ORIGINAL RESEARCH

A Double Blind, Randomized, Comparative Evaluation of Efficacy of Prak-20 and Garlic in Oral Submucous Fibrosis - A Preliminary Study

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ABSTRACT

Oral submucous fibrosis (OSMF) is a potentially malignant condition, chiefly associated with the practice of chewing arecanut. Though numerous treatment modalities have been tried but all are palliative and have no curative value. Hence, present preliminary clinical trial was undertaken to evaluate the efficacy of PRAK-20; a herbomineral compound and Garlic in the management of OSMF. **METHODS:** Forty study subjects with OSMF were included in the study. Patients were divided into two groups with 20 subjects in each group. Group A received garlic, 2 pearls; thrice daily and Group B received one 500mg PRAK-20 capsule, three times a day for three months. Results were analyzed with SPSS 19.0 version using ANOVA, paired t- test, unpaired t- test. **RESULTS**: Garlic and PRAK -20 showed a statistically significant reduction in burning sensation by81.8% and 75.4% respectively, improvement in mouth opening by 3.5±0.1mm and 4.6±1.0 mm respectively and tongue protrusion by 4.4±0.1 mm and 4.9±1.5 mm respectively. Maximum mouth opening of 6mm and 10 mm was found in group A and B respectively. **CONCLUSION:** The parameters showed a significant improvement in both the groups. Though Garlic had shown better results in terms of reduction in burning sensation; PRAK-20 had shown better results in other parameters. Improvement in the clinical parameters obtained in our patients is a promising finding towards establishing the use of garlic and PRAK-20 as a therapeutic agent in OSMF.

KEYWORDS: Oral submucous fibrosis, PRAK-20, Garlic Pearls.

INTRODUCTION

Oral submucous fibrosis (OSMF) is a potentially malignant condition, which is associated with significant functional morbidity and an increased risk of malignancy. Epidemiological, in vitro experimental and clinical studies, have shown that chewing areca nut) is the major etiological factor for OSMF. Other etiological factors proposed are chillies, lime, tobacco, nutritional insufficiencies such as iron and zinc, immunological disorders, and collagen disorders.[1] OSMF has been reported mostly among Indians and other Asiatic. The prevalence ranges up to 0.4% in Indian rural population.

Chewing habits have prevailed in India for more than two millennia. At present, a multitude of chewing products that contain the main ingredients of betel quid, such as areca nut, chatechu and lime are available in the market. Many surveys conducted in India shows the association between the usage of gutkha and OSMF. A major alteration in betel quid/areca nut use transpired in India when factory made mixture of areca nut, lime, a catechin-containing substance, fragrance and tobacco was introduced to the market in small aluminium foil sachets. This product was termed gutkha. Chewing mixes that do not contain tobacco are termed as 'pan masala' and those containing tobacco as an additional ingredient are called 'gutkha'.

Management of OSMF is one of the challenges faced by the oral physicians as the etiologies are multiple and a proper treatment modality is not available. Different modalities have been tried and listed in the literature. To list a few; steroids[2], antioxidants,[3] enzymes like collagenase,[4] chymotrypsin,[5] and hyaluronidase,[6] peripheral vasodilators,[7,8] levamisole,[9] lycopene,[10] placental extracts,[11] immune milk,[12] Interferon-γ,[13] physiotherapy[14,15,] and surgical treatment[16] , yet they have been palliative and proven to be of minimal benefit.

Ayurveda is a form of alternative medicine, native to India and also one of the most primeval and methodical medicinal systems in the world. There are hundreds of herbs used throughout the world that are beneficial in various disorders. Herbs when used in their complete

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form are used by the body in an efficient manner. Garlic is one such therapeutic modality. It possesses immunomodulatory, antioxidant, anti-inflammatory and vasorelaxive properties that have been studied with good results.

Also, herbalists document that combination of herbs act synergistically and dilute the toxicity. And one such herbo-mineral compound is PRAK-20, which is a combination of 19 herbs having antifibrotic, anti-inflammatory, immunomodulatory and hematinic properties (Table1).

So the present study had been planned to evaluate and compare the efficacy of PRAK-20 and garlic in the treatment of OSMF.

