Original Article

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Dentistry Section

Efficacy and Safety of Intralesional Xantinol Nicotinate in the Treatment of Various Stages of Oral Submucous Fibrosis

UDITA SINGH

ABSTRACT

Introduction: Oral Submucous Fibrosis (OSMF) is one of the most prevalent potentially malignant disorders seen in South east population since ages. Despite the extensive amount of research held in this field, its treatment still remains a challenge. In this study, we present our experience in successfully managing OSMF with intralesional injections of a peripheral vasodilator namely xantinol nicotinate.

Aim: To determine the efficacy and safety of intralesional xantinol nicotinate in the treatment of various stages of OSMF.

Materials and Methods: This parallel, prospective, clinical study included 60 patients clinically diagnosed with oral submucous fibrosis divided into two groups. Group I patients were subjected to intralesional xantinol nicotinate injections bi-weekly for a period of four months while Group II patients were given intralesional saline injections biweekly for four months. All the patients were instructed to perform home mouth opening physiotherapy exercises. At each visit, parameters like increase in interincisal distance, cheek flexibility, tongue protrusion and relief from burning sensation and any side effects were measured and recorded. The drop out figure was zero.

Results: At the end of four months, in Group I, there was an increase in mean values of interincisal distance, cheek flexibility and tongue protrusion ($p<0.001$). For burning sensation a significant decrease in mean value was observed ($p<0.001$). Whereas, in Group 2 the difference between pre-treatment and post-treatment values was not statistically significant ($p>0.001$). On comparing the results of Group 1 and Group 2, statistically significant difference was observed ($p<0.001$).

Conclusion: Xantinol nicotinate, a peripheral vasodilator, when injected intralesionally in OSMF patients not only provides relief from burning sensation but also results in increased mouth opening, tongue protrusion and cheek flexibility.

Keywords: Adjunct, Antioxidant, Potentially malignant disorder, Peripheral vasodilator, Supportive therapy

INTRODUCTION

Oral Submucous Fibrosis (OSMF) is a well-recognised, potentially malignant disorder affecting oral cavity and pharynx. It is commonly found in South and Southeast Asian population especially affecting those in Indian subcontinent. The history of this disease trails to antiquity when it was first described by Sushruta in 400B.C. It was first reported from India in 1953 and now has become an epidemic with 2.5 million people being affected per year with this disease [1].

Pindborg et al., proposed a definition for OSMF which includes almost all its features, which says OSMF is "an insidious chronic disease affecting any part of oral cavity especially pharynx. Although it may be preceded and or associated with vesicle formation it is always associated with juxtaepithelial inflammatory reaction followed by fibroelastic changes of lamina propria with epithelial atrophy leading to stiffness of oral mucosa causing trismus and inability to eat" [2]. The aetiology of this disease is multifactorial and its pathogenesis is still elucidated. The predisposing factors are consumption of areca nuts, tobacco products and excessive use of chillies, nutritional imbalance including decreased iron content, genetic susceptibility and auto immune basis. The strongest risk factor for OSMF is chewing of betel quid containing areca nut. Few studies on OSMF patients showed decreased levels of serum iron, vitamin B complex and folic acid [1]. Pain is usually not a symptom of the disease. It is characterised by gradual reduction in mouth opening and tongue movements which in turn lead to difficult phonetics and dysphagia. Restricted mouth opening is caused by progressive build-up of fibrous bands in the cheeks and adjacent structures of mouth [3]. Treatment of OSMF still remains a challenge. Despite the advancements in treatment modalities, OSMF till date remains a disorder that causes irreversible and irreparable damage to the tissues. Thus, the treatment is aimed in relieving the patient from burning sensation and restricted mouth opening and tongue movements.

Current medical treatment modalities include the use of micro-nutrients and minerals (Vitamin A, B complex, C, D, E, iron, copper, calcium, zinc, magnesium selenium etc.), lycopene, turmeric, interferon, steroids, placental extracts and physiotherapy. But each one has its own limitations [1,2].

Pathologically, excessive deposition of collagen fibers leads to occluded blood vessels which in turn lead to hyper-coagulabilty of blood. Hyper coagulated blood acts as an obstacle in the path of nutrients and therapeutic substances to reach the affected tissues. This may be one of the prime reasons behind failure of drug treatment in OSMF. Extrapolating this reason, we hypothesized that xantinol nicotinate, a peripheral vasodilator when injected intralesionally may prove to be highly effective in the treatment of OSMF.

Hence, the aim of the present study was to determine the efficacy and safety of intralesional xantinol nicotinate in the treatment of various stages of OSMF.

