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REVIEW ARTICLE

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Hemorheological effect of pentoxifylline for the treatment of Oral Submucous Fibrosis: a review

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ABSTRACT

Oral submucous fibrosis (OSMF) is a chronic mucosal inflammatory debilitating disease previously confined to Asian countries. Now, OSMF is becoming a global health-care problem due to the migration of many Asians to many parts of the world. OSMF is premalignant condition occurs due to the habit of betel quid chewing. Management of OSMF includes conservative approach and surgery. Physiotherapy, promotion of oral mucosal blood flow, vitamins and mineral supplements, fibrinolytic agents, antioxidants, and nutrients are the common conservative treatments towards OSMF. Hemorheology is the study of flow properties of blood and blood elements (In Greek, "Haima" means blood; "Rheology" means the flow of blood). Pentoxifylline (PTF) has been classified as a hemorheological drug and a phosphodiesterase inhibitor. Oral mucosal ischemia and epithelial atrophy in OSMF can be treated by PTF, which dilates the blood vessels in stromal tissues and improves peripheral blood flow and nutrient supply to the fibrosed mucosal tissues. Here, we present a review on the hemorheological effect of PTF for the treatment of OSMF.

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Introduction

Blood is a type of tissue composed of cellular elements like red blood cells (RBCs), white blood cells (WBCs), and platelets and also contains liquid intercellular material i.e., plasma. Blood is a two-phase liquid. It has liquid–liquid emulsion based on the fluid drop-like behavior of RBCs under high shear forces. Hence, depending on the flow conditions, blood tissue can be regarded as a suspension or an emulsion. Blood is considered as a non-Newtonian, shear thinning fluid which becomes thinner as the shear forces increases and blood viscosity increases as shear forces get smaller [1].

Hemorheology deals with the flow and deformation behavior of blood and blood-forming elements. RBCs show high rheological properties in blood because it constitutes 99% of the cellular elements compare to WBCs and platelets [2,3]. Cellular deformability and aggregation of RBCs are the two features which show non-Newtonian rheological behavior [1].

Deformity

It is the ability of the RBCs to reversibly adopt a new shape due to deforming forces and thinning of blood under high shear conditions so that RBCs can flow in streamlines by reducing the friction between them [1,4].

Aggregation

It is the formation of reversible clumps of RBCs under sufficiently low shear stresses to increase blood viscosity [1].

The main rheological properties of RBCs are their tendency to aggregate like a stack of coins

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to form three-dimensional structures. This phenomenon is called as Rouleaux formation. Fibrinogen and other plasma proteins promote RBC formation [5].

Pentoxifylline

Pentoxifylline (PTF) [1-(5-oxohexyl)-3,7-dimethylxanthine] is a derivative of methylxanthine and is an active hemorheological drug used for intermittent claudication and defective regional microcirculation disorders. This drug is also used in the treatment of impaired microcirculation of peripheral and cerebral vascular disorders. PTF is a white to creamy white, crystalline powder, soluble in water and ethanol, and sparingly soluble in toluene [6].

The pharmacological action of PTF is not completely understood. PTF is mediated by inhibition of cyclic nucleotide phosphodiesterases and leads to increased erythrocyte flexibility and platelet and vascular endothelial cells production. This enhances local blood flow and promotes thrombolysis. Hence, PTF stimulates microcirculation and neovascularization in diseases with excessive fibrosis [7]. PTF has been shown to reduce production of collagen, expression of interleukin-6 and transforming growth factor beta 1 (TGF-β1) in rats [8].

Other action of PTF includes increased red cell deformability, leukocyte chemotaxis, anti-thrombin, and anti-plasmin activities, and also decreases red cell and platelet aggregation, granulocyte adhesion, fibrinogen levels, and whole blood viscosity to increase the production of prostaglandins [9,10].

Oral Submucous Fibrosis

Oral submucous fibrosis (OSMF) is a chronic insidious premalignant condition, characterized by changes in the connective tissue fibers of the lamina propria and deeper parts leading to stiffness of the mucosa and restricted mouth opening. This condition is predominantly seen in India, Bangladesh, Sri Lanka, Pakistan, Taiwan, China, and other Asiatic countries. In India, about 0.4% prevalence was seen in the rural population [11].

Etiology of OSMF is multifactorial, which includes areca nut chewing, hereditary, nutritional deficiencies, and immunological factors being few of them [10]. Symptoms include burning sensation, fibrosis of oral mucosa, and difficulties in mouth opening and tongue movement (Figs. 1–3).