Common name	Scientific name	Proportion
Sunthi	Zingiber officinale	12.5 mg
Maricha	Piper nigrum	12.5 mg
Pippali	Piper longum (fruit)	12.5 mg
Haritaki	Terminalia chebulia	12.5 mg
Vibhitaki	Termnallia bellirica	12.5 mg
Amalaki	Emblica officinalis	12.5 mg
Chitraka	Plumbago zeylanica	12.5 mg
Musta	Cyperus rotundus	12.5 mg
Katuki	Picrorrhiza kurroa	12.5 mg
Devadaru	Cedrus deodara	12.5 mg
Vidanga	Embellia ribes	12.5 mg
Kulu/Kushta	Saussuria lappa	12.5 mg
Haridra	Curcuma longa	12.5 mg
Daruharidra	Berberis aristata	12.5 mg
Danti	Baliospermum montanum	12.5 mg
Indrayav	Holarrhena antidysentrica (seeds)	12.5 mg
Pippali mula	Piper longum	12.5 mg
Trivrit	Ipomoea turpethum	12.5 mg
Punarnava	Boerhavia diffusa	25.0 mg
Mandoor Bhasma	Ferric Oxide	250 mg

Table. 1 Composition of PRAK-20

MATERIALS AND METHODS

The present study was a randomized clinical study that was conducted between 2011 and 2013 in the Department of Oral Medicine and Radiology, of our institution with the ethical clearance from the institutional review committee. Totally, 40 clinically diagnosed OSMF patients were enrolled in the study after obtaining a written informed consent. A structured proforma were prepared to collect the relevant information from each patient. All the patients were explained about the need and design of the study. A potential benefit of undergoing a thorough clinical examination and follow up was made known to the patient. Prior to commencement of the treatment, patients were counseled to quit their adverse oral habits such as pan masala, arecanut and gutkha chewing.

Criteria for patient selection

Inclusion criteria

- Patients with OSMF diagnosed clinically.
- Patients who had not taken any management previously for OSMF.
- Patients who are prepared to leave the habit of gutka /arecanut chewing and accepted for regular follow ups.

Exclusion criteria

- OSMF patients with the coexisting systemic illness.
- OSMF patients with co-existing other mucosal lesions.
- History of hypersensitivity to Garlic or any other herbal component of PRAK-20
- Pregnant women and lactating mothers.

The patients registered in the study were arbitrarily allocated to two interventional groups and were blinded as to which group they belonged to. A detailed history of chief complaint along with habit history was elicited, and the intensity of burning sensation was determined using a Numerical Rating Visual Analogue Scale (VAS). One group received garlic, 2 pearls; thrice daily and another group received one 500mg PRAK-20 capsule three times a day for three months. Drugs were dispatched by a third person who was not related to the study. Patients were evaluated every 15 days for the assessment of clinical parameters and were enquired for any side effects for a period of three months with a total of seven readings for each patient. The clinical parameters evaluated at each visit were, burning sensation, mouth opening, tongue protrusion and cheek flexibility.

Drugs used:

1) Garlic pearls supplied by Ranbaxy. Each soft gelatin capsule contained 0.25% w/w garlic oil.

2) PRAK-20 powder was supplied by *Bharat Bhaishajya Shala Pvt. Ltd, Dehradun, India*. Zero sized empty capsules were used. Empty capsules were filled with 500mg of PRAK-20 powder using semi-automated capsule filling machine in Department of pharmaceuticals, Bapuji College of Pharmacy, Davangere.

The interincisal mouth opening was measured using a vernier caliper. The distance from the mesioincisal angle of upper central incisor to the mesioincisal angle of lower central incisor was recorded in millimeters. Cheek flexibility was measured according to the method by Mathur and Jha as quoted by Bailoor and Nagesh. Tongue protrusion was assessed from the normal mesioincisal angle of upper central incisor to the tip of the tongue, when the mouth is wide open in maximally extended position. All the parameters were measured and recorded during patients' every visit.

Based on the mouth opening the study subjects were grouped under the following clinical staging:

Stage 1: >40 mm, Stage 2: 31-40 mm, Stage 3: 21-30 mm, Stage 4: 11-20 mm, Stage 5: 0-10 mm

RESULTS

All the OSMF patients were in the age range of 16-48 years with a mean age of 28.02 years. In group A, the age

range was 16-46 years with a mean of 30.9 years. Similarly, the patients in group B were in the age range of 16-48 years with a mean of 25.15 years. 67.5% of the patients belonged to the second and third decade of their life, and all the 40 patients were males. There were no drop outs during the follow-up period. In our study, all the patients had burning sensation with a range of 10–100% and with a mean of approximately 55.5% in Group A and 70% in Group B.

Difficulty in opening the mouth was present in all the patients, and the mouth opening was in the range of 20–44 mm with a mean of 31.3 mm in Group A and 38.2mm in group B. Tongue protrusion was in the range of 24–63.5 mm, with a mean of 43.7mm and 39.9 mm in Group A and Group B respectively. Cheek flexibility was in the range of 0-3mm with a mean of 1.3 mm and 1.4 mm in Group A and Group B respectively.

