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Comparative study between PRP and hyaluronidase injection on fibrous site for OSMF

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Abstract

Background: OSMF is one of the disorders affecting oral cavity, and sometimes pharynx. It is kind of potential malignant disorder associated with betel nut chewing and some nutritional deficiencies. Medical treatment of OSMF has been not completely systematized and no perfect and broadly accepted treatment is presently accessible for this condition.

Objective: To evaluate the efficacy of PRP and hyaluronidase injections for the management of OSMF.

Materials and Methods: Present study was carried out in 30 patients with OSMF of different clinical grade (Grade III, IV, V). The patients were administered with 0.5 ml of Hyaluronidase 1,500 IU was mixed in 1 ml of lignocaine as well as 0.5 ml of PRP (Platelets rich plasma) injected intralesionally in fibrosis of OSMF, once a week.

Results: Results of ANOVA suggested that after treatment with these two injections there were significant improvement or relief in symptoms were observed. Thus treatments significantly work to relief the symptoms. There was significant difference found between pre and post treatment (p value <0.05).

Conclusion: Treatment with hyaluronidase and PRP is an efficient mean of managing OSMF and can decrease the symptoms and provide relief to the certain extent.

Keywords: Oral submucous fibrosis, PRP, hyaluronidase, mouth opening, areca nut

Introduction

Oral Submucous Fibrosis (OSMF) is a precancerous stage of the oral mucosa. It is a chronic, insidious, generalized, and potentially malignant condition of oral cavity. Entire oral cavity is gradually affected by this condition which results into difficulty in opening the mouth. It is a chronic debilitating state with higher rate of morbidity as it results into progressive incapability to open the mouth, resulting in trouble in eating and thus leads nutritional deficiencies (Karemore and Motwani, 2012) [21]. This condition has been most commonly observed in all among the Indians and also to a slighter level in the other Asiatic people (Pindborg *et al.*, 1984) [1, 12].

Progression of this disease occur due to a chronic, negative change in fibroelasticity, characterized by burning sensation in the oral cavity, blanching, and stiffening of the oral mucosa and oropharynx which results into trismus and difficulty to open the mouth and consequently inability to eat. Symptoms of this disease relied on the development of the lesions and consequently affected sites (Nagraj *et al.*, 2018). However etiology of this disease is not specific but literature suggested that it is mainly occur due to too much consumption of spicy food and also may be due to the nutritional deficiencies like chronic iron and vitamin B complex deficiency, areca nut chewing habits (Joshi, 1953) [3].

Present work describes the comparative efficacy of Hyaluronidase vs PRP injection in OSMF patients. Hyaluronidase basically produced by breaking down of hyaluronic acid (the ground substance in connective tissue) which slow down the viscosity of intercellular cement substance. Better results were observed with respect to trismus and fibrosis (Coman *et al.* 1947) [4].

Whereas, PRP is most commonly observed to be used beneficially in soft and hard tissue healing (Marx *et al.*, 1998; Anitua, 1999) [5-7, 9]. As compared to the peripheral platelet counts, PRP contains 4 to 6 times the normal level of growth factors (Marx *et al.*, 1998) [5, 7, 9].

Normal blood range of human platelet counts are 150000/IL to 350,000/IL. Particularly, PRP (Platelets rich plasma) is a platelet concentration with as a minimum 1 000 000/IL in a 5-mL volume of plasma (Marx *et al.*, 1998; Marx, 2001) ^[5, 7, 9].

PRP is a ample supply of growth factors which play important role in wound healing via clot formation (Marx *et al.*, 1998) ^[5, 7, 9]. According to research, platelets once activated, it will release the alpha secretory granules at the site of injury (Anitua, 1999; Marx, 2001; Whitman *et al.*, 1997; Marx, 1999) ^[5-9]. Addition of thrombin and calcium chloride to PRP observed to be trigger the alpha granules to liberate the active growth factors i.e. platelet-derived growth factor, TGF- β , VEGF, insulin-like growth factor I, epidermal growth factor (EGF), epithelial cell growth factor, and TGF- β 1 and TGF β 2 (Marx *et al.*, 1998; Marx, 2001) ^[5, 7, 9]. These growth factors will stimulate undifferentiated mesenchymal stem cells at the site of wound and excite mitosis in these cells.