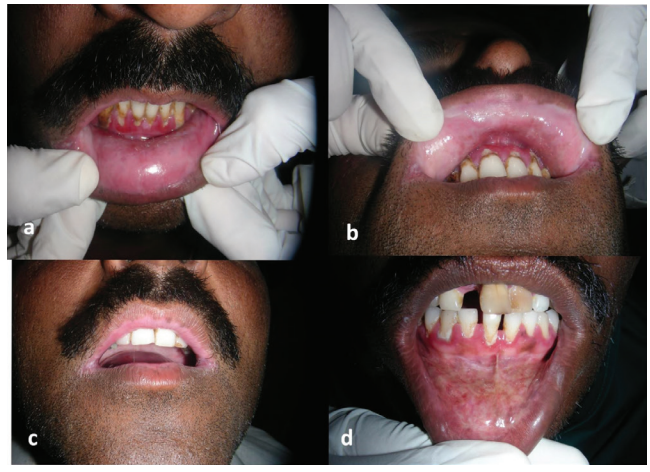

Figure 1. OSMF changes in upper and lower labial mucosa.

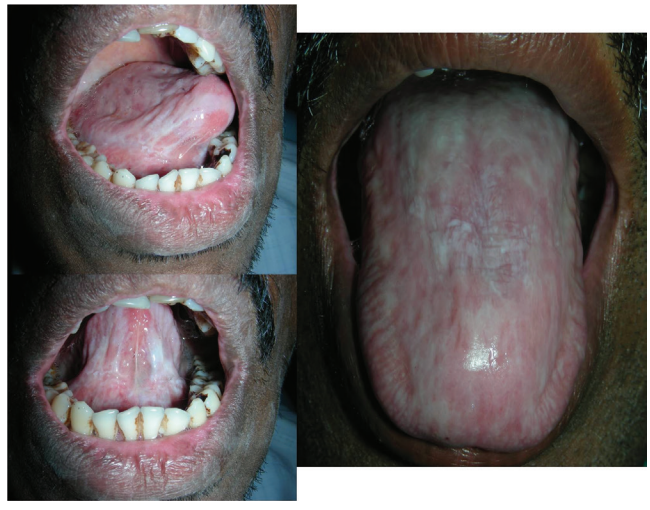

Figure 2. OSMF changes in tongue.

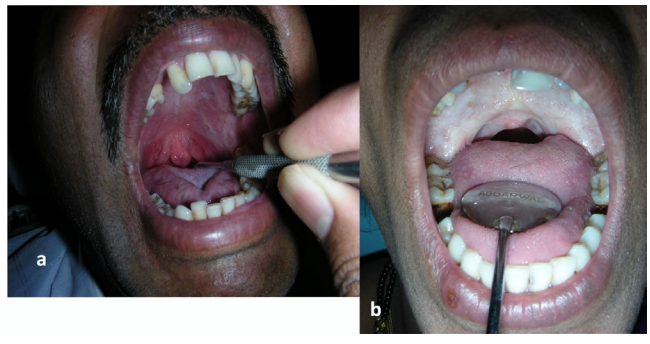

Figure 3. (a) OSMF with bifid uvula. (b) OSMF changes seen in soft palate with shrunken Uvula.

Pathogenesis of OSMF can be categorized into three broad theories. They are as follows: (1) defective collagen homeostasis theory, (2) genetic theory, and (3) autoimmunity theory.

1. Defective collagen homeostasis theory proposes,
   - Alkaloids, flavonoids, and copper which is present in arecanut (*Areca Catechu*) known to stimulate fibroblasts to produce collagen. Slaked lime (calcium hydroxide) added to pan preparation facilitates fibroblastic proliferation; thus, enhances collagen formation.
   - The influence of arecoline on connective tissue growth factor enhances the fibrotic activity in OSMF. Arecoline induces deposition of extracellular matrix (ECM) which is further substantiated by overexpression of transglutaminase-2 (TGM-2) in OSMF. TGM-2 stabilizes ECM protein by cross-linking that has also been implicated in several fibrotic disorders.
   - The localized mucosal inflammation caused by pan/gutkha results in activated T-cell and macrophage recruitment that leads to an increase in cytokines and tumor growth factor beta (TGF-β).
   - Flavonoids (tannins and catechins) inhibit collagenase, stabilize the collagen fibrils, and render them resistant to degradation by collagenase.
2. Genetic theory suggests gene polymorphism related to COL1A1, COL1A2, COLase, Lyoxidase, TGF-β, and cystatin C was associated with the highest risk of OSMF.
3. Autoimmunity theory: a high incidence of antinuclear antibody, smooth muscle antibody, and gastric parietal cell autoantibody was seen in patients with OSMF [12].

