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Evaluation of intralesional steroid theraphy in patients suffered from oral sub mucous fibrosis (OSMF)

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Abstract

Instruct patients regarding the importance of discontinuing the habit of chewing betel quid. Inform patients that eliminating tobacco from the quid product may reduce the risk of oral cancer. Instruct patients to avoid spicy foodstuffs. Instruct patients to eat a complete and healthy diet to avoid malnutrition. Instruct patients regarding maintaining proper oral hygiene and scheduling regular oral examinations. Intervention studies and public health campaigns against oral habits linked to oral submucous fibrosis may be the best way of controlling the disease at the community level. Educate the community regarding the local adverse effects of chewable agents, which although not inhaled, are still not harmless. Hence based on above findings the present study was planned for Evaluation of Intralesional Steroid Theraphy in Patients Suffered from Oral Sub Mucous Fibrosis (OSMF).

The present study was planned in Department of ENT, Nalanda Medical College and Hospital Patna, Bihar, India. The study was conducted from September 2018 to February 2019. Total 30 cases of OSMF were enrolled in the present study. The patients were divided in three study groups as Group I, II and III. Occupational history and personal history with special preference to betel nut chewing, smoking, drinking alcohol was taken. Routine blood test, blood sugar, urine examination and HIV test was done to detect any systemic disease and immunocompromised conditions.

The data generated from the present study concludes that Ultrasound therapy for 15 days improved both mouth opening and burning sensation in OSMF patients, but ultrasound therapy alone was found to have less reduction of burning sensation when compared with combination treatment and only intralesional infiltration of 2 ml dexamethasone (4 mg/ml) and hyaluronidase (1500 IU) treatment. Ultrasound therapy showed synergistic effect in combination with intralesional infiltration of 2 ml dexamethasone (4 mg/ml) and hyaluronidase (1500 IU) by enhancing their absorption into the tissues.

Keywords: intralesional injections, oral submucous fibrosis, ultrasound therapy, etc

Introduction

In 1952, Schwartz coined the term atrophica idiopathica mucosa oris to describe an oral fibrosing disease he discovered in 5 Indian women from Kenya [1]. Joshi subsequently coined the termed oral submucous fibrosis (OSF) for the condition in 1953 [2].

Oral submucous fibrosis is a chronic debilitating disease of the oral cavity characterized by inflammation and progressive fibrosis of the sub mucosal tissues (lamina propria and deeper connective tissues). Oral submucous fibrosis results in marked rigidity and an eventual inability to open the mouth [3, 4]. The buccal mucosa is the most commonly involved site, but any part of the oral cavity can be involved, even the pharynx [5].

The condition is well recognized for its malignant potential and is particularly associated with areca nut chewing, the main component of betel quid [6]. Betel quid chewing is a habit practiced predominately in Southeast Asia and India that dates back for thousands of years. It is similar to tobacco chewing in westernized societies. The mixture of this quid, or chew, is a combination of the areca nut (fruit of the Areca catechu palm tree, erroneously termed betel nut) and betel leaf (from the Piper betel, a pepper shrub), tobacco, slaked lime (calcium hydroxide), and catechu (extract of the Acacia catechu tree) [3]. Lime acts to keep the active ingredient in its freebase or alkaline form, enabling it to enter the bloodstream via sublingual absorption. Arecoline, an alkaloid found in the areca nut, promotes salivation, stains saliva red, and is a stimulant.

The ingredients and nomenclature of betel quid vary by region as detailed below [7, 8]:

Pan: This is freshly prepared betel quid (with or without tobacco).

Gutka (gutkha, guttkha, or guthka): This is a manufactured version of betel quid with tobacco sold as a single-use sachet. It is primarily used on the Indian subcontinent (ie, India, Pakistan, Bangladesh). Betel quid without tobacco is mostly used in Southeast Asian countries (ie, Taiwan, Myanmar, Thailand, China, Papua New Guinea, Guam).

