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Non-Invasive Management of Oral Submucous Fibrosis- Boon or Disguise

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Abstract:
Oral submucous fibrosis is a chronic inflammatory disease that results in progressive juxtaepithelial fibrosis of the oral soft tissues that can cause increasing difficulty in chewing, swallowing, speaking, and mouth opening. Many treatment regimens for oral submucous fibrosis have been proposed to alleviate the signs and symptoms of the disorder. In severe cases, surgical intervention is the only treatment modality, but relapse is a major problem. Even after 6 decades of its description as a separate entity, no concrete treatment is available due to its multi-modal pathogenesis. Thus, adding to the morbidity associated with it. Current article is an attempt to compile the available treatment aids, their current status and future perspectives, so as to aid early intervention of the disease.
This study undertook a review of the literature on drug treatment of oral submucous fibrosis. Drugs like steroids, hyaluronidase, human placenta extracts, chymotrypsin and collagenase, pentoxifylline, nylidrin hydrochloride, iron and multivitamin supplements including lycopene, have been used. Only systemic agents were associated with few adverse effects like gastritis, gastric irritation and peripheral flushing with pentoxifylline, and flushingly warm skin with nylidrin hydrochloride; all other side-effects were mild and mainly local. The drug treatment that is currently available for oral submucous fibrosis is clearly inadequate. There is a need for high-quality randomized controlled trials with carefully selected and standardized outcome measures.

Keywords: *Oral submucous fibrosis, medical management and interventions, review, non-invasive treatment, research*

1. Introduction

Oral submucous fibrosis (OSF) is a potentially malignant condition of the oral cavity characterized by juxtraepithelial inflammatory reaction and progressive fibrosis of the lamina propria and deeper connective tissues of the upper digestive tract involving the oral cavity, oropharynx and frequently the upper third of the oesophagus. OSF results in an increasing loss of tissue mobility, marked rigidity and an eventual inability to open the mouth.[1,2] The most commonly involved site is buccal mucosa, followed by palate, retromolar region, faucial pillars and pharynx.[3]
It is an insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and /or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by fibro-elastic changes of the lamina propria with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat.[4]

2. Discussion/ Management

2.1. Modulators of Inflammation

i. Steroids
ii. Interferon gamma
iii. Placental extracts
iv. Immunised milk

2.2. Modulators of Vascularity or Relief of Ischaemia (Vasoconstrictors)

i. Buflomedil hydrochloride
ii. Pentoxiphylline

2.2.1. Nutritional Support and to Combat Reactive Oxygen Species (Antioxidants)

i. Beta-carotene
ii. Lycopene
iii. Vitamins
iv. Micronutrients

2.2.2. Fibrinolysis

i. Collagenase
ii. Hyaluronidase
iii. Chymotrypsin
iv. Ayurvedic treatment: Turmeric (Curcuma longa L.) Tea pigments Oxitard
v. Aloe V era

2.3. Steroids

Topical application and submucosal injections of corticosteroids are among the initial treatment modalities reported in literature.
They act as immunosuppressive agents by inhibiting the release of inflammatory cytokines by sensitized lymphocytes, thereby decreasing fibroblastic proliferation and deposition of collagen. Corticosteroids such as hydrocortisone, dexamethasone, triamcinolone and betamethasone have been tried. Partial relief was noticed in early stage of the disease, but were less useful in reversing abnormal deposition of fibrotic tissue and restoring the physiologic elasticity of oral mucosa. Significantly better results have been obtained by giving local injections of dexamethasone, hyaluronidase and chymotrypsin together than with single drug alone. Overall, the treatment was associated with high incidence of relapse in majority of cases and prolonged use or overdose invariably produced unwanted side effects.[5-7]

2.4. IFN-Gamma

It plays a role because of its immunoregulatory effect and a known antifibrotic cytokine. Through its effect of altering collagen synthesis, appears to be a key factor. Intralesional injections of the cytokine may have a significant therapeutic effect.[8]

