Original Article

Effect of trans retinoic acid on patients with oral submucous fibrosis-randomized single-blind monocentric study

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Abstract

Various treatment modalities have been practiced for the suppression of premalignant conditions such as oral submucous fibrosis (OSMF) to prevent their differentiation into malignant lesions. Conventional treatment includes steroids, enzymes like hyaluronidase, trypsin, chymotrypsin and placental extracts which are advocated intralesionally and oral drugs like carotenoids, alpha lipoic acid, lycopene, vitamins, microelements and tea pigments have also been advocated. In this study, a total number of 30 patients with OSMF were taken and randomly divided into two groups with 15 patients each according to Khanna and Andrade group of classification 1995. Group 1 (test group) received the test drug Tretiome 20 mg, whereas Group 2 (control group) received an antioxidant lycopene 20 mg/day for a period of 1 month and the effect of the therapy with the changes in the symptoms was recorded every 1 week, 15 days and 30 days of follow-up. The result of this study showed an improvement in the mouth opening of the patients of test Group with a significant decrease in the burning sensation as compared to the control group ($P < 0.05$). Xerostomia and headache were the two most commonly seen side effects which were reported in the patients of the test group, of which headache was associated with the withdrawal symptom of habit cessation and xerostomia was taken care by increase in hydration.

Keywords: Hyalauronidase, intralesional, oral submucous fibrosis, randomized, trans retinoic acid

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INTRODUCTION

According to the WHO, premalignant disorders include leukoplakia and erythroplakia, palatal lesion because of reverse cigar smoking, oral lichen planus, oral submucous fibrosis (OSMF), discoid lupus erythematosus, hereditary disorders such as dyskeratosis congenita and epidermolysis bullosa.[1]

OSMF is a premalignant condition, mainly occurring in the Indian subcontinent which results in the loss of tissue mobility and marked rigidity due to which there is eventual inability to open the mouth because of progressive juxtaepithelial fibrosis of the oral soft tissues [Figure 1].[2] The incidence of OSMF is prevalent in the areas of Southeast Asia. In India, the prevalence increased over the

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past four decades from 0.03% to 6.42%.[3,4] Data published earlier reported an estimate of 5 million OSMF patients in India.[5] OSMF is seen commonly in males between 20 and 40 years of age. The common sites involved are buccal mucosa, labial mucosa, retromolar pads, soft palate and floor of the mouth.[6]

The causative factor for the disease is the habit of chewing areca nut and betel quid or substitute.[7] The clinical presentation of OSMF is mostly the burning sensation, blanching and stiffening of the oral mucosa and oropharynx, and trismus. Appearance of the vertical fibrous bands in the buccal mucosa, faucial pillars and the lips are also evident in the advanced stages.[1] The etiology and the pathogenesis of this entity is not well known, although several hypotheses have been put forward such as areca nut chewing, green chilli, nutritional deficiency, genetic susceptibility, autoimmunity and collagen disorders.[8] The atrophic epithelium apparently predisposes to the development of a squamous cell carcinoma in the presence of carcinogens. In a long-term follow-up study, the annual malignant transformation rate was approximately 0.5%.[9]

There are various treatment modalities formulated for OSMF that are based on the degree of clinical involvement. Mild OSMF is reversible, whereas moderate-to-severe OSMF is irreversible.

Conventional treatment includes steroids, enzymes like hyaluronidase, trypsin, chymotrypsin and placental extracts advocated intralesionally along with oral drugs like carotenoids, Alpha lipoic acid, lycopene, vitamins, microelements and tea pigments have been advocated.[10,11]

The OSMF is associated with impaired nutritional status therefore supplements of multiple micronutrients such as zinc, Vitamin A, B and C, iron, folic acid, copper, calcium and manganese have been helpful.

The traditional treatments include local external glucocorticoid, calcineurin inhibitor, local and systemic retinoids, PUVA irradiation and photochemical therapy and so on.