Pan masala: This is a commercially manufactured powdered version of betel quid without tobacco used in the Indian subcontinent.

Pan Parag: It is a brand name of pan masala and gutka used in India.

Mawa (kharra): This is a crude combination of areca, tobacco, and lime.

Mainpuri tobacco: Popular in parts of northern India, Mainpuri tobacco is a mixture of areca nut, tobacco, lime, and various condiments. Depending on local preferences, sweeteners or spices (ie, cardamom, saffron, clove, anise

seed, turmeric, mustard) are also added as flavorings.

In most patients with oral submucous fibrosis, areca nut was chewed alone more frequently than it was chewed in combination with pan (ie, betel leaf plus lime plus betel catechu, with or without tobacco) [4] or had a higher areca nut content [9].

The pathogenesis of the disease is not well established, but the cause of oral submucous fibrosis is believed to be multifactorial. A number of factors trigger the disease process by causing a juxtaepithelial inflammatory reaction in the oral mucosa. Factors include areca nut chewing, ingestion of chilies, genetic and immunologic processes, nutritional deficiencies, and other factors.

The areca nut component of betel quid plays a major role in the pathogenesis of oral submucous fibrosis. [10, 11, 12, 13]. In a 2004 study, a clear dose-dependent relationship was observed for both frequency and duration of chewing areca nut (without tobacco) in the development of oral submucous fibrosis [14]. Smoking and alcohol consumption alone, habits common to areca nut chewers, have been found to have no effect in the development of oral submucous fibrosis [15], but their addition to areca nut chewing can be a risk for oral submucous fibrosis [15]. Commercially freeze-dried products such as pan masala, guthka, and mawa have higher concentrations of areca nut per chew and appear to cause oral submucous fibrosis more rapidly than self-prepared conventional betel quid, which contains smaller amounts of areca nut [9].

Arecoline, an active alkaloid found in betel nuts, stimulates fibroblasts to increase production of collagen by 150% [16]. In one study, arecoline was found to elevate the mRNA and protein expression of cystatin C, a nonglycosylated basic protein consistently up-regulated in a variety of fibrotic diseases, in a dose-dependent manner in persons with oral submucous fibrosis [17].

In 3 separate but similar studies, keratinocyte growth factor-1, insulinlike growth factor-1, and interleukin 6 expression, which have all been implicated in tissue fibrogenesis, were also significantly up-regulated in persons with oral submucous fibrosis due to areca quid chewing, and arecoline may be responsible for their enhanced expression [18, 19, 20]. Further studies have shown that arecoline is an inhibitor of metalloproteinases (particularly metalloproteinase-2) and a stimulator of tissue inhibitor of metalloproteinases, thus decreasing the overall breakdown of tissue collagen [21].

Insertion/deletion 5A polymorphism in the promoter region of the matrix metalloproteinase-3 gene, which results in alteration of transcriptional activities, has also been found in persons with oral submucous fibrosis but not in those with oral squamous cell carcinoma [22]. Conversely, insertion/deletion 2G polymorphism in the promoter of the matrix metalloproteinase-1 gene has been implicated in oral squamous cell carcinoma but not oral submucous fibrosis [23].

Flavanoid, catechin, and tannin in betel nuts cause collagen fibers to cross-link, making them less susceptible to collagenase degradation [24]. This results in increased fibrosis by causing both increased collagen production and decreased collagen breakdown [4]. Oral submucous fibrosis remains active even after cessation of the chewing habit, suggesting that components of the areca nut initiate oral submucous fibrosis and then affect gene expression in the fibroblasts, which then produce greater amounts of normal collagen [25]. Chewing areca quid may also activate NF-kappaB expression, thereby stimulating collagen fibroblasts and leading to further fibrosis in persons with oral submucous fibrosis [26].