2.5. Placental Extract

The injection placentrax is an aqueous extract of human placenta. The action of placental extract is essentially biogenic stimulation and its use is based on the tissue therapy method. According to this theory when animal and vegetable tissues are severed from the parent body and exposed to unfavourable conditions, but not mortal to their existence, undergo biogenic readjustment leading to development of substance in the state of their survival. Such tissues or their extracts when implanted or injected into the body after resistance of pathogenic factors stimulate metabolic or regenerative process thereby favouring recovery. Such tissues or their extracts when implanted or injected into the body after resistance of pathogenic factors stimulate metabolic or regenerative process thereby favouring recovery
Topical application as well as 2.0 cc submucosal injections of aqueous placental extract have been used in past with variable degree of success rate.[9] A ban was imposed on its use in India due to drug safety concerns, but later on lifted on via Gazette Notification No. G.S.R. 418(E) dated May 30, 2011, of the Ministry of Health & Family Welfare.[10]

2.6. Immunized Milk

Immune milk contains small amount of vitamin A, vitamin C, vitamin B1, Vitamin B2, Vitamin B 6, Vitamin B 12, Nicotinic acid, panthotenic acid, folic acid, iron, copper and zinc. Immune milk has anti-inflammatory components and modulates cytokine production.
Tai et al. in a preliminary study reported improvement in interincisal opening in 26 OSF patients treated with milk (45 g powder twice daily for 3 months) from cows immunized with human intestinal bacteria, which must have suppressed the inflammatory reaction and modulate cytokine production of anti-inflammatory components. After 3months of treatment, 69.2% of patients had significantly increased their maximum mouth-opening by more than
3mm. [11]

2.7. Vasodilators

Pathologically occluded blood vessels (due to collagen deposition and hypercoagulated status of blood) in OSF submucosa, restrict the nutrients and other therapeutic substances from reaching the affected tissue. So, certain cardiovascular drugs have also been tried utilizing their vasodialating properties and ability to reduce the viscosity of blood.[12]
Buflomedil hydrochloride

Lai *et al* (1995) has carried out treatment for OSMF using buflomedial HCL (3 tablets of 450 mg each per day) and topical trimacenolone acetonide 0.1% on mucosal ulcers at bed time. He observed positive results.[13] Buflomedial HCL (peripheral vasodialator) has been found to affect the tissues in diffuse fibrosis to a noticeable degree by the relief of local ischemic effect.

Pentoxifylline

Rajendran *et al* (2006) used pentoxifylline, a methylxanthine derivative that has vasodialating properties. It was administered as 400 mg thrice daily for a period of more than 12 months and observed improvement in symptoms of OSMF.[14] Fibroblasts cultured in the presence of pentoxifylline produce twice as much collagenase activity and decreased amount of collagen, glycosaminoglycans and fibronectins. IL-1 induced fibroblast proliferation was inhibited by the addition of pentoxifylline.

2.8. Antioxidants

It is known that the process of carcinogenesis occurs by generation of Reactive Oxygen Species, which act by initiating lipid peroxidation (LPO).[15] Prevention against LPO mediated damage is done by antioxidants and it has also been reported that oral premalignant lesions can be successfully treated by antioxidant supplementation which led many clinicians to consider antioxidants in the treatment of OSMF. Moreover vitamin deficiency, iron deficiency anaemia, and malnutrition hamper the repair of inflamed oral mucosa, leading to defective healing, thus rendering the atrophic mucosa more susceptible to ROS. Antioxidants stabilize and deactivate the free radicals before they attack cells. Various studies have reported that vitamins A, B complex, C, D, E and minerals like iron, copper and magnesium, when used as standard or adjunct therapy are effective in controlling the signs and symptoms of OSF.

2.8.1. Vitamin A

Statistically significant study conducted in the previous decade observed that Vitamin A given at a concentration of 50,000 IU would cause symptomatic improvement.[16] It is well evident that vitamin A plays an important role in maintaining normal growth and repair of epithelial tissues.

2.8.2. Vitamin E

Vitamin E has been extensively studied for its role in the treatment of OSMF. Reddi (1993) suggested that Vitamin E given concomitantly with the Hyalase and betamethasone was better than as compared with Hyalase and betamethasone alone.[17] The efficacy of vitamin E was attributed to its antioxidant property.

2.8.3. Vitamin C

Singh (1996) observed that vitamin C given in combination with placentrax and liver extract gave better results than institution of vitamin C alone.[18] It was believed that Vitamin C reduces the oedema between the collagen bundles and helps in regeneration of new collagen bundles with good approximation.