Vasculature and OSMF

OSMF is a pathological fibrosis with oral submucosal deposition of collagen [13]. OSMF leads to progressive loss of vascularity in the diseased mucosa, resulting in epithelial atrophy [14]. Decreased vascular areas are seen in an advanced stage of OSMF due to increased fibrosis of the surrounding blood vessels [15]. Malignant transformation in OSMF is due to the ischemic atrophy of oral epithelium due to lack of perfusion secondary to fibrosis which makes mucosa more prone to the effects of locally available carcinogen [16].

Inflammation is mediated by proinflammatory cytokines like tumor necrosis factor (TNF-α). This TNF-α leads to activation of macrophages in the injured tissue, which releases fibrogenic cytokines. Mainly, fibroblast growth factor 2 (FGF2) and transforming growth factor beta 1 (TGF-β1) are the fibrogenic cytokines. FGF2 acts as chemotactic and mitotic for fibroblasts. TGF-β1 stimulates fibroblast proliferation which leads to fibrosis of oral mucosa. PTF is known to suppress the synthesis of TNF-α; thus, acts as an anticytokine therurapeutic drug [17].

Pentoxifylline and OSMF

PTF is readily absorbed from the gastrointestinal tract and its peak plasma level is achieved within 2 hours, but it undergoes first pass hepatic metabolism. The usual adult dosage of PTF is 400 mg three times daily after meals [18].

In humans, PTF is metabolised into at least seven different metabolites. They are M1–M7. PTF is 3,7-dimethyl-1(5′-oxo-hexyl) xanthine.

M1 is reduction of the 5′-oxo group from PTF gives 3,7-dimetyl-1(5′-hydroxyhexyl) xanthine. Metabolism of M1 takes place in the liver and in the erythrocytes, yielding S-M1 as a major metabolite and R-M1 as a minor metabolite. Hepatic metabolism produces the carboxylic acid metabolites M4 and M5. M5 is the major excreted form. M1 and M5 showed erythrocyte deformability and platelet aggregation *in vitro* and causes *in vivo* hemorheological effects of PTF [19].

PTF acts in different mechanism on the fibrosed oral mucosa.

1. PTF inhibits cyclic adenosine monophosphate (cAMP) phosphodiesterase, which increases cAMP and adenosine triphosphate (ATP) on the cell wall of RBCs. Thus, enhances the deformability of RBCs and leads to increased blood flow in the fibrosed area [20].
2. PTF inhibits intercellular adhesion molecule expression, which minimizes adhesion of leucocyte to endothelial cells. This leads to increased prostacyclin production and inhibits platelet aggregation [20].
3. PTF decreases plasma fibrinogen concentration and increases fibrinolytic activity. Thus, enhances vascular blood flow [20].
4. PTF acts by increasing red cell deformability, leukocyte chemotaxis, anti-thrombin and anti-plasmin activities, and also decreases red cell and platelet aggregation, granulocyte adhesion, fibrinogen levels, and whole blood viscosity [9,10].
5. PTF reduces the adhesiveness of polymorphonuclear cells, decreases the levels of TNF-α & interleukin-6. This drug also restores the depressed endothelial function and vascular contractility [21].

Physical therapy	Medical management	Surgical intervention
• Physical exercise regimen • Splints or other mouth opening devices • Microwave diathermy • Postoperative physiotherapy • Vigorous mouth opening • Wooden tongue spatula [22].	**Modulation of inflammation and immunity** • Steroids • Interferon C • Immunized milk • Placental extracts • Levamisole • Colchicine **Promotion of blood flow** • Pentoxyphylline • Buflomedil hydrochloride • Nylidrin **Anti-oxidants, nutrients and micronutrients therapy** • ß-carotene • Lycopene • Tea pigments • Vitamins and mineral Supplements **Other drugs** • Anti-TGF β drugs, • Copper chelators • Borneol • Garlic extracts, • Oxitard, • Aloe vera • Turmeric [22].	**Extraoral flaps** • Split thickness skin graft • Superficial temporal fascia pedicled flap • Temporalis pedicled flap • Nasolabial flap • Platysma myocutaneous muscle flap **Intraoral flaps** • Tongue flap • Palatal island flap • Buccal pad of fat **Microvascular-free flaps** • Radial forearm free flap • Anterolateral thigh flap **Allografts** • Collagen membrane • Alloderm [22].

Management of OSMF

There are a number of treatment modalities which have been advised to manage both the symptoms and treatment of the abnormal fibrotic tissue that occurs as the disease progresses [22].