Areca nuts have also been shown to have a high copper content, and chewing areca nuts for 5-30 minutes significantly increases soluble copper levels in oral fluids. This increased level of soluble copper supports the hypothesis that copper acts as an initiating factor in persons with oral submucous fibrosis by stimulating fibrogenesis through up-regulation of copper-dependent lysyl oxidase activity [27, 28]. Further, a significant gradual increase in serum copper levels from precancer to cancer patients has been documented [29], which may have a role in oral fibrosis to cancer pathogenesis.

The role of chili ingestion in the pathogenesis of oral submucous fibrosis is controversial. The incidence of oral submucous fibrosis is lower in Mexico and South America than in India, despite the higher dietary intake of chilies [30]. A hypersensitivity reaction to chilies is believed to contribute to oral submucous fibrosis [4]. One study demonstrated that the capsaicin in chilies stimulates widespread palatal fibrosis in rats [31], while another study failed to duplicate these results [32].

A genetic component is assumed to be involved in oral submucous fibrosis because of the existence of reported cases in people without a history of betel nut chewing [10] or chili ingestion. Patients with oral submucous fibrosis have been found to have an increased frequency of HLA-A10, HLA-B7, and HLA-DR3 [4].

An immunologic process is believed to play a role in the pathogenesis of oral submucous fibrosis. The increase in CD4 and cells with HLA-DR in oral submucous fibrosis tissues suggests that most lymphocytes are activated and that the number of Langerhans cells is increased. The presence of these immunocompetent cells and the high ratio of CD4 to CD8 in oral submucous fibrosis tissues suggest an ongoing cellular immune response that results in an imbalance of immunoregulation and an alteration in local tissue architecture. These reactions may be the result either of direct stimulation from exogenous antigens, such as areca alkaloids, or of changes in tissue antigenicity that lead to an autoimmune response.

Further, the major histocompatibility complex class I chain–related gene A (MICA) is expressed by keratinocytes and other epithelial cells and interacts with gamma/delta T cells localized in the submucosa. MICA has a triplet repeat (GCT) polymorphism in the transmembrane domain, resulting in 5 distinct allelic patterns. In particular, the phenotype frequency of allele A6 of MICA in subjects with oral submucous fibrosis is significantly higher and suggests a risk for oral submucous fibrosis.

Some authors have demonstrated increased levels of proinflammatory cytokines and reduced antifibrotic interferon gamma (IFN-gamma) in patients with oral submucous fibrosis, which may be central to the pathogenesis of oral submucous fibrosis.

Iron deficiency anemia, vitamin B complex deficiency, and malnutrition are promoting factors that derange the repair of the inflamed oral mucosa, leading to defective healing and resultant scarring [4]. The resulting atrophic oral mucosa is more susceptible to the effects of chilies and betel nuts.

Some authors have found a high frequency of mutations in the APC gene and low expression of the wild-type TP53

tumor suppressor gene product in patients with oral submucous fibrosis, providing some explanation for the increased risk of oral squamous cell carcinoma development in patients with oral submucous fibrosis [10]. Other studies have suggested that altered expression of retinoic acid receptor-beta may be related to the disease pathogenesis.

The term oral submucosal fibrosis derives from oral (meaning mouth), submucosal (meaning below the mucosa of the mouth), and fibrosis (meaning hardening and scarring) [4]. Chewable agents, primarily betel nuts (Areca catechu), contain substances that irritate the oral mucosa, making it lose its elasticity. Nutritional deficiencies, ingestion of chilies, and immunologic processes may also have a role in the development of oral submucous fibrosis [3]. See Pathophysiology.

Oral submucous fibrosis is rare in the United States and is found only in the immigrant members of the South Asian population who chew betel nuts. Worldwide, estimates of oral submucous fibrosis indicate that 2.5 million people are affected, with most cases concentrated on the Indian subcontinent, especially southern India [3]. The rate varies from 0.2-2.3% in males and 1.2-4.57% in females in Indian communities [4]. Oral submucous fibrosis is widely prevalent in all age groups and across all socioeconomic strata in India. A sharp increase in the incidence of oral submucous fibrosis was noted after pan parag came onto the market, and the incidence continues to increase. Oral submucous fibrosis also occurs in other parts of Asia and the Pacific Islands [3]. Migration of endemic betel quid chewers has also made oral submucous fibrosis a public health issue in many parts of the world, including the United Kingdom, South Africa, and many Southeast Asian countries [40].

