Review Article

Pentoxifylline Therapy in the Management of Oral Submucous Fibrosis – A Review

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ABSTRACT

Aim: Oral sub mucous fibrosis is a high risk pre malignant condition predominantly seen in the Indian subcontinent. The aim of the study was to review the effect of Pentoxifylline on the clinical and pathologic course of OSMF.

Material and methods: A review study was done to analyse the efficacy of Pentoxifylline in the treatment of OSMF. We searched over PubMed and Google database for studies meeting our eligibility criteria (august 2006 to July 2017). A total of 270 patients who were clinically diagnosed as OSMF from a total of 6 studies with one meta-analyses, 2 randomized control trial, three clinical trials were included for this review.

Results: Pentoxifylline is a methyxanthine derivative, which showed considerable improvement in mouth opening, tongue protrusion, difficulty in speech and swallowing. The total symptom score improved by 85.8% in Pentoxifylline. Dexamethasone and Pentoxifylline showed significant mouth opening and reduction in burning sensation.

Conclusion: Pentoxifylline can bring about significant improvement in all clinical signs of maximal mouth opening, tongue protrusion, burning sensation thereby improving the quality of life. Conflicting to the above findings, one randomized clinical trial showed no significant advancement in burning sensation, mouth opening, tongue protrusion.

Introduction

Oral sub-mucous fibrosis is a premalignant condition of the oral cavity and oropharynx seen predominantly in the Southeast Asian countries and in the Indian sub- continent. The pathophysiology of this condition is complex, and various factors such as, ingestion of spicy food, genetic susceptibility, nutritional deficiencies, altered salivary constituents, autoimmunity and collagen disorders are thought to be involved in the pathogenesis. The alkaloids and tannins of areca nut have been proved to induce the chronic inflammation in the mucosa trigger the fibro-genetic reaction. The condition is preceded by burning sensation of the oral cavity, vesicles, ulceration and pain. It is characterized by blanching and depigmentation of the oral mucosa, reduced movement and depapillation of tongue and progressive reduction of mouth opening. Nasal twang due to fibrosis of nasopharynx and hearing impairment due to stenosis of Eustachian tube may be observed in advanced stages of the condition[4].

Pentoxifylline is a tri-substituted methyl xanthine derivative, with numerous biologic activities including vasodilation, anti- inflammatory, immune-modulatory, fibrinolytic property. It is termed as a "rheologic modifier." It improves microcirculation and decreases aggregation of platelet as well as granulocyte adhesion. It increases leukocyte deformability as well as inhibits neutrophil adhesion and activation[3]. It increases production of prostaglandin E2 and prostaglandin I2 by vascular epithelium and maintain cellular integrity and homeostasis after acute injury. In addition, it causes degranulation of neutrophils, promotes natural killer cell activity and inhibits T-cell and B-cell activation. Pentoxifylline has also shown a direct effect on inhibiting burn scar fibroblasts[4]. The present review was carried out to analyse the efficacy of Pentoxifylline in the management of OSMF.

Material And Methods

The following sources were searched from august 2006 to July 2017: PubMed, Google database. The following keywords were used, oral sub mucous fibrosis and treatment, Pentoxifylline, dexamethasone, local heat therapy and multivitamin tablets. The primary focus of this search was meta-analysis[1], randomized control trials which used Pentoxifylline in the treatment of OSMF. clinical trials without randomization and other experimental studies were considered. The outcome measures used were improvement in symptoms and signs of OSMF like ulceration, burning sensation, blanching and trismus.

Results

6 studies that met the selection criteria (one meta-analyses, 2 randomized control trial, three clinical trials were

included for this review with a total of 270 patients. One meta-analyses, analysed the efficacy of Pentoxifylline in the treatment of OSMF. Four studies compared the efficacy of placebo**,** multivitamin tablet, dexamethasone and local heat therapy with Pentoxifylline.

Discussion

Oral sub mucous fibrosis is a chronic progressive scarring oral disease which is common in patients chewing areca nut in Indian subcontinent. It is a common premalignant condition affecting the oral mucosa. It is characterized by progressive build-up of constricting bands of collagen in the cheek and the adjacent structures of mouth, oropharynx which can severely restrict mouth opening, tongue movements as well as it causes problems with speech and swallowing[5]. Treatment of OSMF is based on severity of the disease, various treatment modalities have been elucidated to alleviate symptoms and signs associated with OSMF. If the disease is noted prior to the development of trismus, cessation of the betel habit will often resolve the objective signs and subjective symptoms. once trismus have been developed the goal of the therapy is to maintain the oral function and also to limit the progression of the disease[5]. As OSMF is a chronic mucosal inflammatory disease, control of the inflammation or the factors contributing the inflammatory tissue reaction should form the basis of definitive management. Combination of drugs such as steroids, human placental extracts, hyaluronidase, chymotrypsin, collagenase, Pentoxifylline, iron and multivitamin supplements including lycopene have been used. Laser ablation and surgery which includes the cutting of fibrous bands of the jaw muscles and TMJ have been used for more extreme cases[5]. However, the present review analysed the meta-analysis, randomized controlled trial, as well as clinical trial providing additional insight of the trials so that the types of interventions needed can be evaluated with the evidence.

