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SURGICAL REPAIR VERSUS INTRALESIONAL INJECTIONS OF HYALURONIDASE AND HYDROCORTISONE FOR THE MANAGEMENT OF ORAL SUUBMUCOUS FIBROSIS- A COMPARITIVE PROSPECTIVE STUDY

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Conflicts of Interest: Nil

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Abstract:

Background: Oral submucous fibrosis (OSMF) is a most prevalent potentially malignant disorder associated with betel quid chewing frequently observed in the Indian population. The incidence has been found to about 13% of the general population, varying from 0 to 4% depending on the geographic location.

Objective: Aim of this clinical trial was to compare the efficacy of two treatment modalities on different stage OSMF to improve mouth opening and to evaluate other sign and symptoms. To compare the efficacy of Z- plasty surgery versus intralesional hyluronidase with Dexamethasone for improving mouth opening in the Oral sub mucous fibrosis.

Material and Method: This prospective comparative study consisted of 80 patients suffering from oral sub mucous fibrosis of Grade I, II and III based on the clinical grading by Gupta et al. Group A were treated with nutritional and iron supplement with intralesional injection therapy using Hyaluronidase, Dexamethasone, and Placentrex and topical application of Triamcinolone Acetonide 0.1%. Group B patients were treated by Z- plasty surgery and nasolabial flap repair. Mouth opening, burning sensation, painful ulceration, blanching of oral mucosa and pallor was evaluated preoperatively, after 1 month and after 3 month follow up.

Result: local and systemic therapy employing nutritional and iron supplement with intralesional injection therapy using Hyaluronidase, Dexamethasone, and Placentrex and topical application of Triamcinolone Acetonide 0.1% caused a marked improvement in the patient. Surgical treatment also gave promising results in Grade III patients where first regimen was not sufficient. Mouth opening was found to be highly significant. Burning sensation, painful ulceration, blanching of oral mucosa and pallor was observed in very less candidates and with significant reduction in severity and discomfort.

Conclusion: Conservative as well as surgical repair can definitely help to reduce the OSMF intensity in all grades. We are happy to conclude that habit break counselling in school age children and college going individuals can reduce the prevalence to OSMF.

Keywords: Burning sensation, Hyalouronidase, Intralesional injections, Oral sub mucous Fibrosis (OSMF), Premalignant condition.

Introduction:

Oral sub mucous Fibrosis is a well known clinical entity since the time of Sushruta when it was known as Vidari.[1] It has been a subject of controversy ever since SchWartZ[1] described an arcaine and inexplicable Fibrotic condition affecting the oral cavity in 5 Indian women of East Africa in 1952.[2] The incidence has been found to about 13% of the general population, varying from 0 to 4% depending on the geographic location from certain parts of the world including South-East Asia, South Africa and the Middle East Asia.[2] On epidemiological survey shows this disease was found in India especially in southern states with prevalence of 0.36% Ernakulum in Kerala, 0.4% in Srikakulam district in Andra Pradesh, 0.16% in Bhavnagar in Gujarat, 007% in Bihar and 0.03% in Maharashtra. The prime causes suspected are prolonged use of chilly (capsicum), betel nut, tobacco, alcohol, Pan-masala and Pan which are considered to be local factors.[3,4]

Oral submucous fibrosis is a chronic, complex, premalignant (1% transformation risk) condition of the oral cavity, characterized by juxta-epithelial inflammatory reaction and progressive fibrosis of the submucosal tissues.[5]

Pindborg J.J. et al[3] described oral sub mucous fibrosis as an insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx although occasionally preceded by or associated with vesicle formation, it is always associated with a juxta-epithelial inflammatory reaction followed by a fibro elastic change of the lamina propria with epithelial atrophy leading to stiffness of oral mucosa and causing trismus and inability to eat.[3,4]

The most common initial symptoms are burning sensation, ulceration and recurrent stomatitis. Intraoral petechiae, defective gustatory sensation and dryness of mouth, and/or hypersalivation have also been indicated as early symptoms. Pain in the ear or a decrease in the patient's hearing ability may

also occur if the fibrosis extends into the pharynx and causes a blockage of the eustachian tube.

The selected patients were clinically divided in to various grades based on the clinical grading by Gupta et al in 1992. The grading was slightly modified for the ease of the treatment and Goel et al in 2015as follows.

