International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319 – 6718, ISSN (Print): 2319 – 670X
www.ijpsi.org || Volume 4 Issue 6|| June 2015 || PP.07-10

Oral Submucous fibrosis and the role of curcumin in its treatment: A review

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ABSTRACT: *Oral submucous fibrosis is a chronic insidious disease which was previously designated as a premalignant condition but presently categorized under potentially malignant disorders (WHO 2005). Oral submucous fibrosis is highly prevalent in south Asia as people of south Asia consume large amounts of areca nut when compared with rest of the world. Curcumin is the active component of turmeric which is a south Asian spice commonly used for cooking. Curcumin has some important biological properties such as anti-inflammatory, antioxidant and anti-cancer activity. Numerous studies have reported curcumin's role in the prevention and reduction of fibrosis caused by harmful factors. The aim of this review is to provide an update about curcumin's role and action in oral submucous fibrosis.*

KEY WORDS – *Oral submucous fibrosis, curcumin, potentially malignant disorders.*

I. INTRODUCTION

Oral submucous fibrosis (OSF) is a chronic inflammatory disease, which has been categorised by WHO as one of the potentially malignant disorders (WHO workshop, 2005). Schwartz first described it in 1952. OSF was defined by PindborgJJ &Sirsat SM in 1966, as"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 a juxta-epithelial inflammatory reaction followed by a fibroelastic change of the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat. About 5 million people of the Indian population are reportedly affected. The main clinical features include trismus, mucosal pain on consuming spicy foods reduced interincisal distance, stomatopyrosis, reduced tongue movement, palpable fibrotic bands in buccal mucosa, discoloration and desquamation of oral mucosa. In early OSF, there is dysguesia, dryness of the mouth, blisters in the palate and oral mucosa. In advanced stages, there is blanching of the mucosa, fixation of soft palate, shortening of uvula, persistent or recurrent glossitis/stomatitis. Malignant transformation rate of OSMF is 7.6 % over a period of 10 years has been reported.

II. AETIOPATHOGENESIS

OSF is associated with placement of betel quid in the oral cavity. Betel quid is a substance or mixture of substances placed in the mouth or chewed and remaining in contact with the mouth, usually containing one or both of the two basic ingredients areca nut and slaked lime usually with tobacco and sometimes with sweeteners and condiments wrapped in betel leaf in raw or any manufactured or processed form. Slaked lime releases alkaloid arecadine from areca, nut that causes submucosal changes. Epithelial alterations and carcinogenesis can be attributed to tobacco contact.An imbalance in collagen synthesis and degradation in oral mucosa is generally believed to be the main cause of OSF. The disease is considered a type of collagen metabolism disorder as it causes disturbance in the homeostatic equilibrium between synthesis and degradation of extra cellular matrix.Myofibroblasts play an important role in the development of oral submucous fibrosis (OSF). The basic mechanism is that, there is an increase in TGFβ, which stimulates the production and deposition of extracellular matrix, and a decrease in collagenase activity causing increased crosslinking of collagen. Cytokines and growth factors produced by activated inflammatory cells may promote fibrosis by inducing proliferation of fibroblasts, upregulating collagen synthesis and downregulating collagenase production.

III. CLINICAL FEATURES AND DIAGNOSIS

As stated earlier, the prodromal symptoms of early OSF include a burning sensation in the mouth on consuming spicy food, appearance of blisters, ulceration and recurrent inflammation of the oral mucosa, excessive salivation, defective gustatory sensation and dryness of the mouth. The chief complaint is, inability to open the mouth. An interincisal distance of 20mm or less is considered severe. In advanced cases, the jays may even be inseparable. Females are more susceptible to these changes.Vesicles, Petechiae, Melanosis, xerostomia,

and a generalised oral burning sensation(stomatopyrosis) are usually the first signs and symptoms. The buccal mucosa, retromolar area and soft palate are most commonly affected sites. There is a blotchy, marble like pallor and progressive stiffness of subepithelial tissues. Betel quid chewers may exhibit a brown-red discolouration of the mucosa with an irregular surface that tends to desquamate. This is termed betel chewer's mucosa. In addition, some authors have reported betel quit lichenoid lesions, characterised by white parallel, wavy striae.