MATERIALS AND METHODS

Study Design: This parallel, concurrent, randomised clinical study was conducted in the Department of Oral Medicine and

Maxillofacial Radiology, Kothiwal Dental College and Research Centre, Moradabad, Uttar Pradesh, India, from December 2012 to March 2014. Ethical approval was obtained from the Ethical Committee of Kothiwal Dental College and Research Centre, Moradabad under M.J.P. Rohilkhand University, Bareilly, Uttar Pradesh, India. Sample size was calculated using the formula: n= [Zα/2^ơE] [2]. Thus, the study included 60 patients clinically diagnosed with OSMF. Pregnant patients and those with history of recent myocardial infarction, cerebrovascular accidents, severely compromised cardiac function, and caffeine or theophylline intolerance were not included in the study. Patients who were hypersensitive to the drug 'xantinol nicotinate' or with positive drug history of anticoagulants were also excluded. Prior to the study, an informed written consent was requested from every participant. After taking written informed consent, detailed case history and thorough clinical examination, the patients were randomly divided into control group and experimental drug group. Staging of OSMF was done according to the criteria proposed by More CB et al., in 2012 which are as follows [4]:

CLINICAL

STAGE I (S1): Stomatitis and or blanching of oral mucosa.

STAGE II (S2): Presence of palpable fibrous bands in buccal mucosa and/or oropharynx with or without stomatitis.

STAGE III (S3): Presence of palpable fibrous bands in buccal mucosa and/or oropharynx and in any other part of oral cavity with or without stomatitis.

STAGE IV (S4)

a. Any one of the above stage with premalignant lesions like leukoplakia, oral erythroplakia etc.

b. Any of the above stages with oral carcinoma.

FUNCTIONAL

M1: Interincisal mouth opening is up to or more than 35mm.

M2: Interincisal mouth opening is between 25mm-35mm.

M3: Interincisal mouth opening is between 15mm-25mm.

M4: Interincisal mouth opening is less than 15mm.

Before proceeding with the treatment, blood pressure monitoring, pulse recording, hypersensitivity test (for xantinol nicotinate) and blood test(total leucocyte count, differential leucocyte count, bleeding time, clotting time, hemoglobin percentage and platelet count) were carried out.

Parameters Studied: Baseline values of inter-incisal distance, tongue protrusion, cheek flexibility and burning sensation (using visual analog scale) were recorded. Inter-incisal distance is the distance between the mesio-incisal angle of maxillary central incisor and mandibular central incisor at maximum mouth opening. It is measured by keeping a ruler vertically and asking the patient to open the mouth to the maximum and noted in millimetres. Tongue protrusion is the distance between the mesio-incisal angles of mandibular central incisor to the tip of tongue when maximally extended with mouth wide open. Burning sensation is the subjective assessment of patient's pain expressed in terms of 0-10 rated numeric scale, where '0' means no pain and '10'means maximum pain. Cheek flexibility is measured as the distance between two points marked on the ala-tragus line. If we divide the ala-tragus line in three equal halves, then V2 is the point marked at 1st one-third from the angle of mouth. V1 is the same point when the patient is instructed to blow his cheeks. The difference between these two points is called cheek flexibility (V2-V1).

Treatment Modalities: In Group I, the patients were given intralesional injections of xantinol nicotinate (Trade name: Complamina, manufactured by German Remedies, division of Cadila Healthcare Limited). Thirty age and sex matched patients comprised the control group. They were subjected to intralesional saline injections for four months. All the patients were instructed to perform mouth opening physiotherapy exercises at home.

Assessment for Efficacy of Treatment: At each follow-up visit, improvement in mouth opening, tongue protrusion, cheek flexibility, and relief from burning sensation was measured and recorded in performa.

Assessment for Safety of Treatment: Careful monitoring of patients was done by the investigator during and after the injection of the drug. Following the treatment, the patients were made to sit comfortably in the waiting lounge and observed for any side effects of the drug. The side effects were noted in the performa and appropriate treatment given.

STATISTICAL ANALYSIS

The data was tabulated using Microsoft excel 2010 and statistically analysed. The statistical tests employed were chi-square test, paired t-test and student t-test. Chi-square t-test was used as a test of goodness of fit. Paired t-test was used to compare intragroup values while student t-test was used for intergroup comparison. The confidence interval was 95% and level of significance was 0.05. The statistical analysis was done using Statistical Package for Social Sciences (SPSS) Version 15.0. The values were represented in number (%) and mean±SD.