Clinical Grading:

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

The management of oral sub mucous fibrosis falls under two broad categories medical and surgical. The medical management includes intralesional injections of hyalouronidase and hydrocortisone, placental extract, interferon gamma and topical application of triamcinolone acetonide with systemic intake of vitamins, antioxidants and iron supplements. The recent medical treatment includes oral administration of milk from cows immunized with human intestinal bacteria.

Visceral Organ involvement evidenced by systemic fibrosis has not been explored much in oral sub Mucous Fibrosis. The investigations in this aspect were limited to loco regional sites of nasooropharynx and oesophagus, whether the oral Sub Mucous Fibrosis is a part of the systemic spectrum of disease involving multiple organs is an interesting pursuit.

In the initial phase of the disease, the mucosa feels leathery with palpable fibrotic bands. In the advanced stage the oral mucosa loses its resiliency and becomes blanched and stiff. The disease is believed to begin in the posterior part of the oral cavity and gradually spread outward.

Other features of the disease include xerostomia, recurrent ulceration, pain in the ear or deafness, nasal intonation of voice, restriction of the movement of the soft palate, shrunken uvula, thinning and stiffening of the lips, pigmentation of the oral mucosa, dryness of the mouth and burning sensation, decreased mouth opening and tongue protrusion.

Z-plasty is a versatile plastic surgery technique that is used to improve the functional and cosmetic appearance of scars. It can elongate a contracted scar or rotate the scar tension line. The middle line of the Z-shaped incision (the central element) is made along the line of greatest tension or contraction, and triangular flaps are raised on opposite sides of the two ends and then transposed. The length and angle of each flap are usually the same to avoid mismatched flaps that may be difficult to close. Some possible complications of Z-plasty include flap necrosis, haematoma (blood clot) formation under the flaps, wound infection, trapdoor effect and sloughing (necrosis) of the flap caused by wound tension and inadequate blood supply.

Aim of this clinical trial was to compare the efficacy of two treatment modalities on different stage OSMF to improve mouth opening and to evaluate other sign and symptoms.

MATERIAL AND METHODS

This was a prospective comparative study performed on 80 patients having restricted mouth opening by oral sub mucous fibrosis in the department of Otorhinolaryngology, LLRM, Medical College, Meerut, (U.P). The study consisted of 80 patients suffering from oral sub mucous fibrosis of various grades of age range between 20-40 years in the period of one year since January 2018 to June 2019. The study was approved by the Institutional Research Ethics Committee and written informed consent was obtained from all participants.

Patients were divided in 2 groups according to age 5-8 year, 8-10 year and 10-12 year group. On the first visit of the patient all details of patients like name, age, sex, occupation and address was recovered. A detailed complete case history was taken. Routine

blood and Urine investigations with a thorough check-up by a physician along with a cardiovascular investigation like electrocardiography and echocardiography to rule out endomyocardial fibrosis was done. All the findings were recorded in a preformed proforma.

The assessment of inter incisal distance (Mouth opening) was based on the following grades: 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

Management: following medicinal protocol was provided by previous research.

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
- Intra lesional 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 interincisor 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.

Group A were treated with nutritional and iron supplement with intralesional injection therapy using Hyaluronidase, Dexamethasone, and Placentrex and topical application of Triamcinolone Acetonide 0.1%. Group B patients were treated by Z- plasty surgery and nasolabial flap repair. Mouth opening, burning sensation, painful ulceration, blanching of oral mucosa and pallor was evaluated preoperatively, after 1 month and after 3 month follow up.

Statistical analysis: All the data was tabulated and transferred on MS excel sheet. Data analysis was carried out using statistical package for social science (SPSS, V 21) software. In all cases "p" value of less than 0.05 was indicative of statistical significance.

RESULTS

This was a prospective and comparative study for the management of oral sub mucous fibrosis. Eighty patients were divided into two groups. Group A (N=60) patients with Grade I and Grade II mouth opening were treated by local along with systemic administration of fibrolytic drug, corticosteroid injection with oral antioxidants. Group B (N=20) patients were undergone surgical management i.e. z-plasty with nasolabial grafting.

In Group A, total Grade I patients were 36 (45%) out of which 20 male and 16 female had the disease. Similarly, total Grade II patients were 24 (30%) out of which 16 male and 8 female had the disease. All these individuals were treated by nonsurgical local and systemic therapy.