IV. PATHOLOGY

Structural and microstructural changes- the epithelial changes in different stages of OSF are predominantly hyperplasia (early) and atrophy (advanced) associated with an increased tendency for keratinising metaplasia. Subepithelial changes- on the basis of histopathological appearance, four different stages have been defined- very early, early, moderate advanced, advanced. This grouping was based on the amount and nature of subepithelial collagen, presence or absence of edema, physical state of mucosal collagen, overall fibroblastic response, state of blood vessels, and predominant cell type in inflammatory exudate.

Significant hematological abnormalities have been reported in OSF, including an increased erythrocyte sedimentation rate, anemia, eosinophilia, increased gamma globulin, decrease in serum iron and increase in total iron binding capacity (TIBC). The percentage saturation of transferrin also decreased and a significant reduction in total serum iron and albumin was found.

V. TREATMENT

Review of the natural history of OSF indicates that it is an insidious disorder, which progresses with time. In clinical practice, there are a number of treatments for OSF, ranging from medical and surgical interventions, physical therapy, and habit control (i.e. cessation of areca nut use). Often a combination of strategies is used.People with OSF characteristically complain of two problems: inability to open their mouths and function normally, and a burning sensation and intolerance to spicy foods that are often the mainstay of the Asian diet, leaving an individual disadvantaged both physically and psychologically. Based on the clinical features, the aims of treatment are to reverse these signs and symptoms, stop disease progression, and in addition, to minimize the risk for malignant transformation. There is an array of reported medical interventions including dietary supplementation mainly for proteins, vitamins, anti-oxidants, anti-inflammatory agents or immunomodulatory drugs (principally corticosteroids) and proteolytic agents (such as hyaluronidase and placental extracts), and anti-cytokines. Such agents may be administered orally, topically or via submucosal injection.. Physical therapy may be used as a single modality or combined with other interventions.Surgical interventions are generally reserved for more advanced cases of OSF. These treatment modalities have not been proven completely effective in treating osmf**.**

VI. ROLE OF CURCUMIN IN OSMF

Curcumin, 1, 7-bis (4-hydroxy-3-methoxyphenol)-1, 6-heptadiene-3, 5-dione, is the primary active substance isolated from Curcuma Longa L. rhizome. It is inexpensive, widely available and has almost no side effects; it has been long used as a spice and pigment in food processing industry. Curcumin has some important biological properties such as anti-inflammatory, antioxidant and anti-cancer acticity(Goel et al., 2008). Recently, many studies have reported curcumin's role in the prevention and reduction of fibrosis caused by harmful factors (Venkatesan et al., 2007; Osawa, 2007).

Myofibroblasts, typically considered to be activated fibroblasts, play an important role in morphogenesis, oncogenesis, inflammation, wound healing and fibrosis in most organs and tissues (Watsky et al., 2010).

Myofibroblast persistence is a key feature of fibrotic diseases including OSF, scleroderma, and hepatic, pancreatic, and pulmonary fibrosis(Gabbiani, 2003; Angadi et al., 2011). Myofibroblasts can be detected in the OSF-affected tissues; this phenomenon is related to the severity of OSF (Angadi et al., 2011). Myofibroblasts not only synthesize collagen, but also produce numerous inflammatory mediators, chemokines, and growth factors (Powell et al., 1999), intensifying and prolonging the inflammation in OSF by activating the inflammatory corpuscles. This self-excitation of inflammation increases the expression of fibrogenic cytokines such as TGF- β 1, and enhances fibrosis. The possibility of inhibiting proliferation and inducing apoptosis in myofibroblasts offers a new, promising therapy line in the treatment of OSF.