Pentoxifylline is an anti-inflammatory, vaso-dilating, immune-modulatory, fibrinolytic drug. The pharmacokinetics of Pentoxifylline is that, it is almost completely observed after oral administration, 400mg releases short peak plasma Pentoxifylline concentrate 2- 3 hrs post administration. It is extensively metabolised. Active main metabolite 1 (5-hydroxy),3,7, (dimethyl-xanthine) is measurable in twice the concentration in plasma of that of its parent substance. It is eliminated by kidneys. The pharmacodynamics is that it improves capillary blood flow by increasing erythrocyte flexibility and reducing blood viscosity.

Pentoxifylline increases the production of prostaglandins (specifically E2 & I2) by vascular epithelium which is important in maintaining cellular integrity and haemostasis after acute injury[4]. The degree of vascularity of the diseased mucosa in OSMF as well as a matter of dispute, Pentoxifylline improves red blood cell membrane deformability by increasing the amount of membrane adenosine tri phosphate. It also alters red blood cell membrane, protein phosphorylation patterns, increases protein kinase activity and decreases calcium 2^{+} - dependant k^{+} efflux[6] which promotes vasodilating property. Its immunomodulatory actions[3] include increase in leucocyte adhesion. It also neutrophil degranulation and the release of peroxides, promotes natural killer cell activity and the production of tumour necrosis factor and inhibits T and B cell activation. The results of experimental studies[7] have shown that fibroblast cultured in the presence of Pentoxifylline produced twice as much collagenase activity and decreased amounts of collagen, glycosaminoglycan's, and fibronectin. Interleukin-1 – induced fibroblast proliferation is also inhibited by Pentoxifylline which promotes fibrinolytic property.

Most side effects caused by Pentoxifylline involve the gastro intestinal tract and central nervous system. The most frequent gastro intestinal complaints include nausea, vomiting, bloating, flatus and bleeding. The overall incidence of adverse effects was higher in patients who received Pentoxifylline in capsule forms than in those who received commercially available sustained release tablets which showed slow drug delivery and minimize gastric intolerance[2,3,4,5,6]. Their side effects are dose related and can be minimized by dose reduction.

Pentoxifylline 400mg twice daily, used for 3 months showed considerable improvement in mouth opening, tongue protrusion, difficulty in speech and swallowing, when compared to placebo in OSMF patients. Significant improvement was noticed when Pentoxifylline administrated 400mg twice daily for a period of 3 months and later hiked to 3 times daily for a period of 6-7 months[4,5]. Long- term 7 months Pentoxifylline therapy showed significant improvement in mouth opening, reduction of burning sensation, intolerance to spicy food, reduction in anterior and perioral fibrotic bands when compared to multivitamin therapy and local heat therapy but with no significant improvement in tongue protrusion and fibrotic bands in the posterior buccal mucosa and bands in the junction of hard and soft palate[3].

The total symptom score improved by 85.8% in Pentoxifylline and 38.2% in multivitamin group. Pentoxifylline therapy also showed significant

improvement in inter-incisal mouth opening and reduction in burning sensation when compared to standard intra-lesion combination treatment regime of dexamethasone, lignocaine, hyaluronidase injection[6]. Intra- lesion injection is painful and sometimes intolerable to the patients with high dropout ratio. Meta- analysis, on the effect of Pentoxifylline showed maximum benefit when used for longer duration of more than one month with statistically significant improvement in the signs and symptoms of OSMF.

Contradictory to the above findings, one randomized clinical trial showed no improvement in burning sensation, mouth opening, tongue protrusion and histopathological parameters like microvascular density, severity of fibrosis and inflammatory components but significant improvement noticed in the average area percentage occupied by blood vessels and this highlighting finding might be due to vasodilating property of Pentoxifylline[2].

Conclusion

Treatment of OSMF has been a challenge ever since the evolution of the disease. Newer drugs have been persistently evolving for the management of this complex disease. Pentoxifylline can bring about significant clinical improvements in the symptoms like mouth opening and tongue protrusion on long term usage (7 months), thereby improving the quality of life of the affected individuals. Even though Pentoxifylline does show vasodilation at the histological level, clinical improvement is at par with other drugs and local therapies used which showed no significant improvements over the short term usage of Pentoxifyl line[2]. However, it has been shown few side effects in the patients who were administered the drug. Pentoxifylline can be used as promising alternative treatment modalities to intra-leisional steroid for the treatment of OSMF.

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