RESULTS

In the study, maximum number of patients were in OSMF Stage II (46.7%) followed by those in Stage III, I and IV [Table/Fig-1]. Post-treatment assessment was made at two and four months respectively. At two months post-treatment interval, it was observed that relief from burning sensation was significantly higher in Group I as compared to Group II ($p<0.001$). Statistically, no significant difference between two groups was observed with respect to other parameters studied ($p>0.05$) [Table/Fig-2].

At four months post-treatment interval, a statistically significant difference was found between two groups. It was observed that mean inter-incisal opening ($p<0.05$), cheek flexibility ($p<0.05$) and relief from burning sensation ($p<0.001$) in Group I was significantly higher as compared to that in Group II. Statistically, no significant difference between two groups was observed with respect to mean tongue protrusion ($p=0.443$) [Table/Fig-3].

Stage Wise Comparison: At four months post-treatment interval, it was observed that mean percentage increase in interincisal

S.No.	Stage	Group I		Group II	
		No.	%	No.	%
1.	I	6	20.0	6	20.0
2.	II	14	46.7	14	46.7
3.	III	7	23.3	7	23.3
4.	IV	3	10.0	3	10.0

[Table/Fig-1]: Showing distribution of patients in the study. Majority of the patients belonged to stage II, followed by stage III, I and IV.
$\chi 2=0$ (df=3); p=1 where $\chi 2$ is chi-square test; df is degree of freedom and p is the level of significance.

S.No.	Parameter	Group I (n=30)		Group II (n=30)		Significance of Difference	
		Mean	SD	Mean	SD	"t"	"p"
1.	Inter-incisal opening (mm)	31.90	7.75	28.53	9.02	1.550	0.127(ns)
2.	Tongue protrusion (mm)	23.00	4.88	23.93	5.77	-0.677	0.501(ns)
3.	Cheek flexibility (mm)	3.53	1.04	3.07	0.87	1.885	0.064(ns)
4.	Burning sensation (VAS)	3.60	0.93	6.90	1.52	-10.154	<0.001(s)

[Table/Fig-2]: Intergroup comparison of clinical parameters after two months of treatment
SD is standard deviation, t is paired t test and p is the level of significance.
ns: not significant; s: significant.

S.No.	Parameter	Group I (n=30)		Group II (n=30)		Significance of Difference	
		Mean	SD	Mean	SD	"t"	"p"
1.	Inter-incisal opening (mm)	36.07	7.75	29.40	8.91	3.093	0.003(s)
2.	Tongue protrusion (mm)	24.97	5.08	24.23	6.06	0.508	0.614(ns)
3.	Cheek flexibility (mm)	4.00	1.14	3.07	0.91	3.500	0.001(s)
4.	Burning sensation (VAS)	0.37	0.61	6.53	1.66	-19.127	<0.001(s)

[Table/Fig-3]: Intergroup comparison of clinical parameters after four months of treatment.
SD is standard deviation, t is paired t test and p is the level of significance.
Ns: not significant; s: significant

Interincisal Distance			
	Pre-op (Mean±SD)	Post-op (Mean±SD)	Difference (%)
Stage I	38±2.52	44.33±1.50	63.33
Stage II	28.71±2.61	37.07±4.48	83.57
Stage III	19.00±2.38	25.00±2.58	60
Stage IV	12±2.64	17.33±4.16	53.33
Tongue Protrusion			
Stage I	30.66±1.03	34.5±1.04	38.40
Stage II	24.14±2.17	31.64±2.70	74.98
Stage III	13.42±2.99	18.71±4.02	52.90
Stage IV	8.00±2.01	11.66±1.52	36.66
Cheek Flexibility			
Stage I	31.16±1.32	33.33±1.86	21.66
Stage II	24.21±1.88	29.57±2.84	53.57
Stage III	14.71±1.97	20.42±4.15	57.14
Stage IV	8.00±2.00	11.33±3.51	33.33
Burning Sensation			
Stage I	5.66±0.81	0.83±0.75	48.34
Stage II	6.35±1.00	0.64±0.74	57.08
Stage III	6.85±1.06	2.42±1.51	44.29
Stage IV	8.33±0.57	4.33±1.15	40.03

[Table/Fig-4]: Stage wise comparison in group I at the end of four months.

opening was maximum in Stage II and minimum in stage IV patients. For tongue protrusion, mean percentage increase was maximum in Stage II and minimum in Stage IV. For cheek flexibility, change was random in nature and did not show a significant association with stage of disease. For burning sensation maximum percent reduction was seen in Stage II patients [Table/Fig-4].