On overall comparison for the treatment outcome, it was noted that in Group A there was 81.8% reduction in burning sensation by the 6th visit. It was also noted that there was 3.5mm increase in mouth opening, 4.4 mm tongue protrusion and on an average 0.2mm increase in cheek flexibility. Group B showed 75.4% reduction in burning sensation when reported at the 6th visit. There was on an average 4.6 mm improvement in mouth opening, 4.9mm in tongue protrusion and 0.4mm improvement in cheek flexibility. (Table 2, Graph 1,2,3,4)

Stage wise treatment response showed better results in initial stages of I and II.

Although no side effects were noted in our study; two patients reported of increased appetite in Group B, which was in a way positive outcome about the study.

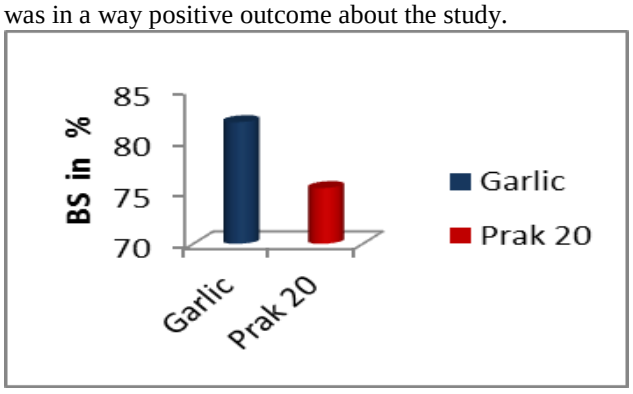

Fig 1

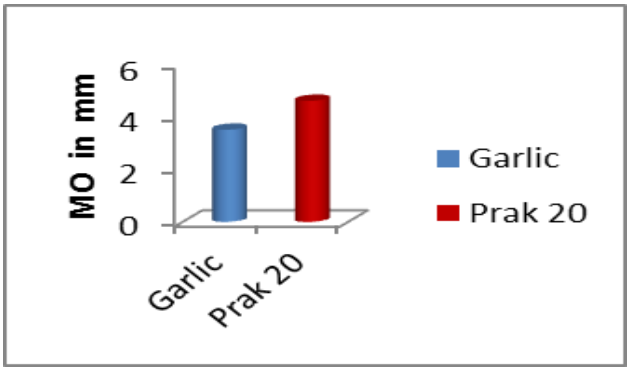

Fig 2

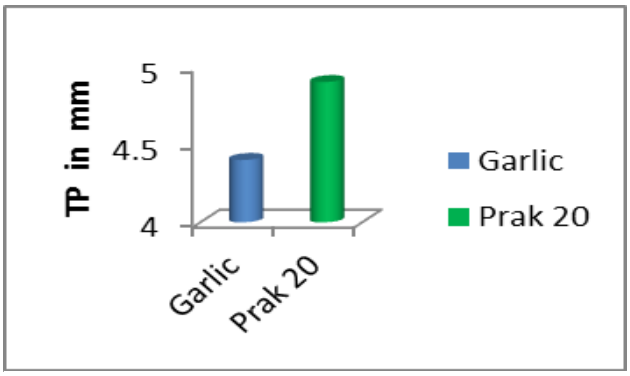

Fig 3

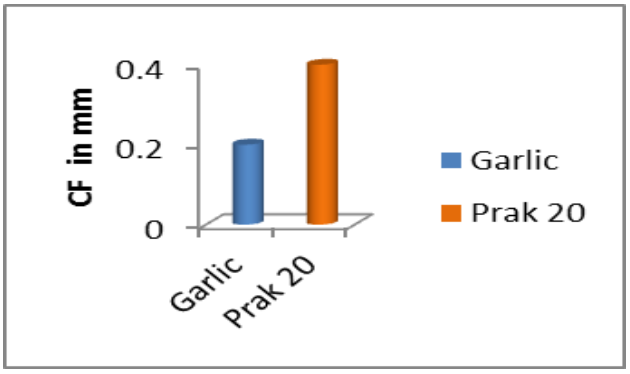

Fig 4

Graph-1-4: Comparison of overall improvement in Burning sensation (BS- Graph 1), mouth opening (MO – Graph- 2), tongue protrusion (TP- Graph- 3) and cheek flexibility (CF- Graph- 4) between two groups

DISCUSSION

Betel quid is composed of the nut of the areca palm, the leaf of the betel pepper and slaked lime. It has been reported that approximately 200 million persons chew arecanut regularly throughout Asia.[17]