In Group B, total Grade III patients were 20 (25%) out of which 12 male and 8 female had the disease. This also shows male predominance in the study population. The M:F ratio was 3:2. All these findings are described in following Table 1.

Table 1: Demographic characteristics

Group	Grade	Male	Female	Total
A	I	20	16	36 (45%)
	II	16	8	24 (30%)
B	III	12	8	20 (25%)
Total		48 (60%)	32 (40%)	80

Few symptoms like restricted mouth opening, burning sensation, painful ulceration, blanching of oral mucosa, pallor etc are evaluated.

In Group A, an average mouth opening was found to be 31.2 mm in Grade I and 26.6 mm in Grade II patients. In Group B, even Grade III patients improved to an average of 38.6 mm mouth opening.

In Group A, out of 60 patients, only 12 patients of Group I and 10 patients of Group II have burning sensation. In Group B, out of 20 patients 14 patients still showed burning sensation.

In Group A, out of 60 patients, only 7 patients of Group I and 12 patients of Group II have painful

ulceration. In Group B, out of 20 patients, only 7 patients of Group III have painful ulceration.

In Group A, out of 60 patients, only 8 patients of Grade I and 10 patients of Grade II have Blanching of oral mucosa. In Group B, out of 20 patients, only 7 patients of Grade III have blanching of oral mucosa.

In Group A, out of 60 patients, only 6 patients of Grade I and 8 patients of Grade II have pallor of oral mucosa. In Group B, out of 20 patients, only 12 patients of Grade III have pallor of oral mucosa. All the post operative sign and symptoms were found to be statistically significant.

Table 2: Post treatment reliving follow up of sign and symptoms after one month.

Symptoms	Group A (after 8 weeks)		Group B	p-value
	Grade I	Grade II	Grade III	
Limited mouth opening (mm)	31.2	26.6	38.6	0.002
Burning sensation	12	10	14	0.05
Painful ulceration	7	12	16	0.01
Blanching of oral mucosa	8	10	11	0.001
Pallor	6	8	12	0.05

Post operative follow up for both treatment modalities were evaluated and discussed as mentioned in Table 3. Mouth opening was improved to an average range for Grade I found to be 37.2 mm, for Grade II was 32.6 mm and for Grade III it was 40.4 mm inter incisal distance. Mouth opening was found to be highly significant.

Burning sensation, painful ulceration, blanching of oral mucosa and pallor was observed in very less candidates and with significant reduction in severity and discomfort.

Table 3: Post operative follow up of sign and symptoms after three months.

Symptoms	Group A		Group B	p-value
	Grade I	Grade II	Grade III	
Limited mouth opening (mm)	37.2	32.6	40.4	0.001
Burning sensation	7	6	7	0.01
Painful ulceration	2	4	5	0.002
Blanching of oral mucosa	3	6	6	0.001
Pallor	2	3	6	0.005

Figure 1: Surgical repair of Grade III OSMF.[25]

DISCUSSION

This was a prospective and comparative study for the management of oral sub mucous fibrosis. This was performed on pre diagnosed restricted mouth opening caused by Grade I, II and III. Eighty patients were divided into two groups. Restricted mouth opening, burning mucosal sensation, painful ulceration, blanching of oral mucosa and pallor was severely observed in all candidates. Group A (N=60) patients with Grade I and Grade II mouth opening were treated by local along with systemic administration of fibrolytic drug, corticosteroid injection with oral antioxidants. Group B (N=20) patients were undergone surgical management i.e. z-plasty with naso-labial grafting. According to Anand R et al[1] in 1994, Pinborg J.J. et al[3] in 1996, Chaturvedi V.N. et al[4] in 1990 suggested local treatment for Grade I and II patients. We have also tried same regimen for the study.

Our study showed male predominance in the study population. The M:F ratio was 3:2. This finding was similar to the study conducted by *Borges, A. F. et al[14] in 1973 and Hove C et al[15] in 2001, Hudson D et al[16] in 2000 showed similar results. Male predominance is higher as the habit of betel leaf and areca nut chewing are more common in males than females.*

Haque M.F. et al[6] in 2001, Interferon Gamma, Guptha et al[8] in 1992, in their study of treatment modalities in Oral Submucous Fibrosis, also revealed about the male predominance in which habits play a major role in etiopathogensis of the disease.