Hence this study was done to compare the effectiveness of intralesional hyaluronidase and PRP injections in the management of OSMF.

Materials and Methods

Present study was carried out in 30 patients with OSMF of different clinical grade (Grade III, IV, V). Clinically OSMF was diagnosed on the basis of symptoms of burning sensation in the mouth on eating of spicy or hot food, dryness of mouth, occurrence of vesicles oral ulcers in the

mouth, and unable to open the mouth opening. Patients who were found to be medically weak or compromised and those who have already gone through the earlier treatments were not involved in present study. Patients of different age group i.e. 21-30 years; 31-40 years; 41-50 years and 51-60 years, differ in severity of symptoms or clinical grading of OSMF were also checked for comparative efficacy of hyaluronidase and PRP after administration.

On the basis of severity of symptoms patients were divided into four groups (Table no 2). Records were made on the history of patients's personal habits specially for chewing habits, Period of use and symptoms like burning sensation and mouth opening were recorded. Intraorally, observations were done on blanching of oral mucosa, occurrence of vesicles and ulcers, palpable bands, alterations in tongue movement were recorded.

Platelet rich plasma was prepared from the patient's own blood in the same visit using a double spin technique, then 0.5 ml of PRP will be injected per 1 cm² at the site of fibrosis of OSMF. The patients were administered Hyaluronidase 1,500 IU was mixed in 1 ml of lignocaine. 0.5 ml of this solution was injected intralesionally in fibrosis of OSMF, once a week. Observation will be taken by measuring postoperative mouth opening each week and burning sensation using a visual analogue scale. ANOVA was done to compare pre and post treatment results. $P < 0.05$ was considered most significant.

Results and Observations

Table 1: Age wise distribution of OSMF patients and comparative efficacy of hyaluronidase and PRP injections

S. No.	Age (in years)	Clinical grade	Hyaluronidase vs PRP injection
1	21-30	III	Administration of PRP adequately work (with chances of reoccurrence)
2	31-40	IV	Hyaluronidase work better to relief the symptoms; However PRP is not as much effective as hyaluronidase
3	41-50	IV	Only hyaluronidase works
4	51-60	V	Only hyaluronidase works

*In more severe cases surgery is recommended

Table 2: Comparative efficacy of hyaluronidase and PRP injections in Relief of symptoms in different group (Total n =30)

S. No.	Group I (n=10) Relief of symptoms (%)		Group II (n=7) Relief of symptoms (%)		Group III (n=8) Relief of symptoms (%)	Group IV (n=5) Relief of symptoms (%)		
	A	B	A	B	A	B	A	B
1	95%	75%	88%	70%	85%	62%	45%	10%
P value	<0.05	<0.045	<0.048	<0.041	<0.044	<0.039	<0.045	<0.001

*A: Injection hyaluronidase 1500 IU, 0.5 ml injected intralesionally twice a week for 10 weeks.

B: 0.5 ml of PRP (Platelets rich plasma) injected per 1 cm² of eroded oral mucosa.

Group I= Burning sensation, dryness of mouth, vesicles or ulcer in the mouth without tongue Involvement.

Group II= including above symptoms+ reduction of mouth opening.

Group III= including above symptoms+ also tongue involvement.

Group IV= OSMF along with histopathologically proven cancer.

Results suggested that administration of PRP injection on fibrous site observed to be effective in middle age patients with the stage III of cancer (with pretty good ability to open mouth and tongue movement) (Table 1). Similarly, percentage of relief of symptoms associated with OSMF is more with hyaluronidase rather than PRP injection. However PRP itself is good for younger patients with mild symptoms but study suggested it is very difficult to manage OSMF in older age people with PRP injections. Hyaluronidase is best option to manage this disease to the certain level. But in last stage surgical removal is an only option.

