Evaluation of Role of Oxitard Capsules in the Treatment of Oral Submucous Fibrosis

SINGH B.P., NEELAM MITTAL, VISHAL SHARMA, PALANI

ABSTRACT

Oral submucous fibrosis is a chronic debilitating disease of the oral cavity. It is characterized by inflammation and progressive fibrosis of the oral submucosal tissues. Present study evaluates the role of Oxitard capsules in the treatment of oral submucous fibrosis. This study comprised of 48 cases who attended the Out Patient Department of Sir Sunderlal Hospital of Banaras Hindu University, Varanasi for chronic oral mucosal fibrosis lesions. Oxitard was given to all the patients a dose of 2 capsules, twice daily for a period of 3 months. All the patients were evaluated at monthly intervals for a period of 3 months, for the parameters like difficulty in opening mouth, hyperkeratosis, pain and lesion size. All the parameters were evaluated by a random score as 0 – nil, 1 – mild, 2 – moderate, 3 – severe.

The parameters of difficulty in opening the mouth, pain over the lesion, and hyperkeratosis reduced significantly. There was mild decrease in the size of the lesion. This study indicates that Oxitard capsules used in cases of oral submucous fibrosis showed statistically significant improvement in the symptoms like difficulty in opening the mouth, pain in the mouth and hyperkeratosis. Oxitard capsules was safe in the dose administered and well tolerated by the patients.

Key Words: oral submucosal fibrosis, Oxitard, hyperkeratosis

INTRODUCTION

Oral submucous fibrosis is a chronic debilitating disease of the oral cavity. It is characterized by inflammation and progressive fibrosis of the submucosal tissues. In this condition, the patient usually complains of burning sensations in the mouth, particularly while taking hot and spicy foods. This is often followed by the formation of multiple ulcerations or inflammatory reactions in the oral mucosa. There can be excessive salivations or decreased salivations and defective gustatory sensations. It is observed that males are more frequently affected with this disease than the females.

In the initial phase of the disease, palpation of the mucosa causes a wet leathery feeling. In the advanced stage the oral mucosa loses its resiliency and becomes blanched and stiff. Usually it is believed that the disease initiates from the posterior part of the oral cavity and it gradually spreads to the anterior locations. Other features of the disease include pain in the ear or deafness, nasal phonation of voice, restriction of the movement of the soft palate, bud-like shrunken uvula, thinning and stiffening of the lips, pigmentation of the oral mucosa, dryness of the mouth and impaired mouth movements.

The common causes of oral submucous fibrosis are products, which cause irritation such as pan masala and gutkha, excessive consumption of red chillies, immunological diseases, extreme climatic conditions, prolonged deficiency to iron and vitamins in the diet.

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 catechu chewing, ingestion of chillies, genetic and immunologic processes, nutritional deficiencies, and other factors.

Management of oral submucosal fibrosis include advising the patient to avoid chewing betel nut and tobacco, spicy foods and consumption of chillies should be minimal, to maintain proper oral hygiene. Specific treatment include steroids, placental extracts, IFN gamma, lycopene, pentoxyfylline, surgical excision, laser removal of the lesion etc.

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This study was planned to evaluate the role of Oxitard capsule, a herbal antioxidant formulation, in
the management of oral submucosal fibrosis.

This formulation contains the extracts of *Mangifera indica*, *Withania somnifera*, *Daucus carota*,
*Glycyrrhiza glabra*, *Vitis vinifera*; powders of *Emblica officinalis* and *Yashada bhasma*; and oils of *Triticum sativum*.

**Aim:** To evaluate the role of Oxitard capsules in the treatment of oral submucous fibrosis.

**MATERIALS AND METHODS:**

**Study design**

An open clinical evaluation was conducted on 48 cases who attended the Outpatient Department of Sir
Sunderlal Hospital of Banaras Hindu University, Varanasi, India, for chronic oral mucosal fibrosis lesions.

**Inclusion criteria**

Inclusion criteria included adult patients of either sex with oral submucous fibrosis with
hyperkeratosis, difficulty in opening the mouth and pain.

**Exclusion criteria**

Patients with evidence of pregnancy, lactation, any patients with severe psychiatric / cardiac,
gastrointestinal disorders or metabolic disorders were excluded from the study.

**Study procedure**

The present study comprised of 48 cases who attended the Out
Patient Department of Sir Sunderlal Hospital of Banaras Hindu University, Varanasi for chronic oral mucosal fibrosis lesions. Detailed history of tobacco or betel nut chewing and the course of the fibrosis were elicited. A thorough examination was conducted and signs and symptoms were recorded. Patients entered into the study after signing the voluntary consent form. Oxitard was given to all the patients at a dose of 2 capsules twice daily for a period of 3 months.

