into 3 zones, and approximately equal amounts was deposited in each zone bilaterally, by a single observer, at a frequency of twice a week for a period of 3 months, giving a total of 24 doses. The injections administered 2 ml of Hyaluronidase and Triamcinolone Acetonide 40 mg/ml by a hypodermic insulin needle.

Outcome Assessment
After treatment, subjects were evaluated at intervals of 15 days for a period of 3 months. The parameters evaluated were: i)Pain and burning sensation by VAS ii) Mouth opening iii) Tongue protrusion and iv) Cheek flexibility

Statistical Analysis
All the recorded data of the subjects were tabulated and entered in Microsoft Excel sheet and statistical analysis was performed using Statistical package for social science (SPSS, version 21, Inc.,Chicago, IL,USA). Student's t test was applied to compare and evaluate efficacy of intralesional Steroid Triamcinolone Acetonide and Hyaluronidase during all visits of treatment. Paired correlation was done between subsequent visits by Pearson correlation test. A p value of ≤ 0.5 was considered statistically significant.

RESULTS
A total of 50 subjects of OSMF were included for the study who met the inclusion criteria and only 30 subjects were enrolled after informed consent.

Distribution of patients according to age and gender
The age of the subjects selected for the study ranged from 15 to 40 years with the mean age of 26.70±6.215years. Out of the total sample of 30 subjects, 29(96.7%) were males and 1(3.3%) was female. Among the 30 subjects, 9(30%) were within the age group of 26-30 years, 8(26.7%) were between 21-25 years, 6(20%) were between 15-20 years, 5(16.7%) were between 31-35 years and only 2 (6.7%) subjects were in the age group of 36 to 40years [Figure 4].All the 30(100%) subjects presented with symptoms of burning sensation, reduced mouth opening, reduced cheek flexibility and restricted tongue protrusion, which are usually noted in grade II OSMF.

Distribution of patients according to duration of symptoms of OSMF, adverse habits, duration and frequency of chewing
20(66.7%) subjects gave history of symptoms since 1-4 year, 9(30%) had symptoms since more than 4 year and only 1(3.3%) had symptoms since less than 1 year. Out of the 30subjects 26(86.7%) were non tobacco smokers. Only 4(13.3%) subjects had the habit of smoking either bidi (1, 3.3%) or cigarette (3, 10%). All the 30 subjects had the habit of chewing gutkha . The most frequent brand of commercially available gutkha used by subjects were Rajshri (26, 86.6%) followed by Totachap (3, 10%) and Paan masala (1, 3.3%). 27(90%) subjects had the habit of chewing gutkha 6-10 times per day and 3(10%) had for 0-5 times/day. Out of the 30subjects 22(73.3%) subjects had a habit since 1-5 years, 7(23.3%) for more than 5 years and only 1(3.3%) patient had a habit for less than 1 year. 29(96.7%) subjects gave duration of chewing for 0-5 min, and only 1(3.3%) for 6-10 min.

Outcome of Presenting Complaints

Burning Sensation
The mean burning sensation recorded by Visual analog scale (VAS) at the initial visit was 8.06±2.95 (p =0.000) and the end of the trial i.e at the eighteenth visit, the mean burning sensation was 0.08±0.40 (p=0.328). Thus suggesting a highly significant reduction in mean burning sensation 7.98±2.55 (p=0.000,t = 11.071) [Figure 5].
Pain recorded by VAS scale was 1.0833±0.82970 (p=0.000) for first and second visit, for eighteenth visit it was 0.04±0.20412 (p=0.328), thus suggesting highly significant decrease of mean pain score at end of the trail, 1.0416±0.62588(p=0.000).

Mouth opening
Results showed that average interincisal mouth opening at the time of initial presentation was 24.13±3.10 mm, during each subsequent visit there was increase in

mouth opening, with maximum increase in second (0.7500±0.98907 mm,p=0.001)) and third (0.7083±0.99909 mm ,p=0.002) visit.In the sixth visit the mean increase of mouth opening was 0.2917±1.08264 mm (p=0.200) but after sixth week statistical significant differences were not observed and there was decrease in mouth opening till eighteenth visit (0.0417±0.20412 mm,p =0.328). The mean increase in mouth opening was 0.4583±0.83297 mm(p=0.000, t=-5.324) from initial till eighteenth visit of treatment [Figure 6].