In patients with moderate to advanced OSMF, surgical therapy is beneficial. Graft used for covering the defect following the excision of bands include skin grafts, tongue flaps, buccal fat pad, amnion graft, nasolabial flaps, and palatal island flaps. Additional procedures such as temporalis myotomy and bilateral coronoidectomy may be performed to enhance mouth opening.[3] A mucosal graft is the best treatment for OSMF, as it is an ideal graft to cover the oral mucosa but is limited by the quantity of oral mucosal available for grafting. Split skin grafting has been tried, but it has a high failure rate as fibrotic areas have less vascular supply. Skin is not suitable for grafting in elderly people due to atrophy and inelasticity.[7] Various previous studies[3,10,11] reported successful reconstruction without complication using nasolabial flap in the management of OSMF. We have also approached nasolabial full thickness flap including skin, mucosa and buccal fat. Results were found to be very promising as suggested by *Hudson D et al[16] in 2000 in his study about Z-plasty and nasolabial flap in OSMF patients.*

They concluded that nasolabial flap proved to be very useful in the immediate single stage reconstruction of anterior intraoral defects along with the improvement in overall functional outcome. Buccal fat pad may also be used to cover the defects after excision of the fibrous bands. Harvesting of buccal pad fat is easy, but the anterior reach of the flap is often inadequate and cannot be used for larger defects.[9] *Borges, A. F. et al[14] in 1973, Hove C et al[15] in 2001, Hudson D et al[16] in 2000 suggested in about Z-plasty and nasolabial flap to improve vertical height and mouth opening.*

We have evaluated few symptoms like restricted mouth opening, burning sensation, painful ulceration, blanching of oral mucosa, pallor etc pre operatively at the end of first month and 3 months after treatment.

In Group A, an average mouth opening was found to be 31.2 mm in Grade I and 26.6 mm in Grade II patients. In Group B, even Grade III patients improved to an average of 38.6 mm mouth opening. Piyush P ET al[10] in 2019, in their study on comparison of therapeutic response of Lycopene and curcumin, also showed similar results of mouth opening.

In Group A, out of 60 patients, only 12 patients of Grade I and 10 patients of Grade II have burning sensation. In Group B, out of 20 patients 14 patients still showed burning sensation. Haque M.F. et al[6] in 2001, in their study by use of interferon Gamma revealed similar reduction in burning sensation.

In Group A, out of 60 patients, only 7 patients of Group I and 12 patients of Grade II have painful ulceration. In Group B, out of 20 patients, only 7 patients of Grade III have painful ulceration. In Group A, out of 60 patients, only 8 patients of Grade I and II have Blanching of oral mucosa. In Group B, out of 20 patients, only 7 patients of Grade III have blanching of oral mucosa. In Group A, out of 60 patients, only 6 patients of Grade I and 8 patients of Grade II have pallor of oral mucosa. In Group B, out of 20 patients, only 12 patients of Grade III have pallor of oral mucosa. All the post operative sign and symptoms were found to be statistically significant.

Haque M.F. et al[6] in 2001, in their study by use of Interferon Gamma in grade II OSMF, showed similar findings on reduction of painful ulceration, severity of blanching and pallor of oral mucosa.

Haque et al[6] using gamma-interferon treatment and Guptha et al[8] in 1992 suggested various treatment modalities in Oral Submucous Fibrosis, *has shown improvement in the patients mouth opening (inter incisal distance) with net gain of 8 ± 4 mm (42%), the range being 4-15 mm.* Goel, S *et al in their review on various treatment modalities revealed that excision of fibrous bands can also be managed by CO2, KTP, laser, Nd : YAG, Al-Gr laser energy to 532 nanometer wavelength.* [22]

Post operative follow up for both treatment modalities were evaluated and discussed in the literature. Mouth opening was improved to an average range for Grade I found to be 37.2 mm, for Grade II was 32.6 mm and for Grade III it was 40.4 mm inter incisal distance. Mouth opening was found to be highly significant in both the treatment modalities. Other features like burning sensation, painful ulceration, blanching of oral mucosa and pallor was observed in reducing intensity and discomfort in very less candidates after 3 months. All the follow up of symptoms were found to be highly significant. our results were similar to the findings

supported by Hazarey V. K. et al[23] (2015) and Heber, D. et al[24] (2002) in their literature about the different treatment modalities of OSMF. It was observed that patients receiving hyaluronidase alone showed a quicker improvement in the burning sensation and painful ulceration produced by the effects of local by-products, although combination of dexamethasone and hyaluronidase gave better long-term results than other regimens. Some of the patients had side effects of hyaluronidase such as gastric distress were treated by antacid drugs and local hematoma like complications by multiple intralesional injections was reduced by using delicate insulin syringe in mostly horizontal direction of mucosal surface.