Approximately 7% patients (2 patients) in Group I reported vesicle formation at the injection site on the left buccal mucosa on the next day after giving injections. Symptomatic treatment in form of mouthwash containing benzydamine hydrochloride (0.15g/100ml) was started. Both the patients showed complete recovery within five days.

DISCUSSION

In this parallel, concurrent, randomised control study, we tried to investigate the efficacy of intralesional xantinol nicotinate, a peripheral vasodilator in the treatment of OSMF. To the best of our knowledge this is the first study in which the intralesional xantinol nicotinate has been tried in the management of OSMF. Xantinol nicotinate, pharmacologically, is classified as a vasodilator belonging to the class of purine derivative agents used as peripheral vasodilators. It is one of the most potent forms of niacin (B3) which easily passes through cell membrane. Its general properties are similar to those of nicotinic acid to which it is slowly hydrolysed [5]. It has been employed for its vasodilator action in treatment of cerebral and peripheral vascular disorders. Nutritive microcirculation is enhanced by increasing erythrocyte elasticity, improving the flow properties of the blood and reducing peripheral resistance while simultaneously improving cardiac function [6,7]. Results of one clinical study concluded that xantinol nicotinate could improve tumour perfusion. Efficacy of both radiotherapy and chemotherapy treatment was improved after xantinol nicotinate pre-treatment [7].

Nicotinic acid is a well-known vasodilating agent and xantinol, a theophylline derivative enhances its actions. In a study done by Cheng et al., it was found that vasodilating effect of nicotinic acid is due to increased synthesis and secretion of prostaglandin D2, a type of prostacyclin in the serum [8]. Prostaglandin D2 directly stimulates vasodilation. Bieron et al., supports these findings and states that nicotinic acid also increases the release of nitric oxide, another endogenous vasodilator. They further stated that xantinol enhances the physiological response to these two mediators, increasing their secondary messenger's actions [9]. Aside from the antiplatelet activities, xantinol nicotinate was found to be fibrinolytic by two mechanisms: reduction of fibrinogen levels and increase in tissue plasminogen activators, which dissolves clot [10]. Thus, in this manner relief from burning sensation and increased interincisal distance is achieved. Increased tonicity of the muscles in turn leads to improved tongue protrusion and flexibility of the cheeks.

The adverse effects of xantinol nicotinate which have been reported in literature include peripheral flushing, gastrointestinal upset, vertigo, rashes and flu like symptoms and blurred vision [5,7]. In our study, transient peripheral flushing and warmness of upper trunk was noted in approximately 90% patients that could be easily managed by dose reduction or on prolonged use. These symptoms were noted by subjective assessment of the patients. Similar side effects were also noticed by Rajendran R et al. They conducted a pilot study to assess the effect of pentoxifylline, a peripheral vasodilator in 15 OSMF patients. In this study, patients were given 400mg pentoxifylline orally thrice daily for seven months. They reported that approximately 3% patients suffered from dyspepsia, nausea and/ or vomiting and 1% patients reported bloating, flatus and bleeding [3]. Nausea and vomiting were not observed in our study patients as we injected xantinol nicotinate intralesionally. Two patients in Group I reported vesicle formation at the injection site on the left buccal mucosa on the next day after giving injections. However, complete resolution was seen on symptomatic treatment. Similar vesicles were also reported by Mehta V et al. They treated a patient of thromboangitis obliterans with inj. xantinol nicotinate IV 3000mg, 4500mg and 6000mg respectively in 250ml of normal saline over three consecutive days. On day 2, patient developed itchy vesicles and edema on the left forearm at the site of IV cannula. Diffuse erythema of face, trunk and proximal extremities were also noted. Patients were advised to stop the injection and were treated symptomatically with anti-histaminics and topical steroids with which the patient recovered completely in about a week [7].

LIMITATION

Less number of patients and lack of histopathologic confirmation of treatment's outcome are the two major limitations of the study. Based on the findings of this study we propose intralesional xantinol nicotinate as an efficacious, cost effective and safe drug for recalcitrant cases of OSMF. As a future prospect, the author is conducting a study to compare the efficacy of the xantinol nicotinate with corticosteroids in OSMF.

CONCLUSION

Intralesional injections of xantinol nicotinate are promising treatment modality for OSMF. However, more number of large clinical trials are required to establish its efficacy.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Lecturer, Department of Oral Medicine and Radiology, Kothiwal Dental College and Research Centre, Moradabad, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Udita Singh,
A116 Jigar Colony, Moradabad-244001, Uttar Pradesh, India.
E-mail: udita73singh@gmail.com

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