Oral submucous fibrosis occurs on the Indian subcontinent, in Indian immigrants to other countries, and among Asians and Pacific Islanders as a result of the traditional use of betel quid endemic to these areas [3].

The male-to-female ratio of oral submucous fibrosis varies by region, but females tend to predominate. In a study from Durban, South Africa, a distinct female predominance was demonstrated, with a male-to-female ratio of 1:13 [41]. This was later confirmed by others, with a male-to-female ratio of 1:7 [42]. In addition, a female predominance in areca nut chewing was also noted in this region. Studies in Pakistan reported a male-to-female ratio of 1:2.3 [4].

Conversely, a case-control study of 185 subjects in Chennai, South India revealed a male-to-female ratio 9.9:1 [15]. In Patna, Bihar (also in India), the male-to-female ratio was 2.7:1 [43]. With the onset of new commercial betel quid preparations, trends in sex predominance and age of occurrence may shift.

The age range of patients with oral submucous fibrosis is wide and regional; it is even prevalent among teenagers in India. In a study performed in Saipan, 8.8% of teenagers with a mean age of 16.3 years (± 1.5 y) were found to have oral submucous fibrosis. Generally, patient age ranges from 11-60 years [4]; most patients are aged 45-54 years and chew betel nuts 5 times per day [4].

Oral submucous fibrosis has a high rate of morbidity because is causes a progressive inability to open the mouth, resulting in difficulty eating and consequent nutritional deficiencies. Oral submucous fibrosis also has a significant mortality rate because of it can transform into oral cancer, particularly squamous cell carcinoma, at a rate of 7.6% [4]. No treatment is effective in patients with oral submucous fibrosis, and the condition is irreversible. Reports claim improvement of the condition if the habit is discontinued following diagnosis at an early stage.

Patients with oral submucous fibrosis have an increased risk of developing oral cancer. The malignant potential and the origin of cancer are attributed to the generalized epithelial atrophy associated with oral submucous fibrosis. Tobacco is the component of the quid believed to be most associated with cancer development. However, the carcinogenic property of the areca nut was discovered after noticing that cancer occurred in patients who chewed the nut without tobacco [25]. In vitro, betel nut extracts increase the rate of cell division, reduce cell cycle time, induce DNA strand breaks, and induce unscheduled DNA synthesis. Whether the use of tobacco in addition to areca nuts is responsible for the increased risk of oral cancer is controversial because evidence is conflicting.

Instruct patients regarding the importance of discontinuing the habit of chewing betel quid. Inform patients that eliminating tobacco from the quid product may reduce the risk of oral cancer. Instruct patients to avoid spicy foodstuffs. Instruct patients to eat a complete and healthy diet to avoid malnutrition. Instruct patients regarding maintaining proper oral hygiene and scheduling regular oral examinations. Intervention studies and public health campaigns against oral habits linked to oral submucous fibrosis may be the best way of controlling the disease at the community level. Educate the community regarding the local adverse effects of chewable agents, which although not inhaled, are still not harmless.

Hence based on above findings the present study was planned for Evaluation of Intralesional Steroid Theraphy in Patients Suffered from Oral Sub Mucous Fibrosis (OSMF).

Methodology

The present study was planned in Department of ENT, Nalanda Medical College and Hospital Patna, Bihar, India. The study was conducted from September 2018 to February 2019. Total 30 cases of OSMF were enrolled in the present study. The patients were divided in three study groups as Group I, II and III. Occupational history and personal history with special preference to betel nut chewing, smoking, drinking alcohol was taken. Routine blood test, blood sugar, urine examination and HIV test was done to detect any systemic disease and immunocompromised conditions.

