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REVIEW ARTICLE

Evaluation of Medicinal Interventions for the Management of Oral Submucous Fibrosis: A Systematic Review of the Literature

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ABSTRACT

Oral submucous fibrosis is a chronic, progressive scarring disease associated with both significant morbidity including pain and limited mouth opening and an increased risk for malignancy. This systematic review evaluated the different medicinal (i.e. nonsurgical) interventions available for the management of oral submucous fibrosis.

An automated literature searches of online databases from January 1960 to December 2013 were performed and only studies with high level of evidence based on the guidelines of the Oxford Centre for evidence-based medicine were selected. Thirteen studies (3 randomized controlled trials and 10 clinical trials/controlled clinical trials) were included and drugs like steroids, hyaluronidase, human placenta extracts, chymotrypsin and collagenase, pentoxifylline, nylidrin hydrochloride, iron and multivitamin supplements including lycopene were used. There is a clear lack of evidence on the available drug treatment for oral submucous fibrosis and further high quality randomized controlled trials are needed to evaluate the different therapeutic agents.

Keywords: Oral submucous fibrosis, Drugs, Steroids, Systematic review, Treatment.

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INTRODUCTION

Oral submucous fibrosis was first illustrated by Schwartz in 1952 as 'idiopathic tropica mucosae oris', but Joshi was the one who subsequently gave it the present term.[1,2] Oral submucous fibrosis is a potentially malignant condition that involves juxtaepithelial inflammatory reaction and subsequent fibrosis of the lining mucosa of the upper digestive tract including the oral cavity, oropharynx and frequently the upper third of the esophagus. This results in decreased tissue elasticity, apparent stiffness and ultimately limited mouth-opening.[3,4] Oral submucous fibrosis mostly affect Asian population, including India, Pakistan, Bangladesh, China and Sri Lanka, where use of betel quid is very popular. However, migration of betel quid users to other parts of the world have made it a public health issue. More importantly, oral submucous fibrosis can transform into oral cancer, and particularly squamous-cell carcinoma, at a rate in the range of 7 to 13%.[5]

A range of etiological factors have been proposed including areca nut chewing, capsaicin, autoimmunity, hypersensitivity, genetic susceptibility and prolonged vitamins and micronutrients deficiencies.[6-10] However, there is clear evidence now that indicates areca nut to be the major cause of oral submucous fibrosis. Various mechanisms for the etiopathogenesis of oral submucous fibrosis have been proposed; increased synthesis of collagen and decreased secretion of colleganese as a result of the long-term use of areca nut,[11,12] up-regulation of Lysyl oxidase causing increased collagen cross-linking,[13] deficiency in collagen phagocytosis and effect of fibrogenic cytokines,[14,15] and deficiencies in micronutrients and vitamins.[5]

In the past decades, though a variety of treatment modalities of oral submucous fibrosis have been proposed, most of them are inefficient mainly because they only provide symptomatic relief and do not have long-lasting effects. The available medicinal treatments include steroid injections, exogenous enzymes, multi-

vitamins and micronutrients, peripheral vasodilators and other therapeutic agents. The use of a wide array of treatment modalities for oral submucous fibrosis not only demonstrates the complex nature of the disease, but also highlights the fact that there is a need to have a universal treatment protocol. Thus, the aim of the present study was to systematically evaluate the published literature on the efficacy of currently available therapeutic agents used in the treatment of oral submucous fibrosis.

MATERIALS AND METHODS

Search Strategy

Detailed automated literature searches of Medline, EMBASE, ISI Web of Science and the Cochrane Library databases from January 1960 to December 2013 were conducted. The search strategy was based on the recommendations of the Oxford Centre for Evidence-Based Medicine. The following keywords and Boolean operators were used, 'oral submucous fibrosis and drug treatment', 'oral submucous fibrosis and enzyme', 'oral submucous fibrosis and steroid', 'oral submucous fibrosis and hyaluronidase', 'oral submucous fibrosis and vitamin', 'oral submucous fibrosis and antioxidant', 'oral submucous fibrosis and micronutrient'.

The primary focus of the search involved systematic reviews and meta-analyses of randomized controlled trials (evidence level 1a), randomized controlled trials (evidence level 1b), clinical trials without randomization (evidence levels 2a), and other experimental studies (evidence level 2b). Case-control (evidence levels 3) and case-series studies (evidence levels 4) were not included in the evaluation.