Results of ANOVA suggested that after treatment with these two injections there were significant improvement or relief in symptoms were observed. Thus treatments significantly work to relief the symptoms. The entire treatment group showed statistically significant differences in p value.

Discussion

OSMF is a chronic premalignant condition of oral mucosa. Deposition of fibrous tissue in the submucosal layer of the pharynx, palate, fauces, cheek, lips, and esophagus (El-Labban and Cannif, 1985) ^[10] is most common cause of this condition. This disease is most common in Indians due to habits of consumption of the areca nut in flavoured

formulations or as a component in the betel quid chewed by the communities in these countries.

OSMF is recognized to be multifactorial in origin (Pundir *et al.*, 2010) [11]. Mechanism of development of OSMF involves enhanced collagen synthesis and concomitant reduction in breakdown of collagen (Murti *et al.*, 1995) [1, 12]. Several factors affected the fibrosis. One of the important factors is areca nut; this leads to the enhanced collagen production due to the synthesis of genetically diverse fibroblast. Due to unregulated Lysyl oxidase activity (in the presence of copper in betel nut), enhanced crosslinking of collagen in fibroblasts occur. Furthermore, this collagen structure is stabilized by catechin and tannins found in areca nut (Auluck *et al.*, 2008; Rajendran and Sivapathasundharam, 2012) [13, 14].

It was observed that all patients included in this study had the chewing habits of locally available areca nut and tobacco products. Blanching of the buccal mucosa, soft palate, palpable fibrous bands, decreased cheek flexibility, reduction in the mouth opening, and burning sensation were the clinical symptoms observed in all OSMF group (100% of the sample). In addition restricted mouth opening was a significant symptom in most of the patients involved in this study. Similar findings were also given by Guduru *et al.*, (2019) [15].

Results revealed that administration of PRP injection at the fibrosis site of OSMF is more significant in younger patients of Age 21-30 years with mild symptoms. This might be due to the production of one of the growth factor i.e. PDGF by platelets, which is recognized as an important protein for hard- and soft-tissue healing (Marx *et al.*, 1998; Barry and Murphy, 2004) [5, 7, 9, 16]. In addition, platelets serves as a greatest source of this specific growth factor, which enhance healing of injuries by enhancing granulation tissue development and subsequent mitosis division, vascular synthesis, macrophage activation, and concomitant activation of other growth factors (Marx *et al.*, 1998; Price *et al.*, 1991) [5, 7, 9, 17]. At the injury site, PDGF has been observed to be stimulated accumulation and migration of stem cells (Rudkin and Miller, 1996; Rosen, 2006) [18, 19]. Consequently leads the synthesis of matrix bone formation and angiogenesis by stimulating increased levels of VEGF (Rosen, 2006) [19]. This might lead activated soft-tissue healing just because of neovascularisation process taking place (Rosen, 2006) [19].

Findings suggested that administration of hyaluronidase is better in case of old age patients with inability to open mouth and tongue movement. However administration of both PRP and hyaluronidase individually is not permanent reversing of these conditions. Continuous administration with intermittent gap provide relief to burning sensation and other pain but as this disease is progressive in nature hence surgical methods employed to treat OSMF.

The patients can able to tolerate short and long term administration of hyaluronidase as well as PRP therapy in moderate dosages.

Hyaluronidase leads break down and dissolution of fibrous bands consequently given that relief from symptoms. It leads the breaking of hyaluronic acid, which is a ground matter of connective tissue, thus lessen the thickness of intracellular cement substance. Furthermore, the part of hyaluronic acid in collagen synthesis is also prohibited by the utilization of hyaluronidase. It is observed that,

hyaluronidase is able to provide improved results in patients with unable to open mouth (Kakar *et al.*, 1985) [20].

Thus results suggested that both the treatments have good efficacy but there administration and thus efficacy depends on severity and age of patients.

Conclusion

Findings of present study suggested that both the treatment regimens comprising of hyaluronidase as well as PRP are effective for the treatment of OSMF depends on age as well as severity of condition, both for improvement of mouth opening as well as reduction of burning sensation.

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