



Efficacy of Madhupippalyadi Yoga Prathisarana Nishadi Taila Kavala with and without Rasayana Yoga Orally in the management of Oral Submucous Fibrosis – An open labelled randomized comparative clinical trial.

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ABSTRACT

Background: Oral Submucous Fibrosis is predominantly an addiction induced pathology of oral cavity that significantly reduces the quality of life of people, mainly in South east Asian countries. This debilitating disease arises from chronic chewing of pan masala like chewing substances. Towards the end stage, there will be inability to open the mouth, pain, dysphagia and finally causing referred pain in the ear or deafness and nasal intonation of voice. **Materials and methods:** Total 42 patients of OSMF were registered and were randomly allocated into two groups adopting computerised randomisation technique as follows with Group A (n=21): *Madhupippalyadi Yoga* for *Prathisarana*, *Nishadi Taila* for *Kavala*, *Rasayana Yoga* internally and Group B (n=21): *Madhupippalyadi Yoga* for *Prathisarana*, *Nishadi Taila* for *Kavala*. **Results and Discussion:** In group A, cured improvement was seen in 4.76% (1 patient) Marked improvement was found in 47.62% of patients (10 patients) in group A, while 28.58% relief (6 patients) was found in group B. Moderate improvement was found in 47.62% of patients (10 patients) in group A, while 71.42% relief (15 patients) was found in group B.

Keywords: *Madhupippalyadi Yoga*, *Nishadi Taila*, *Rasayana Yoga*, Oral Submucous Fibrosis, *Mukharogas*

INTRODUCTION

Oral submucous fibrosis (OSMF) is a chronic, insidious, generalized, and debilitating condition of the oral mucosa predominantly encountered in South-East Asian countries. Consumption of the areca nut in flavored formulations or as an ingredient in the betel quid chewed by the communities in these countries is considered as the etiological predisposition in the development of the disease. It is a chronic

debilitating disease of the oral cavity resulting from such habits like mawa, pan-masala, gutkha, betel nut and betel quid chewingⁱ.

The relative risk for users is almost 100 times and betel quid is an extremely potent carcinogen. The two main adverse effects of betel quid use are oral cancer and submucous fibrosis. However, other risks include carcinoma of the pharynx and oesophagus and possibly diabetesⁱⁱ. Quid containing tobacco carries the highest risk for carcinoma. Areca nut alone carries the highest risk for submucous fibrosis, but also causes carcinoma at a lower rate.

Worldwide estimate of OSMF indicates that 2.5 million people are affected with most cases connected on the Indian subcontinents especially southeast Indiaⁱⁱⁱ. With a reported prevalence ranging up to 0.4% in Indian rural populations, several million individuals are estimated to suffer from this malady. It has a malignant transformation rate as high as 7.6%

The male/female ratio of OSMF varies by region but females tend to predominate. It is widely prevalent in all age group and across all socioeconomic strata in India. It can occur in 11-60 years range, most of the patients aged between 45-54 years.^{iv}

Long-term indulgence in such habits will cause periodontitis and recession of the adjacent gingiva. In the earliest stages, there may be burning sensation and scattered small vesicles. Later, fibrosis and loss of vascularity cause extreme pallor of the affected area, which then appears almost white and marble-like. Symmetrical fibrosis develops in the buccal mucosa, soft palate or inner aspects of the lips. The fibrosis starts immediately below the epithelium but extends to deeper tissues until they eventually become so hard that they cannot be indented with the finger. It is believed, that the disease initiates from the posterior part of the oral cavity and then it gradually spreads to the anterior locations^v.

Progressively, muscles of mastication are eventually involved. Thus, there will be inability to open the mouth, pain, dysphagia and finally causing referred pain in the ear or deafness and nasal intonation of voice. At this stage, the epithelium appears smooth, thin and atrophic. Ultimately, mouth opening may become so limited that eating and dental treatment become difficult, and tube feeding may become necessary^{vi}.

Along with poor socioeconomic status and nutritional deficiency, other factors like genetic predisposition, autoimmunity derangements and alcohol- smoking consumption are also considered as precipitating factors of OSMF^{vii}.