It has been reported in a study that Curcumin inhibits cell proliferation in fibroblasts and myofibroblasts MTT assay revealed that curcumin treatment significantly decreases the proliferation of fibroblasts and myofibroblasts, in a dose-dependent manner. This effect is more pronounced in myofibroblasts; the growth inhibitory rate for myofibroblasts incubated with curcumin was double of that for the similarly treated fibroblasts.

Curcumin induces cell cycle arrest in myofibroblasts Cell cycle analysis shows that curcumin treatment results in a dose-dependent increase in the proportion of myofibroblast cells in G0/G1 phase.

Curcumin induces cell apoptosis in myofibroblasts. The mechanism by which Curcumin mediates is pro-oxidant effects remain unclear. It has been suggested that mitochondria play a role in Curcumin-induced apoptosis. It is possible that Curcumin activates mitochondrial enzymes that lead to production of reactive oxygen species (ROS). This induction of ROS by Curcumin may occur through its interaction with thioredoxin reductase, thus altering it's activity to NADPH oxidase, which could then lead to the production of ROS. There have also been reports suggesting that Curcumin quenches ROS production and tugs acts as an antioxidant while others have reported that Curcumin quenches ROS production at low concentrations and induces ROS production at high concentrations. It also has been stated that micronutrients enhance the levels of vitamins A and C as well as selenium, in the supplemented groups, with a concomitant regression of precancerous lesions present on the palate. No side effects have been reported.

VII. DISCUSSION

Most of the treatment modalities for OSMF in practice are circumstantial and most of the studies that tested various treatment regimens lacked good design and follow up. Treatment of OSMF has largely been symptomatic. Though there are many therapeutic procedures available for OSMF, prevention is likely to be more effective then treatment.

A study published in 2010 has suggested that mitochondria play a role in curcumin induced apoptosis.The FDA has approved curcumin as "generally regarded as safe"; It is widely used in food industry as a spice and coloring agent. The safety of curcumin, combined with its potential efficacy and low cost, makes it an ideal therapeutic drug for OSF, a disease prevalent mainly in the developing countries.

H.K.E.S College of Pharmacy Gulbarga conducted a study in 2012 to determine the efficacy of mucoadhesive gel formulation of curcumin in treating OSF. The formulation was then planned for in-vivo studies using mice as model animal. In first phase of histopathological studies of OSMF induction in mice, a gross change of mucosa was observed and increased significance seen with the use of gutkha gel from 1 month application to 6 months applications. In second phase of treatment part of OSMF using prepared curcumin semi-solid preparation the encouraging results were observed. There was a marked reduction (more than 50%) of OSMF seen from the histopathological studies.

Recently, studies have suggested the use of curcumin in treating OSF in humans. Curcumin inhibits proliferation, disrupts the cell cycle, induces apoptosis, and decreases the expression levels of type I and III collagen; and it clearly demonstrates curcumin'santifibrotic potential in vitro. Further studies need to be carried out to prove the efficiency of curcumin in treating OSMF.

VIII. CONCLUSION

Oral submucous fibrosis (OSF) is a chronic, insidious disease that is associated with significant functional morbidity and an increased risk for malignancy. It initially affects the lamina propria of the oral mucosa and as the disease progresses it involves the submucosa and the deeper tissues including muscles of the oral cavity with resulting loss of fibroelasticity. The clinical manifestations include blanching and stiffening of the oral mucosa leading to limitation in oral opening. the disease could be described as primarily as a collagen metabolic disorder with changes observed in the extracellular matrix of the lamina propria and in the deeper mucosal tissues of the oral cavity because of both increased collagen synthesis and/or reduced collagen degradation. Treatment aims at reversing the signs and symptoms and stopping the disease progression. Does not regress with habit cessation. Treatment includes Intralesional injection of corticosteroids, interferon-γand long term followup. There is a 19 times risk than normal for cancer development. Curcumin has been proven effective in the treatment of OSF in recent times.

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