Data Collection and Extraction

Titles and abstracts of the studies that fulfilled the selection criteria were screened by the authors and checked for agreement. Full texts of studies judged by the title and abstract to be relevant were independently and manually assessed. Following data were extracted for each study: year, country, description of the sample (size, age, gender, habit profile), study design (study type, intervention types), outcomes measured, follow-up information, and details about statistical analyses.

RESULTS

Based on the selection criteria, 13 studies were included, that consist of 3 randomized controlled trials and 10 clinical trial/controlled clinical trials. Six studies reported use of Vitamins, antioxidants and minerals,[16-21] four studies reported use of steroids,[16,17,22,23] enzymes, such as hyaluronidase and chymotrypsin use were reported in four studies,[16,17,22,23] three studies reported use of peripheral vasodilators,[17,19,24] turmeric use was reported in two studies,[25,26] and one study each reported the use of Interferon Gamma, Immune milk and tea pigment.[20,27,28] The studies included all the results are summarized in Table 1.

DISCUSSION

Oral submucous fibrosis is very resistant to treatment and many treatment regimens that are currently available only target at alleviating the signs and symptoms of the disease. Usually, medicinal treatments are used in the early stages of the disease, and surgical treatment favored at late or advanced stage. Since, oral submucous fibrosis is a chronic mucosal inflammatory disorder, the basis of definitive management should be focused on minimizing the inflammation and/or controlling the elements guiding the inflammatory process. The combination of various drugs including steroids, enzymes, antioxidants, multivitamins and minerals have been used. Although, some of the drugs have found to be beneficial in relieving the signs and symptoms of oral submucous fibrosis, there is lack of credible evidence in the literature of the efficacy of any particular interventions and therefore it is fairly challenging to compare or even combine their effects in a scientifically meaningful manner.[29]

Steroids

Steroids are extensively utilized for the treatment of oral submucous fibrosis because of their immunosuppressive and anti-inflammatory properties. They not only oppose the action of soluble factors released by sensitized lymphocytes following activation by specific antigens, but also inhibit the proliferation of inflammatory factors and increase the apoptosis of inflammatory cells. Several corticosteroids such as short-acting (hydrocortisone), intermediate-acting (triamcinolone), and long-acting (betamethasone and dexamethasone) have been utilized for the treatment of oral submucous fibrosis.[16,17,22,23] Although, they were useful in relieving signs and symptoms at an early stage, they lack effectiveness in overturning the abnormal accumulation of fibrotic tissue and reinstating suppleness of the soft tissue. Intralesional injections of dexamethasone, hyaluronidase and chymotrypsin independently or in combinations yielded significantly better outcomes than using one drug alone.[22] Overall, steroids are useful in relieving signs and symptoms of oral submucous fibrosis and/or may be used as adjunct therapy.