Group I: Patients were given intralesional infiltration of 2 ml dexamethasone (4 mg/ml) + hyaluronidase 1500 IU dissolved in 0.5 ml of 2% lignocaine twice a week for 8 weeks.

Group II: Patients were given a combination treatment of intralesional infiltration of 2 ml dexamethasone (4 mg/ml) + hyaluronidase 1500 IU dissolved in 0.5 ml of 2% lignocaine twice a week for 8 weeks and ultrasound therapy for 15 days.

Group III: Patients were given only ultrasound therapy for 15 days.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria: Patients with group II OSMF were

included in this study.
Exclusion criteria: Patient with a known history of systemic diseases where steroids were contraindicated and pregnant women.

Results & Discussion

Corticosteroids are one of the most widely used drugs due to their anti-inflammatory, anti-allergic and immunosuppressive effects. Today they are used as systemic, topical, intra-articular and intralesional in the clinic. They were first used systemically in a patient with severe rheumatoid arthritis in 1948 by Hench *et al* [33]. Consequently a further 15 patients were successfully treated. In 1950, their discovery of the effect of cortisone brought Hench, Edward and Reichstein the Nobel Prize in Medicine and Physiology [34]. Beneficial effects of intra-articular corticosteroid (hydrocortisone acetate) injection was first published in 1951 [35]. In 1956, prednisolone was introduced by Rothermich and Phillips [36] as an satisfactory and more potent alternative for intra-articular injections. Boland and Liddle [37]. compared methylprednisolone with prednisolone and found them equally effective. Triamcinolone acetonide was applied in the treatment of dermatoses by Robinson [38] in 1958. Later, triamcinolone hexacetonide was reported to be a potent synthetic corticosteroid for intra-articular usage [39]. In the 1970s, corticosteroids were administered in intra-osseous lesions such as bone cysts [40, 42]. Intralesional steroid injection (ISI) has been performed in both of bone and mucosal lesions of oral and maxillofacial region since 1980. Currently, this method is widely accepted as an alternative or aid to surgical treatment especially in large reactive lesions.
Oral submucous fibrosis is a chronic, progressive, potentially malignant oral disorder which results in rigidity and stiffness of the oral mucosa with loss of tissue mobility and eventual inability to open the mouth [43]. Various treatment modalities are being used for the management of OSMF, which include either medical and surgical management or a combination of both. An enormous number of medications are being employed in the treatment of this disease. Nevertheless, no single medication could control the signs and symptoms in all the patients. Intralesional steroid injection is one of the modalities for the symptomatic relief of burning and may also be combined with hyaluronidase and placental extract intralesional injections to improve mouth opening. [44].

Table 1: Demographic Details

Parameters	No. of Cases
Sex	
Male	24
Females	6
Age	
21 – 30 years	11
31 – 40 years	10
41 – 50 years	4
51 – 60 years	3
60 & above years	2
Total	30

Table 2: Change in mean mouth opening levels & VAS Score

Parameters	mouth opening levels after 2 weeks	mouth opening levels after 8 week	VAS Score
Group I	1.3	7.6	40%
Group II	2.5	3.2	43%
Group III	1.6	8.4	20%