	BS (VAS)			MO (mm)			TP (mm)			CF (mm)		
Group	BL	6th Visit	Improvement	BL	6th Visit	Diff	BL	6th Visit	Diff	BL	6th Visit	Diff
A	55.5 ± 29.9	10.5 ±17.0	81.8%	31.3 ± 8.3	34.8 ±8.2	3.5 ±0.1	43.7 ± 12.7	48.1 ±12.6	4.4 ±0.1	1.3 ±0.9	1.5 ±1.0	0.2 ± 0.1
B	70.0 ± 24.4	14.5±12.3	75.4%	28.2±4.7	32.8±5.7	4.6 ±1.0	39.9±7.3	44.8±5.8	4.9 ±1.5	1.4 ±1.6	1.8 ±1.6	0.4 ± 0.0

MO- mouth opening; BS- burning sensation; CF-cheek flexibility; TP- tongue protrusion; mm- millimeter;
Tab 2: Differences in the clinical parameters from baseline to 6th visit between two groups

In the present study, all the 40 cases were males and majority of the patients i.e. 27 (67.5%) in belonged to the second and third decade. This is in accordance with the study conducted by in Patna and Nagpur.[18,19] This signifies that the youngsters are being entangled in the shackles of OSMF.

Use of arecanut in different forms with or without tobacco has unfortunately permeated the ordinary household compromising immensely the health of the consumers. The onset of OSMF and cancer of the oral cavity are among the major fatal sequels to their usage and India already is globally leading in this.

As the definition of OSMF itself says about the nature of the disease, being progressive and irreversible; the primary aim should be towards making the patient quit the habit. There is yet no definitive treatment for OSMF, the modalities listed in the literature shows only palliative therapies.

Literature shows good results with the usage of Aloe vera and curumin for OSMF and also in recent times ayurveda is gaining an insight in the treatment of numerous incurable diseases. One such therapeutic modality is garlic, which possess many medicinal properties. Also, recent publications suggest that antioxidant function of garlic oil is most likely performed through increased availability of ß carotene and thus could be an asset in OSMF treatment.

The herbo-mineral compound PRAK-20,could be another potential treatment modality with its pool of medicinal properties.

On evaluating the clinical parameters, it was seen that burning sensation was present in all the patients. Due to atrophy of the epithelium OSMF patients suffer from burning sensation which further hampers their dietary intake and leads to nutritional deficiencies. In our study all the patients (100%) had shown the reduction in the burning sensation. 37.5% (15/40) patients had shown complete remission. Overall improvement ranged from 10 - 100 on VAS with a mean of 50.25%. In our treatment modalities, it was found that there was a reduction in the burning sensation by 81.8% in Group A and 75.4% in Group B (Table 2 ,Graph 1).

In a study where topical aloe vera gel was used in the treatment of OSMF reported a decrease in the burning sensation by 65%.[20] In our study, both the groups had shown superior results than obtained by aloe vera application. Also the results obtained in terms of reduction in burning sensation was better when compared to results with placental extracts (38.5%)[11] and intralesional IFN- γ (54-60%).[13] Better results were obtained with biweekly submucosal intralesional injections using chymar and dexamethasone and hylase of about 94-100%[5]. Though the results were superior to our study; it should be noted that intralesional injections are very painful and invasive method, where as we have obtained a maximum improvement of about 81.8% without using any invasive procedure and hence the compatibility of the patient will be more. Also post injection complication of fibrosis is not associated with our study.

The deposition of collagen in the submucosal tissues leads to reduction in the blood supply to the mucosa thereby causing atrophy of the epithelium which makes the mucosa prone to trauma and irritants which releases the inflammatory mediators and clot formations and ultimately burning sensation. Vasorelaxive and antithrombotic effect of garlic leads to lysis of the clots formed additionally increasing the mucosal blood perfusion and causing a reduction in the burning sensation. Also, it has been found to possess fibrinolytic activity and increases the capillary perfusion by 55% and augments microcirculation.[21]

On the other hand reduction in burning sensation in Group B can be attributed to the constituents of PRAK -20 which has anti-inflammatory action by inhibiting prostaglandin biosynthesis .They interfere with the inflammatory cascade and the vanilloid nociceptor.[22] Also, it inhibits the inflammatory response by inhibiting the induction of genes encoding cytokines, chemokines, and the inducible enzyme cyclooxygenase and hence modulate the inflammatory pathway. In addition Piper in PRAK -20 has inhibitory activity against COX-1and also reduces the proinflammatory cytokines.[23] Moreover curcuma longa along with other herbs has got anti-inflammatory action and have been reported with good outcomes in the management of OSMF.