Cheek flexibility

On the left side, the mean CF was 10.0 ± 2.55mm, , during first to seventh visit, CF was 9.66±1.82 mm and it was 10.20±2.32 mm during eighth to eighteenth visit. The mean improvement in cheek flexibility was 0.20 ± 0.73 (p=0.163,t=-1.547). On the right side, during first to sixth visit mean CF was 9.38±1.68 mm , 9.38±1.41 mm during seventh visit,9.58±1.02 mm during eight visit and 9.79±1.02 mm during ninth to eighteenth visit. The mean improvement in CF was 0.41±0.66 (p=0.162,t=1.446) . Thus, there was no significant difference observed in CF on right and left side in all the subjects after treatment [Figure 7,8].

Tongue protrusion

The mean anterior tongue protrusion at initial visit was 33.33 ±5.95 mm, and at eighteenth visit was 34.70±6.34mm. Hence no significant difference in tongue protrusion was observed in all the study subjects in all the 18 visits with mean increase of 1.37±0.39 (p=0.011,t=-2.754)[Figure 9].

Follow-up

At the end of the study protocol, subjects were continued to be under observation for an average period of 12 weeks with no subjects reporting recurrence of burning sensation or decrease in mouth opening. 6 patients didn't turn back for follow up in our study. In the present study oral physiotherapy exercises, balloon blowing exercise, water holding in mouth exercise, incremental ice cream sticks exercise with mouth opening exercise using incremental ice cream sticks and cheek flexibility by blowing balloon exercises was mandatory followed by all subjects even after the completion of treatment protocol [Figure 5-9,10].

Side effects

3 out of 30 subjects (10%) developed oral candidiasis at the site of injections after the tenth injection. Intralesional injections were discontinued with these subjects and antifungal medicine was prescribed.

Figure 1. Measurement of interincisal distance (mouth opening) using vernier calliper.