Physiotherapeutic treatment includes the placement of tongue spatula in between the teeth with increase in the number of spatula in every 5–10 days for increase in mouth opening.[12,13]

Surgical modalities of oral submucous fibrosis remain controversial.[14] Surgical treatment include following limitations such as Inadequate harvesting of BFP due to atrophy in severe cases, esthetic morbidity in terms of postoperative scar, Dysphasia, Disarticulation, Risk of postoperative aspiration, Limited reach and coverage by the flaps, hair growth on flaps, donor site morbidity, secondary debulking procedures and post op contractures of flaps etc.[15]

Several new modalities have been carried out for the effective management of OSMF such as gamma interferon,[16] 8 pentoxyfilline having vasodialating and anti-inflammatory properties,[17] spirulina which is a blue green algae found to be rich in carotenoids having antioxidant property with high amount of beta carotene and superoxide dismutase[18-20].

Hence, the study was carried out to evaluate the efficacy of a newer drug tretinoin that contains trans retinoic acid (RA) which are chemopreventive agents derived from Vitamin A, which can be either natural or synthetic and their main role is to suppress cellular mitosis. It also prevents the malignant transformation, differentiation and proliferation of the epithelial cells, as well as their induction of apoptosis.[21]

Vitamin A derivatives, i.e., trans RA, modulates growth and differentiation of cells and its deficiency enhances susceptibility to carcinogenesis. In this study, chemopreventive mechanism of action (pharmacology) of Vitamin A is discussed, and evaluated the impact of trans RA on the treatment of OSMF of oral cavity and also accessed the toxic effect of the test drug.,[22]

MATERIALS AND METHODS

We have conducted a study with the aim to evaluate the efficacy of a drug tretinoin (supplement of Vitamin A) in the form of soft gel capsule containing trans RA and evaluate the quality of life in patients with Grade I and Grade II OSMF with the objective to evaluate the effect of trans RA in the treatment of OSMF, a premalignant condition in the oral cavity.

The study was conducted in the Department of Oral and Maxillofacial Surgery at I. T. S – Center for Dental Studies and Research, Muradnagar, Ghaziabad, after the ethical approval.

The patients with the complaint of difficulty in mouth opening were addressed along with the previous history of present illness. Any relevant medical history and drug allergy was ruled out. An elaborated habit history was noted including chewing habits, type, form, brand used, frequency and duration of chewing, site of keeping the quid, duration

and whether the quid was swallowed or spit out followed by the thorough clinical examinations.

After the confirmation of the lesion, clinically, the patient was advised routine blood investigations on initial visit for each subject. With the combined efforts of specialized diagnostic team of oral pathology and oral and maxillofacial surgeons along with the relevant collected data, the final diagnosis of OSMF was made.

The patients were explained about the type of treatment, the possible result of the treatment therapy and the complications associated and the post-therapy result. Informed consent was obtained by the patients for carrying out the treatment therapy and the results of the therapy were recorded in every 1 week, 15 days and 30 days of follow-up for 1 month of the therapy.

Patients were actively discouraged from consuming the identified etiologic factors, such as pan masala, gutkha, betel quid, tobacco and other chronic irritants such as hot and spicy food. Patients with anemia were treated and encouraged to eat a well-balanced diet. Impacted or malposed third molars having possible correlation with the prognosis of OSMF treatment were removed. All possible foci of infections were eradicated. Correction of local irritants, such as a sharp tooth, was performed. Fractured and carious teeth were restored. Oral prophylaxis was provided. Patients were assessed after 2 weeks; and after they gave assurance that they had suspended the habit as instructed, further management was continued.

Selection criteria

Inclusion criteria

Patients are divided into Group I and Group II according to Khanna and Andrade classification 1995. Group I Patients: Very early cases: Common symptom is burning sensation in the mouth, acute ulceration and recurrent stomatitis and not associated with mouth opening limitation and Group II Patients: Early cases— Buccal mucosa appears mottled and marble like, widespread sheets of fibrosis palpable, interincisal distance of 26–35 mm.