**Follow up and assessment**

All the patients were evaluated at monthly intervals at the end of 1st month 2nd month and 3rd month for a
period of 3 months, for the parameters like difficulty in opening mouth, hyperkeratosis, pain and lesion size.
All the parameters were evaluated by a random score as 0 – nil, 1 – mild, 2 – moderate, 3 – severe,

**Primary and secondary outcome measure**

The primary outcome measures were clinical recovery from oral submucosal fibrosis for the parameters like difficulty in opening mouth, hyperkeratosis, pain and lesion size. Secondary end points were clinical safety and toxicity profile of Oxitard.

**Adverse events**

All adverse events reported or observed by patients were recorded with information about severity, date
of onset, duration and action taken regarding the study drug. Relation of adverse events to study medication
was predefined as “Unrelated” (a reaction that does not follow a reasonable temporal sequence from the
administration of the drug), “Possible” (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient), “Probable” (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state) and “Certain” (the adverse
events must have definitive relationship to the study drug, which cannot be explained by concurrent
disease or any other agent).

Patients were allowed to voluntarily withdraw from the study
if they had experienced serious discomfort during the study or sustained serious clinical events
requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the
reason for dropout. Non-compliance
(defined as failure to take less than 80% of the medication) was not
regarded as treatment failure, and reasons for non-compliance were noted.

**Statistical analysis**

Results were analysed statistically by students 't' test. The minimum
level of significance was fixed at a 99% confidence limit and p value of <0.05 was considered significant. All
values are expressed as mean ± SEM.

**RESULTS:**

The present study comprised of 48 cases who attended the outpatient
department of Sir Sunderlal Hospital of Banaras Hindu University, Varanasi for chronic oral mucosal fibrosis
lesions. Detailed history of tobacco or betel nut chewing and the course of the fibrosis were elicited (Table 1).

All the patients received Oxitard 2 capsules, twice daily for a period of 3 months and underwent clinical
examination and evaluation of the parameters on entry and at monthly intervals for 3 months. Adverse
effects if any were noted down. The protocol of the study was as per the
ICH-GCP guidelines and the patients

<table>
<thead>
<tr>
<th>Table 1: Demographic Data</th>
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<tbody>
<tr>
<td>Total number of patients</td>
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<tr>
<td>Mean age in years (Mean ± SD)</td>
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<tr>
<td>Mean weight in kgs (Mean ± SD)</td>
</tr>
<tr>
<td>Sex ratio (M:F)</td>
</tr>
<tr>
<td>No. of tobacco chewing patients</td>
</tr>
<tr>
<td>No. of betel nut chewing patients</td>
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</tbody>
</table>
were free to withdraw from the study if they so desired. No other medication was allowed for these patients.

The parameters of difficulty in opening the mouth and pain over the lesion reduced significantly showing statistical significance ($p<0.05$) (Tables 2 and 3). Hyperkeratosis reduced and statistical significant reduction was seen at 3rd month (Table 4). There was mild decrease in the size of the lesion and it was not significant (Table 5).

Two patients experienced mild abdominal discomfort effects. All the patients tolerated the drug well. None of the patients had withdrawn due to adverse effects.

**DISCUSSION:**

Oral submucous fibrosis is a chronic debilitating disease of the oral cavity characterized by inflammation and progressive fibrosis of the submucosal tissues (lamina propria and deeper connective tissues). Oral submucous fibrosis results in marked rigidity and an eventual inability to open the mouth.$^{1,2}$ The buccal mucosa is the most commonly involved site, but any part of the oral cavity can be involved, even the pharynx.$^3$

The condition is well recognized for its malignant potential and is particularly associated with areca nut chewing, the main component of betel quid. 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).$^1$ 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 pathogenesis of the disease is not well established, but the cause

<table>
<thead>
<tr>
<th>Degree of difficulty</th>
<th>Number of patients ($n=48$)</th>
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<tbody>
<tr>
<td></td>
<td>At entry</td>
</tr>
<tr>
<td>Nil-0</td>
<td>09</td>
</tr>
<tr>
<td>Mild-1</td>
<td>12</td>
</tr>
<tr>
<td>Moderate-2</td>
<td>27</td>
</tr>
<tr>
<td>Severe- 3</td>
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*p<0.05 compared to “At entry” values

<table>
<thead>
<tr>
<th>Degree of hyperkeratosis</th>
<th>Number of patients ($n=40$)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>At entry</td>
</tr>
<tr>
<td>Nil-0</td>
<td>6</td>
</tr>
<tr>
<td>Mild-1</td>
<td>18</td>
</tr>
<tr>
<td>Moderate-2</td>
<td>16</td>
</tr>
<tr>
<td>Severe- 3</td>
<td>-</td>
</tr>
</tbody>
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*p<0.05 compared to “At entry” values

<table>
<thead>
<tr>
<th>Degree of pain</th>
<th>Number of patients ($n=42$)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>At entry</td>
</tr>
<tr>
<td>Nil-0</td>
<td>03</td>
</tr>
<tr>
<td>Mild-1</td>
<td>14</td>
</tr>
<tr>
<td>Moderate-2</td>
<td>12</td>
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<tr>
<td>Severe- 3</td>
<td>13</td>
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</tbody>
</table>

*p<0.05 compared to “At entry” values

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Table 2: Effect of Oxitard capsules in difficulty in opening mouth

Table 3: Effect of Oxitard capsules on hyperkeratosis

Table 4: Effect of Oxitard capsules in pain in patients of oral submucosal fibrosis
of oral submucous fibrosis is believed to be multifactorial. A number of factors trigger the disease process by causing a juxtacapillary inflammatory reaction in the oral mucosa. Factors include areca nut chewing, ingestion of chilies, genetic and immunologic processes, nutritional deficiencies, and other factors.