Figure 2. Measurement of cheek flexibility during blowing, using inch tape

Figure 3. Measurement of tongue protrusion using divider and scale

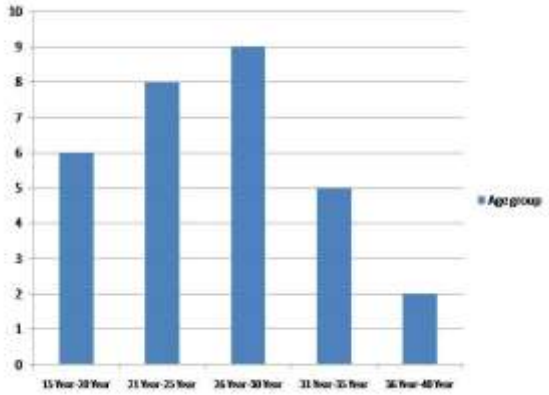

Figure 4. Age distribution among individuals

Figure 5. Shows Visual Analog Scale (VAS) score during treatment and follow-up

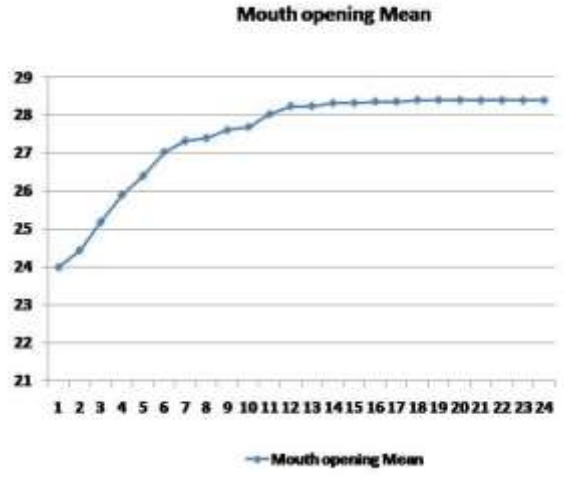

Figure 6. Shows mouth opening during treatment and follow up

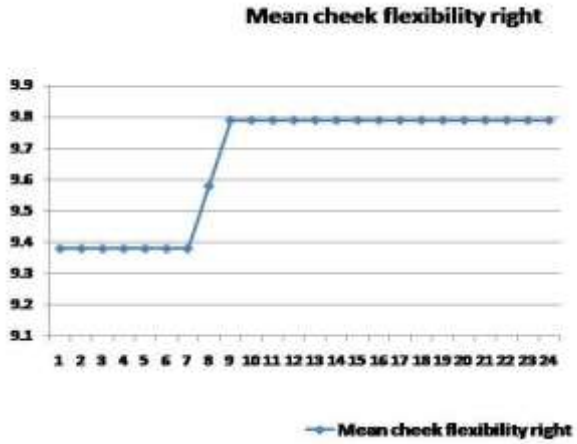

Figure 7. Cheek flexibility on right side during treatment and follow-up

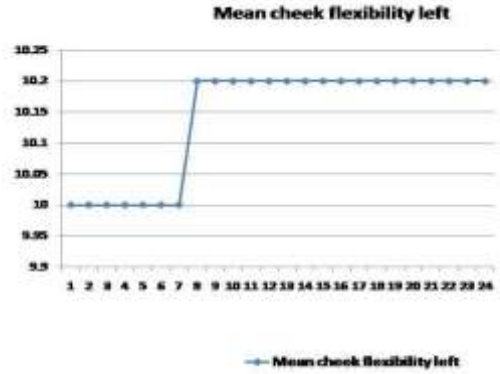

Figure 8. Cheek flexibility on left side during treatment and follow-up

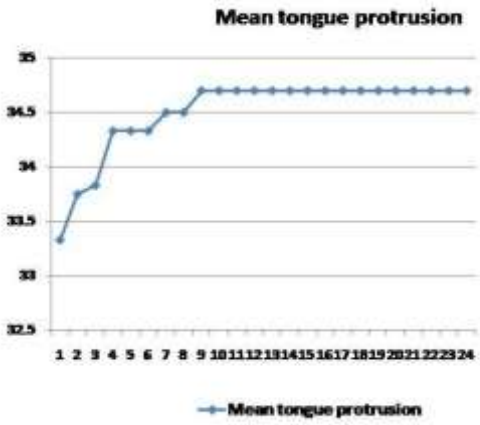

Figure 9. Tongue protrusion during treatment and follow-up

Figure 8: Interincisal mouth opening before and after treatment

Figure 10.Mouth opening before and after treatment.

DISCUSSION

OSMF is a chronic insidious disease of oral mucosa caused by areca nut use, associated with significant morbidity (pain and reduced mouth opening) and increased risk of malignancy. It is characterized by epithelial atrophy and subepithelial inflammatory reaction followed by fibroblastic changes in the submucosa.[10] Nagesh and Bailoor (1993) divided OSMF into three stages based on clinical diagnosis: i) Stage I early OSMF: Mild blanching, no restriction in mouth opening (normal distance between central incisor tips: males 35 to 45 mm, females 30 to 42 mm), no restriction tongue protrusion, ii) Stage II moderate OSMF: Moderate to severe blanching, mouth opening reduced by 33%, cheek flexibility also demonstrably reduced, burning sensation also in absence of stimuli, palpable bands felt. Lymphadenopathy either unilateral or bilateral and demonstrable anemia on hematological examination. iii) Stage III severe OSMF: Burning sensation is very severe patient unable to do day-to-day work, more than 66% reduction in the mouth opening, cheek flexibility and tongue protrusion. Tongue may appear fixed. Ulcerative lesions may appear on the cheek, thick palpable bands and lymphadenopathy.[9]According to this criteria, Grade II patients were selected for this study. Aggarwal G et al, in his study found OSMF prevalence to be 0.2-2.3% in males and 1.2-4.57% in females.[11] Hazarey et al reported the mean age of all cases affected with OSMF was 28.8±10.4 years.[12] Modi M et alfound that, the age range of patients with OSMF is wide, ranging between 20 and 40 years of age.[13] These findings were similar to the present study in which the mean age of the subjects was 26.70±6.215 years. The youngest subject was 19 years old and the oldest patient was 38 years old.