Exclusion criteria

Exclusion criteria were subjects with hypertension, diabetes mellitus, anemic stomatitis, radiation fibrosis, scleroderma, immunosuppressive diseases, peptic ulcer bleeding disorders, cardiac disorders and pregnant women (hazardous to fetus). Patients who have received treatment of oral submucous fibrosis before. Patients who were hypersensitive to the study drugs. Patients falling under the Group III and Group IVA and B of Khanna Andrade group of classification 1995 According to which-Group III: Moderately advanced cases—Trismus, interincisal distance of 15–25 mm, buccal mucosa appeal's pale firmly attached to underlying tissues, atrophy of vermilion border, vertical fibrous bands palpable at the soft palate, pterygomandibular raphe and anterior faucial pillars. Group IVA: Advanced 7 cases—severe trismus, interincisal distance of <15 mm, 8 thickened faucial pillars, shrunken uvula, restricted tongue movement, presence of circular band around entire lip and mouth. Group IVB: Advanced cases – presence of hyperkeratotic leukoplakia and/or squamous cell carcinoma were all excluded.

A total number of 30 patients with OSMF falling under Grade I and II of Khanna and Andrade group of classification 1995 were enrolled in this study. These patients were randomly divided into two groups 1 and 2 with 15 patients each.

Group 1 (test group) received the test drug Tretiome 20 mg with the following drug details.

- Brand name – Tretiome
- Drug name – Tretinoin
- Composition – Each soft gel capsule contains tretinoin 20 mg
- Mode of administration – Oral
- Availability – Tretiome is available in a packing of 30 capsules per container.

A simple random allocation method had been applied. The drug was given in a concealed packing.

Group 2 patients (Control group) received an antioxidant lycopene 20 mg/day which is mostly available in capsule and softgel form taken 10 mg twice daily with meals.

Each patient was reviewed up to 1 month at specific time intervals of 1 week, 15 days and 30 days and various parameters were assessed before, during and after the therapy.

The objective and subjective variables include:

a. burning sensation recorded on visual analogous scale[23] [Figure 2]
b. measurement of maximum mouth opening (distance between the maxillary and mandibular central incisors on maximum opening using vernier caliper or metallic scale in millimeters[23]) [Figure 3]
c. development of pain and soreness
d. ulceration, if any
e. mastication difficulty, if any

f. speech and swallowing problems
g. xerostomia
h. movement of fibrotic areas
i. any toxic effect of the drug
j. patient's overall quality of life
k. relapse rate after discontinuation of the drug (evaluated after 3 months)

Patients are advised to report immediately in case of any adverse drug reaction. Each patient was reviewed up to 1 month at specific intervals and the data obtained were assessed statistically by using SPSS Software Jenome Biophar pvt. Ltd. IBM , IL Chicago. Pre- and posttreatment comparison was done individually for each group and also among the groups.