Table 1: Characteristics of the studies included

Authors	*Study design*	*Sample (n)*	*Therapeutic agents*	*Duration*	*Outcomes (Improvement in signs/symptoms)*
Borle and Borle (1991)	Clinical trial	160	Triamcinolone 10 mg/ml + hyaluronidase 1500 IU	4 weeks	Ulceration – 94.9%; Burning sensation – 89.9%
Gupta and Sharma (1988)	Clinical trial	25	Biweekly intralesional injections of following agents; Dexamethasone (4 mg); Hyaluronidase (1500 IU) Chymotrypsin (5000 IU) Placental extract (2 ml) Hyaluronidase + dexamethasone Chymotrypsin + dexamethasone Hyaluronidase + chymotrypsin + dexamethasone Placental extract + dexamethasone	10 weeks	Ulceration – 50% Burning sensation – 82% Blanching – 56%
Hastak et al (1997)	Clinical trial	25	1. Turmeric oil 600 mg mixed with alcoholic extracts of turmeric 3 g/ day	All the groups were evaluated for 3 months	Turmeric oleoresin was more effective in reducing the number of micronuclei in oral mucosal cells, but in circulating lymphocytes the decrease in micronuclei was comparable in all three groups
		25	2. Turmeric oleoresin 600 mg + alcoholic extracts of turmeric 3 g/ day		
		25	3. Alcoholic extracts of turmeric 3 g/ day as a control		
Haque et al (2001)	Clinical trial	29 (M:18, F:11)	Intralesional interferon gamma twice a week	8 weeks	Trismus – 8.1 ± 2.7 mm
Joshi et al (2003)	Clinical trial	9 healthy volunteers	Turmeric oil 0.6 ml of three times a day for 1 month and 1 ml in three divided doses for 2 months	3 months	Turmeric oil was recommended directly for a Phase II trial in patients with OSF
Kakar et al (1985)	Clinical trial	96	Four regimens of local treatment Dexamethasone Hyaluronidase combination of dexamethasone + hyaluronidase Placental extract	3 months to 2 years	Patients receiving hyaluronidase alone showed quicker improvement in symptoms. Combination with dexamethasone yielded better long-term results
Kumar et al (2007)	RCT	21	Lycopene 16 mg	All the groups were evaluated weekly for 2 months	Burning sensation – 100%; Trismus - 3-4 mm
		19	Lycopene 16 mg and biweekly steroid injections		Burning sensation – 100%; Trismus – 4-6 mm
		18	Placebo		Burning sensation – 5.5%; Trismus – 0.0 mm
Lai et al (1995)	Clinical trial	166	Topical vitamin A, ferrous fumarate and topical betamethasone	3 weeks	Ulceration – 95.5%; Burning sensation – 88.2%
		25 (M:22, F:3)	1. Vitamin B complex 200 mg twice/ day, buflomedial hydrochloride 450 mg thrice/day and topical triamcinolone acetonide 0.1%	Evaluated monthly for 4 weeks	Ulceration – 95%; Burning sensation – 88%
		25 (M:22, F:3)	2. Biweekly intralesional injections of a combination of dexamethasone (4 mg/ml) and two parts of hyaluronidase (200 usp unit/ml) diluted in 1.0 ml of 2% xylocaine	Evaluated monthly for 20 weeks	Ulceration – 94%; Burning sensation – 89% Blanching – 71%; Trismus – 83%
		25 (M:22, F:3)	3. A combination of both (1) and (2).	Evaluated monthly for 20 weeks	Ulceration – 96%; Burning sensation – 91% Blanching – 81%; Trismus – 86%
Li and Tang (1998)	Clinical trial	17	1. Vitamins and tea pigments	N/A	58.3% improvement in signs/ symptoms
		22	2. Vitamin A, B complex, D and E		13.6% improvement in signs/ symptoms
Maher et al (1997)	Clinical trial	117	Vitamins A, B complex, C, D and E and minerals (iron, calcium, copper, zinc, magnesium)	1-3 years	Significant improvement in overall symptoms including trismus – 41%

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Sharma et al (1987)	Clinical trial	58	Nylidrin hydrochloride, vitamins A, E, B complex, iodine, placental extract, Local and systemic corticosteroids and physiotherapy	3-8 weeks	62.1% improvement in overall symptoms
Rajendran et al (2006)	RCT	15	1. Multivitamin, and local heat therapy	All the groups were evaluated monthly for 7 months	Significant improvement in signs/ symptoms
		14	2. Pentoxifylline 400 mg three times daily		
Tai et al (2001)	Clinical trial	26	1. Immune milk treatment (45 gm of immune milk powder twice a day) and oral habit intervention	Both groups were evaluated for 3 months	Burning sensation – 80%; Trismus – 69.2%
		20	2. Oral habit intervention		Burning sensation – 17.6%; Trismus – 0%

OSF: Oral submucous fibrosis; RCT: Randomized controlled trial; M: Male; F: Female; N/A: Not available

Enzymes

A prominent feature of oral submucous fibrosis is its abundant and abnormal deposition of collagen fibers.[30,31] Moreover, an increased number of fibroblasts, inactive collagenase, and the hampered fibrinolytic system may play a significant role in the disease process.[32-34] Therefore, exogenous enzymes may act as an effective drug by breaking down the abnormal fibrotic tissues. Enzymes used for the treatment of oral submucous fibrosis include hyaluronidase, collagenase and/or chymotrypsin. Hyaluronidase disintegrate hyaluronic acid (ground substance of connective tissue) which in turn decreases the viscosity of intracellular cement substance and collagen formation. Hyaluronidase use has found to be more effective in alleviating signs and symptoms of oral submucous fibrosis than steroids.[23] However, the combination of both agents have shown better long-term results than either use of either agents alone.[16,17,22,23] Chymotrypsin is an endopeptidase and breaks down peptide and ester bonds. It possesses proteolytic and anti-inflammatory properties, which is the basis of its use.[22] Intralesional injections of collagenase, a lysosomal enzyme, have also been reported in the literature to be useful by not only improving the mouth opening but also minimizing the symptoms.[35]