OSMF has multifactorial predisposing factors like areca nut/betel nut, tobacco, lime, malnutrition, immunological disorders, collagen disorders, and capsaicin (a prime component in chillies).Habit of chewing areca nut alone or in combination with other quid ingredients is the major etiological factor of OSMF.[2,5] Various theories of pathogenesis have been proposed for this condition. Mathew P et al showed that areca nut plays an important role in pathogenesis of OSMF due to presence of alkaloids, flavanoids and trace elements like copper and by generation of free radicals. Areca nut chewing is known to cause local trauma and injury to the oral mucosa due to its abrasive nature. This could be more severe in users of pan masala and gutkha due to fine particulate nature, with the high probability of particle adhesion to the traumatized mucosa, leading to morphological changes and membrane damage. This continuous local irritation by pan masala, gutkha or areca nut can lead to injury related chronic inflammation, oxidative stress and cytokine production. Oxidative stress and subsequent Reactive oxygen species (ROS) generation can induce cell proliferation, cell senescence or apoptosis, depending upon the level of ROS production. During chronic exposure, these events can lead to preneoplastic lesions in the oral cavity and subsequently to malignancy. Areca nut and its products also cause disturbance in fibroblastic activity, leading to increase in the production of collagen fibres and decrease in the collagen degradation causing fibrosis and other symptoms of OSMF.[14-16]

Habit cessation is the initial step before executing any treatment plan for OSMF. Although wide variety of treatment options are available for this condition, Khanna and Andrade suggested medicinal treatment for early OSMF and surgical management for advanced stage of OSMF.[17] In the present study, for grade II OSMF patients, combination of intralesional Triamcinolone and Hyaluronidase was preferred over the single agent treatment regimen. TA is a long acting steroid, acts as a potent immunosuppressant by opposing the action of cytokines sensitized by lymphocytes following activation by specific antigen. It reduces proliferation of fibroblasts in OSMF, thus reducing number of collagen fibres. Moreover, TA has better local potency and fewer side effects than other steroids.[3]It has been reported that TA alone leads to 5.82 to 6.28 mm increase in mouth opening in comparison to other steroids ,dexamethasone and hydrocortisone.[7,18] With dexamethasone, Khan M K et al[8] observed improvement in mouth opening in 66.6% of their patients, Yadav M et al[4]found increase of 3.13 mm and Aara A et al observed 1.04 mm increase in mouth opening.[19] With hydrocortisone, Khan MK et al[8] observed improvement in 80% of patients and Ghom A observed 7.64 mm increase of mouth opening.[18] Hyaluronidase, acts quickly on collagen from OSMF patients than on normal collagen. Hyaluronidase degrades the hyaluronic acid matrix, lowers the

thickness of intracellular cemental substances and promotes diffusion of injected fluids thus enhancing their action.[3,18] Hyaluronidase when used alone, in a study by Gupta J et al, showed increase of mouth opening from 18.36 to 27.74 mm.[20] But steroids in combination with hyaluronidase bring about moderate to significant improvement in interincisal mouth opening as seen in the clinical trials of Panigrahi R et al[7]in which the mouth opening increased from 21mm to 27.5mm, Khan MK et al[8] noticed improvement in 90% of subjects, Goswami R et al[21]observed improvement in 62% of subjects , and the findings were consistent with the present study. The mean interincisal mouth opening at initial presentation was 24.13±3.10 mm and there was significant increase in the interincisal mouth opening during the treatment with mouth opening of 27.04±4.02 mm up to sixth visit but there was no significant increase in the interincisal mouth opening after sixth visit.