2.8.4. Minerals

Anil *et al.,* (1991) administered Zinc (220mg) in combination with vitamin A and observed good results. Zinc plays essential role in DNA synthesis and cell division.[19] Apart from zinc, Magnesium also plays essential role in many enzyme reactions and exerts stabilizing effects on excitable membranes.

2.9. Fibrinolysis

2.9.1. Collagenase

Collagenase is a lysosomal enzyme, Lai et al found that intralesional injection of collagenase resulted in significant improvement.[13]

2.9.2. Hyaluronidase:

The use of topical hyaluronidase has been shown to improve symptoms more quickly than steroids alone. Hyaluronidase can also be added to intralesional steroid preparations. The combination of steroids and topical hyaluronidase shows better long-term results than either agent used alone.

Hyaluronidase degrades the hyaluronic acid matrix, actively promoting lysis of the fibrinous coagulum as well as activating specific plasmatic mechanisms. Therefore, relief of trismus may be expected through softening and diminishing of fibrous tissue.[20]

2.9.3. Chymotrypsin

Chymotrypsin, an endopeptidase is used as a proteolytic and anti-inflammatory agent in treatment of OSMF. Gupta and Sharma advised the use of chymotrypsin (an endopeptidase which hydrolyses ester and peptide bonds) 5000 IU twice weekly submucosal injections for 10 weeks, as proteolytic and anti-inflammatory agent in the treatment of OSF.[21]

2.10. Ayurvedic Treatment: Turmeric (Curcuma longa L.) Tea pigments Oxitard

Turmeric has been found to inhibit many disease processes through their anti- inflammatory, antioxidant and anticancer properties. Curcuminoids isolated from turmeric, has been found to have effective antioxidant, DNA-protectant and antimutagen action. A study concluded that usage of turmeric oil daily for 3 months had a beneficial role.[22]

Hastak et al. observed in 58 OSMF patients that turmeric given in any form, i.e., alcoholic extracts of turmeric, turmeric oil and turmeric oleoresin were all effective in decreasing the number of micronucleated cells (which are found to be increased in exfoliated oral mucosal cells and circulating lymphocytes of precancerous oral lesions) both in exfoliated oral mucosal cells and in circulating lymphocytes.[23]

Deepa Das *et al.* found that turmeric dispensed in the form of curcumin and turmeric oil was effective in the treatment of OSMF which was evident by the positive changes observed in the histopathological examination after treatment along with the significant improvement in clinical signs and symptoms.[24]

2.11. Anti-Helminthics

Levamisole, a heterocyclic anti-helminthic plays immune modulatory role by mimicking the thymic hormone thymopoeitin. It forms a tertiary structure mimicking thymopoeitin which stimulates lymphocytes or alternatively gets metabolized and the metabolic products affect radical scavenging in the multiplying lymphocytes. Improved mouth opening and reduced burning sensation has been reported on administration of levamisole alone and in combination with anti-oxidants. The recommended dose is Levamisole 150mg OD for 3 days twice a month×3 months.[25]

Contraindications include pregnancy, lactating mothers and renal failure cases. Although not frequent, side effects reported include nausea, fatigue, drowsiness and abdominal pain.[27]

3. Conclusion

The drug treatment that is currently available for oral submucous fibrosis is clearly inadequate. Submucosal injections of dexamethasone, triamcinolone acetonide, Hyaluronidase, Placental extract and Chymotrypsin were effective in OSF in few studies. Here various permutation and combinations of the available medications can be tried to best suit the individual. Severe or grade III cases may require surgical intervention. No single drug has provided a complete relief from symptoms of OSF. Evaluation of the merits and disadvantages of individual items in treatment is not possible owing to the use of combined treatment protocols, which is unavoidable at present because of the empirical nature of each approach. These studies provided a limited amount of unreliable data which did not permit any firm conclusions to be made. The individual mechanisms operating at various stages of the disease–initial, intermediate and advanced–need further study in order to propose appropriate therapeutic interventions. The current authors suspect that no single approach will be sufficient. We propose a treatment plan consisting of counselling of patient along with lycopene/multivitamin/ minerals in the initial stages of OSF. Moderate stages of OSF should be treated with intralesional steroids or pentoxifylline, where as advanced stages should be treated surgically. Moreover, future research needs to be focused on better standardization and follow-up reporting. At last, better understanding of the pathogenic mechanism will be detrimental in providing a new direction to the therapeutic research.

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