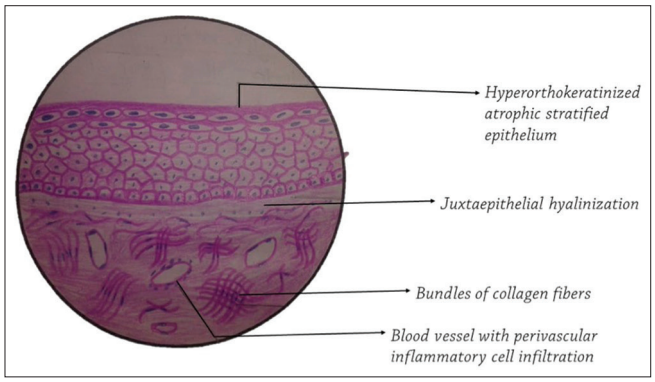


Figure 1: OSMF histopathological digram

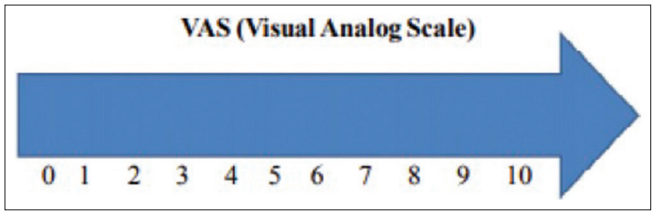


Figure 2: Visual analog scale

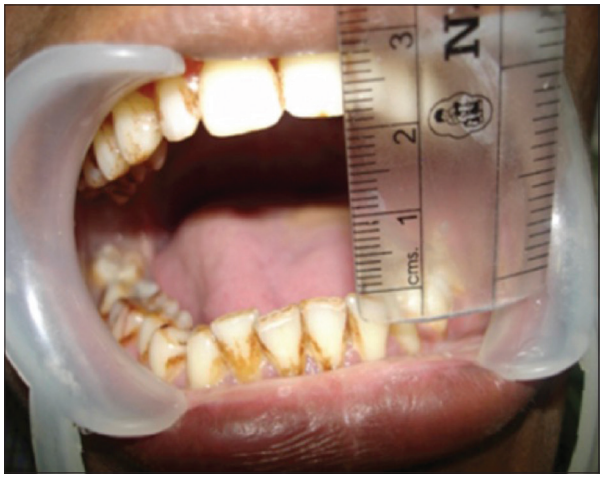


Figure 3: Mouth opening measurement with graduated scale

RESULTS

It was a single-blinded study, only the patients were blinded and were unaware of the treatment they received. During the study period (July 2017 to January 2019), there were a total of 30 patients, out of which 15 patients underwent conventional lycopene therapy, whereas the other 15 patients underwent test drug therapy with Tretiome available as CA ATRA-10 (all-trans RA) in the market for the treatment of Grade I and Grade II OSMF.

The result of this study showed an improvement in the mouth opening of the patients of test Group with a significant decrease in the burning sensation as compared to the control group.($P < 0.05$).

Simple randomization method has been used to divide the patient into two groups.

During the follow-up of each patient, the data collected revealed a significant improvement in the interincisal opening of the patients in Group I as compared to Group II, suggestive of a decrease in the fibrous bands and increase in the flexibility of cheek mucosa, whereas very mild improvements were visible in the control group patients.

There was a marked reduction in the burning sensation [Graph 1] on having spicy food and condiments in the patients on Tretiome from 70% of patients pre treatment to 10% of patients post treatment which ultimately decreased the difficulty of swallowing [Graph 2], pain and soreness in the mouth.

There was no significant difference seen in the movement and size of the fibrotic bands in the pre- and posttreatment patients in the test group but have shown the mean difference of 60000 ± 1.15662 preoperative patients and mean difference of 16.40000 ± 18.54556 after 30 days of the treatment when compared from test and control group.

There was no ulceration observed in the oral mucosa in patients undergoing the Tretiome therapy, whereas only headache was observed in 12 out of 15 patients as a side effect with the possible explanation being the withdrawal symptoms due to habit cessation, on the other hand, there were no such side effects seen in the control group patients.

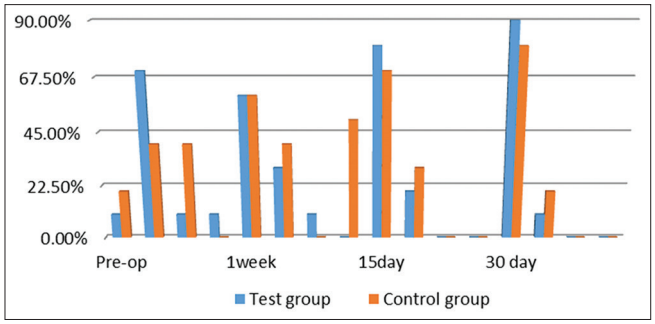
About 80% of patients showed symptoms of xerostomia post therapy in the test group, whereas none of the patient showed signs of xerostomia in the control group [Graph 3].

The quality of life significantly improved due to better mouth opening and decrease in burning sensation. None of the patients showed relapse after the discontinuation of the drug and no toxic drug reaction was seen during and after the drug therapy.