Discussion

Several studies were conducted on the use of PTF in OSMF. Prabhu et al. conducted a randomized clinical trial in 2013. Thirty OSMF patients were categorized randomly into groups I and II. In group I, drug PTF was administered and group II patients were advised conventional therapies only. Pre- and post-treatment biopsies were obtained for the following parameters: Micro-vascular density, the area percentage of blood vessels, the severity of fibrosis, and inflammatory components. Burning sensation of oral mucosa pre- and post-treatment in group I showed quite a significant improvement [10].

Patil et al. [23] evaluated the efficacy of the newer drug PTF in the improvement of various clinical parameters such as mouth opening, tongue protrusion, pain associated with the lesion, burning sensation, difficulty in speech, and swallowing in a larger sample.

Kalkur et al. conducted a study on 50 cases of advanced OSMF conducted as a randomized clinical trial incorporating a control group (antioxidant therapy, Tab Lycored once daily) in comparison to PTF test cases (400 mg tablets, three times daily) whose treatment period was 3 months. There is a marginal increase in mouth opening in the test group than the control group. However, the result of this study was not statistically significant. Significant improvement was seen in the reduction in burning sensation in the PTF group when compared to the control group [24].

According to Sadaksharam et al., they conducted a study to evaluate the therapeutic efficacy of oral PTF in the treatment of OSMF patients by assessing the clinical symptoms and submucosal layer thickness and echogenicity using ultrasonography (USG), both pre- and post-operatively. Thirty study subjects were divided into two groups: oral PTF and dexamethasone groups. Burning sensation, mouth opening, ultrasonographic submucosal thickness, and echogenicity were recorded. PTF group showed marginally better improvement than the dexamethasone group in clinical symptoms as well as echogenicity on the right and left sides. USG, which showed marked changes in submucosal thickness and echogenicity in OSMF patients. Hence, USG can be considered as a valuable tool in assessing the severity,

extension, disease progression, and treatment outcome objectively and efficiently [25].

According to Rajendran et al., 29 OSMF patients were given PTF tablets for 7 months and compared with the control group which is given multivitamin capsules. Study group showed significant improvement at the end of the trial period [26].

Based on several studies oral PTF has been proved to have a beneficial result in treating OSMF because of its anti-inflammatory, fibrinolytic, immunomodulatory, and rheologic modifying property. PTF improves RBC membrane deformability by increasing the amount of membrane ATP. It also alters RBC membrane protein phosphorylation patterns, increases protein kinase activity, and decreases $Ca2^{+}$-dependent K^{+} efflux [25,27].

PTF also shown to have increased collagenase activity and decreased amounts of collagen, glycosaminoglycans, and fibronectin I in fibroblast culture studies. Interleukin-1-induced fibroblast proliferation is also inhibited by PTF [25,27].

Conclusion

OSMF is a complex disease due to the high risk of malignant transformation. The primary mechanism of OSMF is inflammation, increased synthesis, and decreased degradation of submucosal collagen, and fibrotic band formation, which results in juxta-epithelial hyalinization with subepithelial layer inflammatory infiltration in the basement membrane. Main purpose of management of OSMF is improved oral opening and relief of symptoms.

PTF acts as a vasodilator, anti-oxidant, and anti-inflammatory drug. PTF treatment for OSMF is still a challenge. Long administration time for several months is the drawback. OSMF is a significant public health issue; hence, efficient programs for awareness, prevention, and treatment are necessary for global level.

References

[1] Baþkurt OK. Pathophysiological significance of blood rheology. Turk J Med Sci 2003; 33:347–55.

[2] Lowe GDO, Barbenel JC. Plasma and blood viscosity. In: Lowe GDO (ed.). Clinical blood rheology. Vol 1, CRC Press, Boca Raton, FL, pp 11–44, 1988

[3] Merrill EW. Rheology of blood. Physiol Rev 1969; 49:863–88.

[4] Chien S. Red cell deformability and its relevance to blood flow. Ann Rev Physiol 1987; 49:177–92.

[5] Rampling MW. Red cell aggregation and yield stress. In: Lowe GDO (ed.). Clinical blood rheology. CRC Press, Boca Raton, FL, pp 11–44, 1988.

[6] Alarfaj N, El-Tohamy M. New validated potentiometric determination of vasodilator pentoxifylline in its pharmaceutical formulations and biological fluids. J Chin Chem Soc 2011; 58:1–8.

[7] Isaac C, Mathor MB, Bariani G, Paggiaro AO, Herson MR, Goldenstein-Schainberg C, et al. Pentoxifylline modifies three-dimensional collagen latticemodel contraction and expression of collagen types I and III by human fibroblasts derived from post-burn hypertrophic scars and from normal skin. Burns 2009; 35:701–6.