Vitamins, Minerals and Antioxidants

In the presence of the areca nut habit, excessive reactive oxygen species are produced that result in damage to the cell structure. Furthermore, deficiencies of Vitamins and minerals may affect the restoration process of damaged tissues, resulting in delayed and/or defective healing. This result in atrophy of the oral mucosa and makes it more vulnerable to the ill-effects of areca nut.[4] The use of Vitamins including Vitamins A, B Complex, C, D, E and minerals including iron, zinc, magnesium as standard or adjunct therapy has found to be effective for the treatment of oral submucous fibrosis.[16-20] In one study, use of chewable Vitamin A tablets (once daily) and ferrous fumarate tablets (200 mg once daily) was found to be safe compare to the conventional treatment with injections.[16] Other studies have demonstrated that Vitamins use alone yielded only 13.6% improvement in the symptoms of oral submucous fibrosis compare to 41% improvement when used in combination with minerals including iron, zinc, magnesium and calcium.[18-20] Lycopene, a photochemical and an antioxidant, was used in the treatment of oral submucous fibrosis.[21] The study demonstrated a significant improvement in the mouth opening among patients who received 16 mg of lycopene. No side effects were reported and the authors recommended the use of lycopene in the early-stage oral submucous fibrosis.

Peripheral Vasodilators

One of the reason for the inadequate effects of medicinal treatment of oral submucous fibrosis is their inability to reach the affected tissues due to hampered mucosal vascularity. Pentoxifylline, a methylxanthine derivative has been used in the treatment of oral submucous fibrosis. Pentoxifylline not only possess vasodilator properties, but also alters the physiology of fibroblasts and promotes the fibrinolysis process. Furthermore, it causes neutrophil degradation, promotes activity of natural killer cells, and prevents T-cell and B-cell activation.[36] Rajendran et al[24] use pentoxifylline in a randomized clinical trial and showed a significant improvement in the signs and symptoms including mouth opening, tongue protrusion and relief from perioral fibrotic bands in the experimental group than control group. However, the side effects involving the gastrointestinal tract and central nervous system were also reported. Buflomedil is a vasoactive agent which claims to exert beneficial effects on the microcirculation. The use of Buflomedil hydrochloride (450 mg per day) in conjunction with steroids and vitamins demonstrated pleasing results among early-stage oral

submucous fibrosis patients.[17] Nylidrin hydrochloride, a sympathomimetic agent, produces vasodilation of the arterioles of skeletal muscles and facilitate the spread of nutritional and therapeutic agents to the affected ischemic tissue. Its use has found to be more effective in younger and early-onset cases with a success rate of 62.07% in OSF.[19]

Other Drugs

Immune milk, which consists of cow milk immunized with human intestinal bacteria, possess anti-inflammatory characteristics and may influence the pathological pathway of oral submucous fibrosis. Only one study demonstrated the use of immune milk in oral submucous fibrosis.[27] After 3 months of oral administration of 45 gm of immune milk powder, significant improvement in regards to tolerance to spicy food and mouth-opening was noticed in 80 and 62.9% patients respectively.

Interferon gamma (IFN-γ) an antifibrotic cytokine, was used in oral submucous fibrosis. In an open, uncontrolled clinical trial using injections of IFN-γ for 6 months, 42% of the patients showed marked improvement in the symptoms, mouth opening and elasticity of the affected tissues.[28]

Turmeric has been used as a household spice for over centuries. In one study, use of turmeric extract, turmeric oil and turmeric oleoresin showed a marked decrease in the number of micronucleated cells among patients suffering from oral submucous fibrosis.[26] The antioxidant properties of tea pigments are greatly acknowledged and its use in oral submucous fibrosis was studies in one clinical trial. When used in combination with vitamins, it resulted in 58.3% improvement in mouth opening among oral submucous fibrosis patients.[20]

CONCLUSION

The current available medicinal treatments for oral submucous fibrosis are insufficient and no single therapeutic agent has proven to be effective in relieving the symptoms. Furthermore, evaluation of the advantages and disadvantages of a single therapeutic agent was not possible because the studies utilized a combination of therapeutic agents. Based on our results, we recommend use of lycopene/multivitamin/minerals may be beneficial in the initial stages, intralesional steroids or pentoxifylline in the moderate stages and surgical approach in the more advanced stages of oral submucous fibrosis. High-quality randomized controlled trials have to be performed to evaluate new therapeutic agents.

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