MATERIALS AND METHODS

Institutional Ethics Committee (IEC) approval was taken prior to initiation of research vide its letter no. PGT/7/-A/Ethics/2020-21/625. No any adverse drug reaction has been recorded during the course of the trial. Study was registered in Clinical Trial Registry of India no. CTRI/2020/10/037780 [Registered on: 04/12/2020]. Patient information sheet was prepared and the patient informed consent was taken before starting the treatment.

Total 42 patients of OSMF were registered from outpatient department and inpatient department of Shalaky Tantra, IPGT&RA, Jamnagar. They were randomly allocated into two groups adopting computerised randomisation technique as follows:

Group A (n=21) : *Madhupippalyadi Yoga, Nishadi Taila, Rasayana Yoga*

Group B (n=21) : *Madhupippalyadi Yoga, Nishadi Taila*

The patients were given treatment for a period of 45 days. After completion of the treatment, the patients were followed up for 1 month at the interval of 15 days.

Raw herbal drug of *Madhupippalyadi Yoga, Rasayana Yoga* and *Nishadi Taila* were procured from Pharmacy, Gujarat Ayurved University, Jamnagar and authenticated in Pharmacognosy laboratory, IPGT and RA, Gujarat Ayurved University, Jamnagar. Then the medicines were prepared adopting the standard API methods of *Taila* and *Choorna* preparation.

CRITERIAS FOR SELECTION

A. INCLUSION CRITERIAS:

- Age group between 18-60 years of either sex.
- The patients having clinical signs and symptoms: Blanching and stiffness of oral mucosa, altered taste sensation, altered salivation, repeated vesicular eruption and ulceration on buccal mucosa, palate and pillars, burning sensation in mouth, intolerance to eat hot and spicy foods, difficulty in opening mouth.
- Interincisal distance of more than 15 mm.
- Patients previously enrolled in the previous studies of Oral submucous fibrosis will also be included in the present study and their data was maintained separately.

B. EXCLUSION CRITERIAS:

- Age less than 18 years and more than 60 years.
- Extensive fibrosis of all over the oral mucosa, severe trismus with an interincisal distance of less than 15 mm.
- Disease most advanced with premalignant and malignant changes.
- Oral manifestation of scleroderma.
- Oral lichen planus.
- Chronic debilitating conditions like DM, HTN.
- Patients not willing to give up habits of gutkha, pan masala, mawa, tobacco, betel quid or betel nut chewing.

INVESTIGATIONS

1. Haematological Examination: Hb, ESR, TLC, DLC
2. Biochemical examination: RBS

Investigations were done before initiation of interventions for the sake of screening of general health condition.

ASSESSMENT CRITERIA:

The clinical trial was assessed for its efficacy on the basis of following subjective and objective parameters

SUBJECTIVE:

Burning Sensation in Mouth (*Mukhadaha*)

Nil	0
On taking spicy food	1
On taking food	2
Continuous	3

Altered Taste (*Rasagyana*)

Normal	0
Altered /decreased	1

Salivation (*Lalasarava*)

Normal	0
Altered	1
Decreased	2

Intolerance to Spicy Food (*Katu Rasa Ashahishnuta*) in comparison to previous tolerance

Nil	0
Mild	1
Moderate	2
Severe	3

Pain in Mouth (*Mukhavedana*)

Nil	0
While opening	1
Continuous	2

OBJECTIVE:

The Colour of Oral Mucosa

Pink normal	0
Red or deep pink	1
Pale white	2
Blanched white	3

Ulceration in Mouth

No	0
Mild	1
Moderate	2

Severe	3
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Consistency of the Oral Mucosa on Palpation

Soft normal	0
In between soft and leathery hard	1
Leathery hard	2

Fibrous Bands on Palpation

No fibrous bands	0
One or two solitary fibrous bands	1
Bands felt nearly in entire surface	2
Adherent fibrous bands producing binding and rigidity of mucosa	3

Inter Incisor Distance (IID) measurement.

41mm or above considering normal	0
37-40mm	1
33-36mm	2
29-32mm	3
25-28mm	4
21-24mm	5
17-20mm	6
15-16mm	7

STATISTICAL ANALYSIS

The data obtained in clinical study were subjected to statistical analysis by evaluating the significance of the interventions using paired and unpaired t tests. After obtaining the P value, it was observed as insignificant $P > 0.05$, significant $P < 0.05$, highly significant was $P < 0.01$.