[8] Hernandez E, Correa A, Bucio L, Souza V, Kershenobich D, Gutierrez-Ruiz MC. Pentoxifylline diminished acetaldehyde induced collagen production in hepatic stellate cells by decreasing interleukin-6 expression. Pharmacol Res 2002; 46:435–43.

[9] Ward A, Clissold SP. Pentoxifylline: a review of its pharmacodynamic and pharmacokinetic properties and its therapeutic efficacy. Drug Eval 1987; 34:50–97.

[10] Prabhu N, Rao SS, Kotrashetti SM, Baliga SD, Hallikerimath SR, Angadi PV, et al. Pentoxifylline in patients with oral submucous fibrosis—a randomized clinical trial. J Maxillofac Oral Surg 2015; 14(1):81–9.

[11] Anila K, Kaveri H, Naikmasur VG. Comparative study of oral micronucleated cell frequency in oral submucous fibrosis patients and healthy individuals. J Clin Exp Dent 2011; 3:201–6.

[12] Arakeri G, Rai KK, Hunasgi S. OSMF: an update on current theoris of pathogenesis. J Oral Pathol Med 2017; 46(6):406–12.

[13] Dyavanagoudar SN. Oral submucous fibrosis: review on etiopathogenesis. J Cancer Sci Ther 2009; 1:072–7.

[14] Liu J, Chen F, Wei Z, Qiu M, Li Z, Dan H, et al. Evaluating the efficacy of pentoxifylline in the treatment of oral submucous fibrosis: a meta-analysis. Oral Dis 2018; 24:706–16.

[15] Tekade SA, Chaudary MS, Tekade SS, Sarode SC, Wanjari SP, Gadbail AR, et al. Early stage oral submucous fibrosis is characterized by increased vascularity as opposed to advanced stages. J Clin Diagn Res 2017; 11:92–6.

[16] Angadi PV, Rao SS. Areca nut in pathogenesis of oral submucous fibrosis: revisited. Oral Maxillofac Surg 2011; 15:1–9.

[17] Okunieff P, Augustine E, Hicks JE, Cornelison TL, Altemus RM, Naydich BG, et al. Pentoxifylline in the treatment of radiation-induced fibrosis. J Clin Oncol 2004; 22:2207–13.

[18] Parkarwar PC, Anjum A, Zaidi N, Ziauddin SM, Kale L, Khairnar S, et al. Pentoxifylline: applications in dentistry. J Med Pharm Allied Sci 2017; 6(3):645–54.

[19] Magnusson M, Bergstrand IC, Björkman S, Heijl A, Roth B, Höglund P. A placebo-controlled study of retinal blood flow changes pentoxifylline and

metabolites in humans. Br J Clin Pharmacol 2006; 61:138–47.
[20] Berman B, Duncan MR. Pentoxifylline inhibits normal human dermal fibroblast in vitro proliferation, collagen, glycosaminoglycan, and fibronectin production, and increases collagenase activity. J Invest Dermatol 1989; 92:605–10.
[21] Nordin A, Mildh L, Makisalo H, Härkönen M, Höckerstedt K. Hepatosplanchnic and peripheral tissue oxygenation during treatment of hemorrhagic shock: the effects of pentoxifylline administration. Ann Surg 1998; 228:741–7.
[22] Arakeri G, Rai KK, Boraks G, Patil SG, Aljabab AS, Merkx MAW, et al. Current protocols in the management of oral submucous fibrosis: An update. J Oral Pathol Med 2017; 46:418–23.
[23] Patil S, Maheshwari S. Efficacy of pentoxifylline in the management of oral submucous fibrosis. J Oralfac Sci 2014; 6:94–8.
[24] Kalkur C, Sattur AP, Guttal KS. Efficacy of pentoxifylline in the treatment of oral sub mucous fibrosis—a pilot study. WJPMR 2016; 2:49–53.
[25] Sadaksharam J, Mahalingam S. Evaluation of oral pentoxifylline in the management of oral submucous fibrosis—an ultrasonographic study. Contemp Clin Dent 2017; 8:200–4.
[26] Rajendran R, Rani V, Shaikh S. Pentoxifylline therapy: a new adjunct in the treatment of oral submucous fibrosis. Indian J Dent Res 2006; 17:190–8.
[27] Aara A, Satishkumar GP, Vani C, Venkat Reddy M, Sreekanth K, Ibrahim MD. Comparative study of intralesional dexamethasone, hyaluronidase and oral pentoxifylline in patients with oral submucous fibrosis. Glob J Med Res 2012; 12:1–14.