In the present study pain/burning sensation and blanching was present in all (100%) subjects of OSMF.VAS was used to measure the intensity of pain throughout the study protocol. Pain intensity was >8 in 60% of patients at the time of presentation. The mean VAS score at initial presentation was 8.06±2.95. There was significant reduction in the pain intensity during the treatment with mean VAS score of 1.0833±0.82970,VAS reduced to half a point by the tenth visit,0.5417±0.72106.There was no significant reduction of pain after eleventh visit (0.45±0.77) i.e after 3 weeks. Steroids bring about improvement in burning sensation irrespective of class and activity (intermediate, short, long acting) and reduce burning sensation by their broad anti-inflammatory as well as immunosuppressant action.[3,18]Currently steroids used in OSMF patients to relieve burning sensation are hydrocortisone, triamcinolone acetonide, dexamethasone, and betamethasone. Previous studies in which Triamcinolone acetonide with Hyaluronidase was given as weekly or bimonthly injections from 8 to 16 weeks reported significant improvement in pain/burning sensation, and results were comparable to our study.Panigrahi R et al[7]found decrease in VAS score from 8.8 - 0.2, Khan MK et al [8]found 100% improvement, Sikdar SD et al reported 85% improvement, and Goswami R et al found 92% improvement.[21]When TA was used alone, in a study by Panigrahi R et al it has shown lesser improvement in burning sensation withVAS score of 8.9 to 2.8.[8] With steroid dexamethasone and hyaluronidase, Khan MK et al observed 90% improvement[9] and Aara A et al observed 81% improvement.[19]The results were similar or lesser improvement was seen as compared to present study. With steroid hydrocortisone and hyaluronidase, Khan MK et al observed 100% improvement.[8]Results showed that efficacy of hydrocortisone is better than dexamethasone but equal to triamcinolone acetonide. Findings of our study indicate that biweekly intralesional TA(40mg/ml) and hyaluronidase (2 ml) are effective in improving interincisal mouth opening and reducing pain or burning sensation of Grade II OSMF patients.

Combined regimen of TA and hyaluronidase showed minimal improvement in elasticity and suppleness of buccal mucosa at the end of the treatment. Marginal improvement was noted after the eighth visit suggesting that any improvement in CF was a late phenomenon which may accompany the decreased fibrotic bands in the buccal mucosa. CF improved from the initial presentation of 10.00 to 10.2 mm left side, 9.38 mm to 9.79 mm on right side. Findings were similar to study by Aara A et al, in which 3.7mm improvement in CF was seen with dexamethasone injection.[19] They observed 2.3 mm increase in tongue protrusion using dexamethasone.[19]Tongue protrusion in the current study improved from 33.33 mm to 34.70 mm. Thus, minimal improvement was seen in tongue protrusion during subsequent visits. The restriction of tongue movements may be due to involvement of retromolar area and floor of mouth rather than fibrosis of tongue.

All the subjects completed the active therapy for 9 weeks. Subjects were followed up regularly with monthly one visit for 3 months and no recurrence of decrease of mouth opening and increase of burning sensation was reported. Oral physiotherapy exercises were followed by all subjects on regular basis after the completion of treatment protocol.3 out of 30 subjects (10%) developed oral candidiasis at the site of injections after the tenth injection. Intralesional injections were discontinued with these subjects and antifungal medicine was prescribed. For the complete regression of the lesion and for better results to prevent recurrence, treatment plan selected should be accompanied by habit counselling of the patient to quit the deleterious habit, daily oral physiotherapy exercises, intake of healthy nutritious diet supplemented with multivitamins, antioxidants and regular follow up visits.

Conclusion

Oral submucous fibrosis is chronic insidious disease of oral mucosa strongly associated with the use of commercially areca nut product (with or without tobacco) like Gutkha in 100% cases. Burning sensation, decreased mouth opening, blanching, shrunken uvula, fibrous bands are the presenting symptoms in all grade II OSMF subjects. Our findings indicated that biweekly intralesional injections of Triamcinolone Acetonide (40mg/ml) and hyaluronidase (2ml) showed promising results in reducing pain or burning sensation and in improving interincisal mouth opening but there was minimal improvement in cheek flexibility and tongue protrusion. In addition, cessation of deleterious habits

coupled with daily oral physiotherapy exercises is mandatory for effective results.

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