OBSERVATIONS

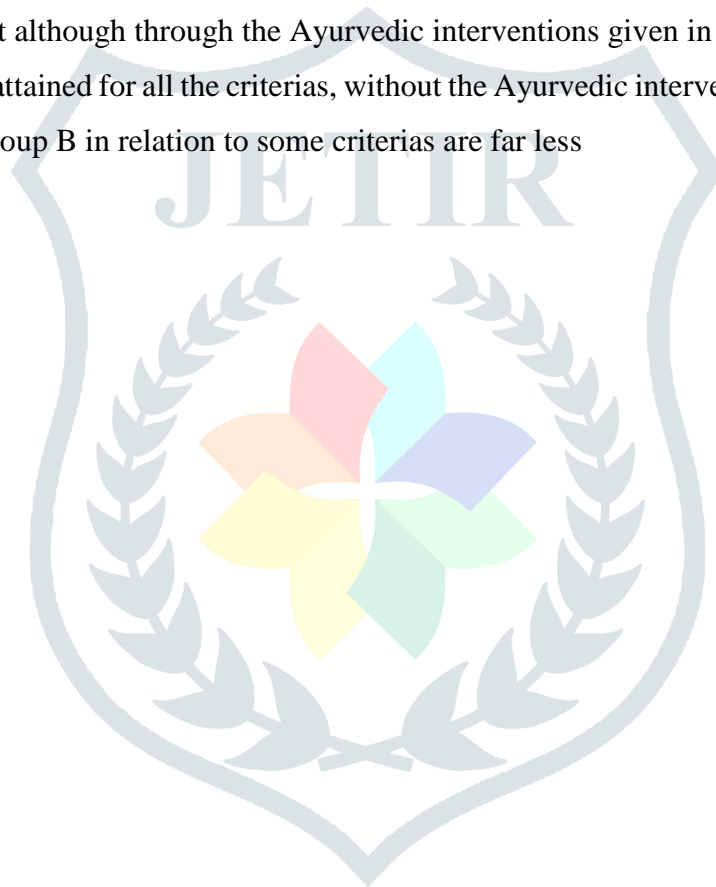
According to the data obtained, 76.19% patients had burning sensation in mouth, 66.66% with intolerance to spicy food, 50% of patients were having complaint of inability to open the mouth and 45.23% patients had pain in mouth. Altered salivation was present as a complaint in 28.57% patients. Altered taste was present in 23.08% patients, 76.19% of patients had pan masala in their chewing habit, while 64.28% patients were having chewing habit of mawa, quid chewing was observed in 47.67%, gutka chewing was present in 35.71% followed by 30.95% patients with chewing habit of betel nut. 19.04% had habit of tobacco chewing, bajar chewing was observed in 16.66%, and that of kharra in 9.5%. Habit of cigarettes smoking was found in only 19.04% patients along with chewing habits.

About 69.04% of patients were taking *Ushna*, *Tikshna* and *Vidahi Ahara*. Around 45.23% patient had fewer intakes of fruits and green leafy vegetables in their diet as well as taking excessive chilies and spices in their diet. 69.04% patients regularly in their diet. While 59.52% patients were taking *Alpa*, *Pramita*,

Ruksha Ahara in diet. In *Viharaja Nidana*, 73.80% patients had oral hygiene which was poor due to *Dantadhavana Dwesha*

RESULTS

In the present study total 42 patients were registered, 21 in group A and 21 in Group B, and all of them completed the course of study. The effect of therapy in 42 patients of OSMF is presented below. On comparing the effects achieved over subjective and objective criterias in both the groups, statistically significant result were obtained in subjective criterias- burning sensation in mouth(*Mukhadaha*), intolerance to spicy food (*Katu Rasa Asahishnuta*), and in objective criteria-ulceration in mouth and insignificant results were found for subjective criterias-altered taste (*Rasagyana*), pain in mouth (*Mukhavedana*) salivation (*Lalasarava*) and in objective criteria- consistency of oral mucosa, blanching of oral mucosa, fibrous bands of oral mucosa and IID, On assessing the outcomes achieved through the study, it can be understood that although through the Ayurvedic interventions given in both groups, statistically significant results were attained for all the criterias, without the Ayurvedic intervention of *Rasayana Yoga*, effects achieved as in group B in relation to some criterias are far less