The symptoms and subjective signs observed are burning sensation exacerbated by spicy or acidic foods, pain often referred to temporal region, increased or decreased salivation, reduced mouth opening, difficulty with mastication, difficulty with phonation and deglutition, vesiculation or ulceration of oral mucosa. With the exception of the individual's habit, the systemic conditions like chronic iron deficiency and vitamin B complex deficiency subsists. Study by Reddy V. et al[21] in 2011 on clinical grading postulated that treatment following intralesional injections of various drugs leads to aggravated fibrosis and pronounced trismus. The resultant worsening of this condition with submucosal injections are attributable to repeated needle stick injury to the soft tissues at multiple sites, clinical irritation from drugs being injected, and to the progressive nature of the disease. The same outcome has been observed with some surgical methods employed to treat OSMF. Conservative line of treatment like topical steroids, vitamins, antioxidants, physiotherapy would give expected symptomatic relief of pain and burning sensation.[8,9] Treatment modalities like intralesional injections of placental extracts that acts essentially by biogenic stimulation based on tissue therapy are also encouraged.16 Clinical trial by Haque et al[6] using gamma-interferon treatment has shown improvement in the patients mouth opening (inter incisal distance) with net gain of 8 ± 4 mm (42%), the range being 4-15 mm.

Post operative follow up for both treatment modalities were evaluated and discussed as mentioned in Table 3. Mouth opening was improved to an average range for Grade I found to be 37.2 mm, for Grade II was 32.6 mm and for Grade III it was 40.4 mm inter incisal distance. Mouth opening was found to be highly significant. Burning sensation, painful ulceration, blanching of oral mucosa and pallor was observed in very less candidates and with significant reduction in severity and discomfort.

In OSMF, there is increased collagen production and decreased collagen degeneration. Injection of hyaluronidase with dexamethasone is an effective method of managing Grade III OSMF and can possibly eliminate the morbidity associated with surgical management. It is a cost effective method of management. We had counseled the patients about habit break strictly as addiction of betel quid or areca nut chewing can cause fibrosis of IL fibers that also helped to a definite increase in mouth opening was observed in all cases which can be attributed to the success of the surgery. As suggested by Anand R et al[1] in 1994, Pinborg J.J. et al[3] in 1996 and Chaturvedi V.N. et al[4] in 1990 in their literature about non invasive local treatment we also tried addition of antioxidants, physiotherapy and physical exercise as a maintenance therapy found to be beneficial in avoiding recurrence of disease and better improvement for quality of life. This study is an added effort in providing evidence-based support to optimize patient care. The subjects falling prey to OSMF can be reduced by educating the upcoming generation in schools and colleges.

CONCLUSION

We have compared two treatment modalities on three grades of OSMF disease. We have found male predominance in the study population, satisfactory results were observed on group A with noninvasive local and systemic treatment. In Group B patients as the mouth opening was very less than 20 mm, surgical intervention was needed. We have treated Grade III subjects with z– plasty along with nasolabial flap repair. Addition of antioxidants, physiotherapy and physical exercise as a maintenance therapy found to be beneficial in avoiding recurrence of disease and better improvement for quality of life. This also suggest that conservative as well as surgical repair can definitely help to reduce the OSMF intensity in all grades. This study is an added effort in providing evidence-based support to optimize patient care.

We are happy to conclude that habit break counselling in school age children and college going individuals can reduce the prevalence to OSMF.