OSMF is a precancerous condition and reports suggest that it is present since the time of Sushruta [45] reported by Schwartz in 1962 and by Joshi in 1953; who described its singleton among the Indians. Many trials have been conducted but as such no definitive treatment is currently available [46]. However, improvement can be obtained passably by intralesional injection of cortisone and hyaluronidase [47]. It was observed that patients receiving hyaluronidase alone showed a quicker improvement in the burning sensation and painful ulceration produced by the effects of local by-products, although combination of dexamethasone and hyaluronidase gave better long-term results than other regimens [48]. However, the addition of dexamethasone has its own advantages and contraindications and a slight improvement in the overall result observed in the combination group justifies the addition of dexamethasone to hyaluronidase.
Burning sensation of the oral cavity and mucosal ulcerations are the initial symptoms of OSMF. As the disease progresses, the manifestations include blanching and stiffening of the oral mucosa leading to restricted mouth opening, along with palpable fibrous bands in the buccal mucosa, circumoral bands in upper and lower labial mucosa, shrunken uvula along with restricted tongue movements [49].
Numerous treatment modalities are currently employed for OSMF, ranging from medical and surgical interventions, physiotherapy after cessation of the habit, and usually, a combination of these are used in clinical practice. With multiple treatment options being used, no single modality can provide complete cure of the disease. However, for symptomatic relief of burning sensation, intralesional steroid treatment for 6-8 weeks is most commonly practiced. According to the systematic review of medical interventions for OSMF by Kerr *et al*., studies had predominantly used intralesional injections of corticosteroids and none of these studies had mentioned complications due to the same in OSMF patients [50].
Combination of dexamethasone and hyaluronidase and placentrex gave better long-term results than other regimens with single drug regimen injection therapy [51]. Study by Borle and Borle postulated that treatment following intralesional injections of various drugs leads to aggravated fibrosis and pronounced trismus [55]. The resultant worsening of this condition with submucosal injections are attributable to repeated needle stick injury to the soft tissues at multiple sites, clinical irritation from drugs being injected, and to the progressive nature of the disease [52]. The same outcome has been observed with some surgical methods employed to treat OSMF. Conservative line of treatment like topical steroids, vitamins, antioxidants, physiotherapy would give expected symptomatic relief of pain and burning sensation [53]. Kumar *et al*. study shows that combined therapy employing nutritional and iron supplements with intra-lesional injection therapy using hyaluronidase, dexamethasone and placentrex in addition to local anaesthetic topical gel and topical application of triamcinolone acetonide 0.1% caused a marked

improvement in patient's signs and symptoms. The clinical outcome is evidenced by improvement in colour of the oral mucosa, decrease in blanching and decreased severity of burning sensation, increased mouth opening and tongue protrusion [54].

Lai DR & Chen HR in their report of clinical evaluation of different treatment methods of OSMF in 150 cases [56]. Patients receiving biweekly submucosal injections of dexamethasone and hyaluronidase showed relaxation in stiffness of their buccal mucosa whereas no improvement of symptoms of trismus and blanching were seen in patients receiving oral vitamin B complex, peripheral vasodilator (buflomedial hydrochloride) and topical triamcinolone acetonide. In their study 75 patients received surgical treatment of excision of fibrous bands with graft placement. They concluded that there is significant improvement in trismus at the end of the surgery, though a decline in inter incisal distance occurs by varying amount as grafts and wounds contract. Borle and Borle did a comparative study of the effect of submucosal injection of triamcinolone in one OSMF group and chewable Vit A, Ferrous fumarate, topical betamethasone in another group. Trismus was more pronounced in the second group after follow up [57].

Numerous treatment modalities that have been implicated to cure the disease are the use of corticosteroids, hyaluronidase, placentrex, IFN, and microwave diathermy, etc. Surgical treatment is also considered by excision of fibrotic tissues and covering the defect with grafts. Though, till date, there is no single method which can be used as the definitive treatment modality for OSMF. Recent literature proves that the combination of drugs produce effective results in the management of this disease. A more extensive clinical trials involving a greater number of cases and including more parameters are necessary to come to a final conclusion about a particular modality in the management of OSMF.

Conclusion

The data generated from the present study concludes that Ultrasound therapy for 15 days improved both mouth opening and burning sensation in OSMF patients, but ultrasound therapy alone was found to have less reduction of burning sensation when compared with combination treatment and only intralesional infiltration of 2 ml dexamethasone (4 mg/ml) and hyaluronidase (1500 IU) treatment. Ultrasound therapy showed synergistic effect in combination with intralesional infiltration of 2 ml dexamethasone (4 mg/ml) and hyaluronidase (1500 IU) by enhancing their absorption into the tissues.

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