Maximum improvement in mouth opening in Group A from baseline to the last visit was 6 mm (in two patients) and minimum was 1 mm (in one patient) with the mean maximum increase of 3.7 mm at 6th visit.

In Group B, maximum improvements in mouth opening from baseline to the last visit was 10 mm (in one patient) and minimum was 0 mm (in 1 patient) with the mean of the differences being 4.5 mm at 6th visit. Our patients in group A showed on an average of an overall improvement of 3.5 ± 0.1 mm, whereas group B showed on an average of an overall improvement of 4.6 ± 1.0 mm. (Table 2, Graph 2)

As no published data reports the treatment of OSMF with garlic or PRAK-20, hence our results cannot be judged in comparison with other studies. However, the results obtained with it are certainly comparable with the ones achieved by lycopene (3.4mm), lycopene and steroid injections (4.6mm), immune milk (3mm) and triamcinolone diacetate (2-3mm).

Studies involving surgical therapy[24] and lasers[16] on 10 patients each showed improvement; which is quite higher as compared to our study but our study was a non-invasive approach. Also the consequences of post treatment scarring is not present our study. Also the results of our study were better when compared to other studies involving lycopene[10], levamisole[9], antioxidants.[25]

Maximum increase in tongue protrusion in Group A was 10mm (in one patient) and minimum was 0 mm (in one

patient), with the mean maximum increase of 4.07 mm. The patient with 0 mm improvement had tongue protrusion of 53 mm; which was within normal limits. Maximum increase in tongue protrusion in Group B was 13.5mm (in one patient) and a minimum of 2 mm (in 3 patients) with a mean increase of 5.1mm. Overall improvement in tongue protrusion in Group A was 4.4 ± 0.1 mm and in Group B 4.6 ± 1.0 mm. In this context both the groups had shown comparable results. Our study results were comparable to other study results involving antioxidant capsules[26] and is superior to aloevera study where maximum improvement was 3.1mm with aloevera and 1.7mm with antioxidant capsules.[20] (Table 2 , Graph 3)

In our study a mere increase in cheek flexibility was seen (Table 2 ,Graph 4). Group A had shown an overall improvement in burning sensation more than Group B; whereas rest of the parameters like mouth opening, tongue protrusion, cheek flexibility was more in Group B. This could be attributed to the different phytochemicals present in many herbs which interact to dilute toxicity and enhance the therapeutic effects of the herb and, thus shown a better result.

One of the pathogenesis of OSMF is, oxidative stress. Garlic has shown potent results with its antioxidant properties. On the other hand PRAK-20; with various components like *Zingiber Officinale,*[27] *Curcuma longa,*[28] *Piper,*[29] *Emblica officinali* has potent antioxidant action. These antioxidant compounds block the chain reaction of oxidation and hence proved beneficial in the OSMF management.

Even though no side effects were noted in our study; two patients reported of increased appetite in Group B which was in a way positive outcome about the study; because generally these patients have loss of appetite which causes decreased nutrition and further consequences. Increased appetite in the patient could be attributed to stimulation of digestive enzymes of pancreas by piperine; a component in PRAK-20.[29]

Limitations of our study can be squirreled as; the study being a hospital based study could have led to heterogeneous distribution of the sample in different clinical stages as patients with the disease in the advanced stages had reported. Also the study was conducted on a smaller sample size and patients taking dietary garlic could have influenced the results of Group B.

Improvement in the clinical parameters obtained in our patients is a promising finding towards establishing the use of garlic and PRAK-20 as a therapeutic agent in OSMF. For a developing nation like ours where the cost of treatment is so high that most patients can't afford it and live with the burden of the disease; these drugs could be promising.

Future studies could be proposed as involving larger sample size and carrying out the multicentric study involving an equal distribution of cases from all clinical stages. Usage of different forms of garlic like powder, aged extracts, etc. and PRAK-20 in paste, gel, mouthwash forms can also be considered.

Initiative should be towards stopping the disease from occurring and the main cause for the occurrence of OSMF is arecanut and its various products. Though various states in India have banned the sale of gutkha, banning gutkha, of course, does not mean banning tobacco. Retailers have evaded the ban as they are selling packets of pan masala and giving a packet of flavored smokeless tobacco, free along with it.[30] This in turn makes this deleterious product and the associated habit persists and the rise in the number of OSMF cases.

OSMF is a preventable disease. Though there is no complete reversal of the disease; the primary aim should be towards preventing the condition from occurring. Hence awareness among the public about the ill effects of these hazardous products should be reinforced by various educational programmes, mass media, and various campaigns to free the common man from the manacles of this incapacitating disease.

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