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

In 3 separate but similar studies, keratinocyte growth factor-1, insulin like growth factor-1, and interleukin 6 expressions, 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. Further studies have shown that arecoline is an inhibitor of metalloprotease-2 and a stimulator of tissue inhibitor of metalloprotease, thus decreasing the overall breakdown of tissue collagen.

Flavanoid, catechin, and tannin in betel nuts cause collagen fibers to cross-link, making them less susceptible to collagenase degradation. This results in increased fibrosis by causing both increased collagen production and decreased collagen breakdown. 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. Chewing areca quid may also activate NF-kappaB expression, thereby stimulating collagen fibroblasts and leading to further fibrosis in persons with oral submucous fibrosis.

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. Further, a significant gradual increase in serum copper levels from precancer to cancer patients has been documented, which may have a role in oral fibrosis to cancer pathogenesis.

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.

Management of oral submucosal fibrosis include advising the patient to avoid chewing betel nut and tobacco, spicy foods and consumption of chilies should be minimal, to maintain proper oral hygiene. Specific treatment include steroids, placental extracts, IFN gamma, lycopene, pentoxyphylline, surgical excision, laser removal of the lesion etc.

Glycyrrhiza glabra has immunomodulatory effect. It is known to have anti-inflammatory, has a role in normalising hoarsness of voice.

The fruits of Vitis vinifera have anti-inflammatory and astrinrent activities. It is used to alleviate the thirst, relieve flatulence and as a mild laxative. As it alleviates pitta, it is salutary to curb burning sensation, agitation and thirst in fevers. The raisins are recommended as tonic in tuberculosis to regain the bodyweight. The raisins are commonly used as a tonic in convalescence.

In Ayurveda, Withania somnifera is considered a rasayana herb, having anti-stress, anti-anxiety, anti-inflammatory, anti-arthritis and anti-convulsive medicinal properties. Hence, it provides overall health and wellness. It also performs as rejuvenator, revitalizer, restorative and tissue builder. This herb is also considered an adaptogen which is an herb that works to normalize physiological function, working on the HPA axis and the neuroendocrine system.

Yashada bhasma contains processed zinc that plays a significant role in protein synthesis, in cell division and in wound healing. It has shown beneficial effects in acne and is known to have antiseptic and astrinrent properties.

Syzygium aromaticum has shown to have antigastric, prevents intractable hiccups, thirst, gastric distension.

Different parts of Mangifera indica have various properties like...
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anti-asthmatic, anti-septic, antiviral, cardiotonic, emetic, expectorant, hypotensive, laxative. Extracts of unripe fruits and of bark, stems and leaves have shown antibiotic activity. In some of the islands of the caribbean, the leaf decoction is taken as a remedy for diarrhea, fever, chest complaints, diabetes, hypertension and other ills.22

*Triticum sativum* or wheat is a good source of mineral nutrients. Wheat is a rich source of tocopherols with high vitamin-E potency that nourishes and prevents loss of moisture from the skin. The oil is used to tone and soften the lips and has a potent antioxidant activity. This protects the skin from scavenging free-radicals, prevents premature aging and reduces ultra violet rays induced damage. It helps in proper drainage of secretions from the sebaceous and other glands of the skin.23

*Daucus carota* is a rich source of vitamin A, which acts as an anti-septic and prevents putrescent changes within the body.24

*Emblica officinalis* is a rich source of vitamin C, which has anabolic, antibacterial and resistance building properties. Pre-treatment with *Emblica officinalis* selectively increases the increased the proliferation of splenic leukocyte to B cell mitogen, LPS and cytotoxic activity against K 562 cells indicating immunomodulating property.25 Preliminary antibacterial screening of aqueous, hexane and alcoholic extracts of *Emblica officinalis* against several pathogenic and opportunistic microorganisms shows encouraging antibacterial activity against test bacteria.26

**SUMMARY AND CONCLUSION:**

This study shows that Oxitard capsules used in cases of oral submucous fibrosis showed significant improvement in the symptoms like difficulty in opening the mouth, pain in the mouth and hyperkeratosis. There was a mild decrease in the size of the lesion through not significant. Oxitard was safe in the dose of two capsules twice daily for 3 months and well tolerated by the patients.

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**REFERENCES:**