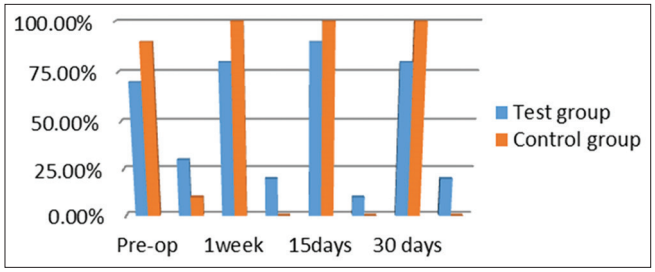
DISCUSSION

The primary objective of the treatment of OSMF is to reduce the severity of disease and prevent malignant transformation. Conservative line of management including various drugs or their combination such as steroids, hyaluronidase, placental extracts, collagenase and nutrient supplements to surgical management such as bands excision and grafting have been used to relieve trismus and improve function (Warnakulasuriya and Ariyawardana, 2016).

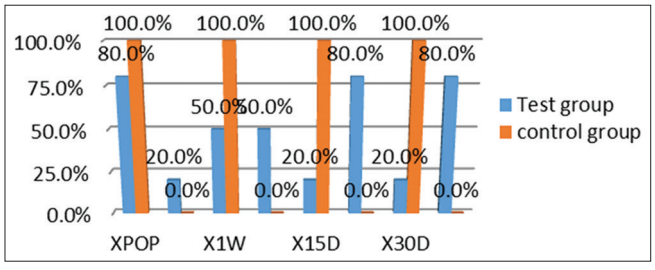
According to J P Caniff, medical management of OSMF is both empirical and unsatisfactory, while treatment with vitamins was ineffective in improving trismus as stated by Lai *et al.* According to Rehana Maher *et al*., multiple micronutrients and minerals showed significant improvement in symptoms with 41% of cases showing some improvement in mouth opening, contrary to which RM Borle and SR Borle showed improvement in symptoms of OSMF with Vitamin A but not in mouth opening.



Graph 1: Percentage frequency distribution of different categories of burning sensation at different time intervals in test and control group



Graph 2: Percentage frequency distribution of difficulty in swallowing at different time intervals in test and control group



Graph 3: Frequency distribution N (%) of presence of xerostomia at different time intervals of 2 groups

Kaugars and Silverman[22] found improvement in the stiffness of the oral tissue in 66.7%, 83.7%, 91.7% and 70.8% of patients treated with dexamethasone, hyaluronidase, a combination of hyaluronidase and dexamethasone and Placentrex, respectively, for 10 weeks.

Retinoids are a group of naturally occurring and synthetic analogue of Vitamin A which suppresses the carcinogenesis in various epithelial tissues and it exhibits effective clinical trials on chemoprevention of oral leukoplakia, secondarily primary tumors in the aerodigestive tract and skin tumors in Xeroderma Pigmentosa patients.

The usefulness of Vitamin A in the treatment of skin diseases has been limited by the inconsistency of the therapeutic response and by the toxicity at pharmacological concentrations. The search of more suitable compounds has led to the synthesis of structural analogs of retinol or RA with increased effectiveness and specificity, combined with lower levels of toxicity.[21]

Retinol is derived in the embryo from the mother which is basically useful in the eye development during the embryonic life. The retinol supplement undergoes a series of irreversible oxidation reactions when it crosses the cell membrane in the presence of ADP and leads to the formation of retinaldehyde which further forms RA which passes freely through the cell membrane.[21] The nucleus of the cell consists of RA-binding proteins called cellular RA-binding protein which are limited in number because of which not all the RA molecules that cross the cell membrane attach to the receptor; therefore, the free RA molecule disintegrates and therefore prevents its toxicity.[24]

Other Vitamin A supplements commonly used were the Cis-form, whereas Tretiome is the transform of RA used in our study with the advantage of being less toxic, but long-term usage may be harmful with several side effects of topical application such as it evokes neurogenic inflammation to induce skin irritation, pruritus, erythema, dryness and when used systemically, it can cause headache, joint pain, inflammatory back pain, etc.

CONCLUSIONS

The encouraging results should prompt a clinical trial on more number of patients to broaden the therapeutic usefulness and applications of our most ancient treatment agents Vitamin A for OSMF patients. This baseline study gives scope for further studies with the systemic use of all forms of RA available for the treatment of OSMF and also for research in the use of drug as a formulation that can be administered locally into the fibrous bands to confirm the above results.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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