REFERENCES

1. Anand R., Pradhan R., Surgical Management of Submucous Fibrosis Ind. J. Dent Res.1994, 1: 4: 3.
2. Schwartz J., 11th International Dental Congress London 1952.
3. Pinborg J.J., Sirsat S.M., Oral Submucous Fibrosis; Oral Surg, Oral Med, Oral Path, 1996, 22: 6: 764-779.
4. Chaturvedi V.N., A.K.Sharma, N.G. Marathe., Intra Oral Injection of Hydro Cortisone and Hyalournidase in Oral Submucous Fibrosis. J. The Indian Practioner, 1990, 575 – 580.
5. Canniff J.P., W. Harvay., M. Harris., Oral Submucous Fibrosis: It's Pathogenesis and Management. Br. Dental Journal 1986:160:429- 434.
6. Haque M.F., Interferon Gammam (IFNX) may reverse Oral Submucous Fibrosis., J. Oral Path Med. 2001, 30: 12 – 21.
7. Rajendran R., Visceral Organ Involvement is Infrequent in Oral Submucous Fibrosis. IJDR., 2001, 12: 1: 7 - 20.
8. Guptha, Dinesh C., Treatment modalities in Oral Submucous Fibrosis, How they stand today? Study of 600 Cases. Indian Journal of Oral and Maxillo Facial Surgery. 1992, 7: 43 – 47.
9. Balaji Rao., Oral Submucous Fibrosis – The Davangere Study Journal of Indian Academy of Oral Medicine and Radiology, 1993, IV – 3: 4.
10. Piyush P, Mahajan A, Singh K, Ghosh S, Gupta S. Comparison of therapeutic response of Lycopene and curcumin in oral submucous fibrosis: A randomized controlled trial. Oral Dis. 2019, 25: 73–79.
11. Macfarlane, G. J., Zheng, T., Marshall, J. R., Boffetta, P., Niu, S., & Brasure, J. Alcohol, tobacco, diet and the risk of oral cancer: A pooled analysis of three case-control studies. European Journal of Cancer Part B: Oral Oncology, 1995, 31, 181–7.
12. Mithani, S. K., Mydlarz, W. K., Grumbine, F. L., Smith, I. M., & Califano, J. A. Molecular genetics of premalignant oral lesions. Oral Diseases, 2007, 13, 126–133.
13. Murti, P. R., Bhonsle, R. B., Pindborg, J. J., Daftary, D. K., Gupta, P. C., & Mehta, F. S., Malignant transformation rate in oral submucous fibrosis over a 17-year period. Community Dentistry and Oral Epidemiology, 1985, 13, 340–1.
14. *Borges, A. F. "The original Z-plasty". British Journal of Plastic Surgery. 1973, 26: 3: 237–246.*
15. *Hove C, Williams E, Rodgers B. "Z-plasty: a concise review". Facial Plast Surg. 2001, 17: 4: 289–94.*
16. *Hudson D., "Some thoughts on choosing a Z-plasty: the Z made simple". Plast Reconstr Surg. 2000, 106: 3: 665–71.*
17. *Burke M (1997). "Z-plasty. How, when and why". Aust Fam Physician. 26 (9): 1027–9.*
18. *Davis W, Boyd J. "Z-plasty". Otolaryngologic Clinics of North America. 1990, 23: 5: 875–87.*
19. Nair U., Bartsch, H., & Nair, J., Alert for an epidemic of oral cancer due to use of the betel quid substitutes gutkha and pan masala: A review of agents and causative mechanisms. Mutagenesis, 2004, 19: 251–2.
20. Rao, S. D., Shekhara, N. C., Satyanarayanan, M. N., & Srinivasan, M. J., Effect of curcumin on serum and liver cholesterol levels in the rat. Nutrition, 1970, 100, 1307–15.
21. Reddy, V., Wanjari, P. V., Banda, N. R., & Reddy, P., Oral submucous fibrosis: Correlation of clinical grading to various habit factors. International Journal of Dental Clinics, 2011, 3: 21–24.
22. Goel, S., Ahmed, J., A comparative study on efficacy of different treatment modalities of oral submucous fibrosis evaluated by clinical staging in population of Southern Rajasthan. Journal of Cancer Research and Therapeutics, 2015, 11: 113–8.
23. Hazarey, V. K., Sakrikar, A. R., Ganvir, S. M., Efficacy of curcumin in the treatment for oral submucous fibrosis - A randomized clinical trial. Journal of Oral and Maxillofacial Pathology, 2015, 19: 145–152.
24. Heber, D., & Lu, Q. Y., Overview of mechanisms of action of Lycopene. Experimental Biology and Medicine, 2002, 2: 27: 920–3.
25. Balaji SM. Versatility of nasolabial flaps for the management of severe trismus in oral submucous fibrosis. Indian J Dent Res 2016;27:492-7.