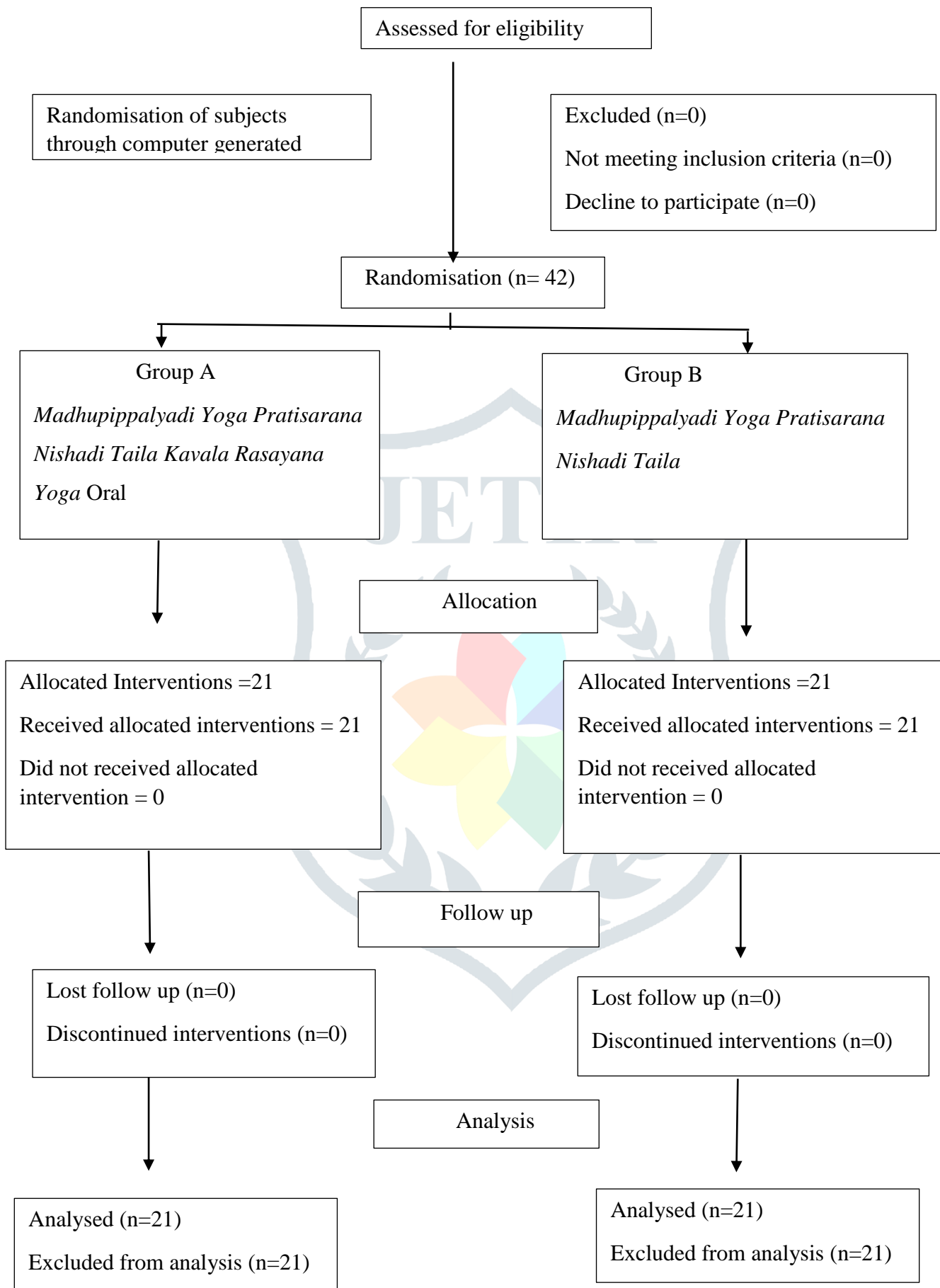


Chart 1: Consort flow chart

Table 1: COMPARISON OF PERCENTAGE RELIEF AND SIGNIFICANCE

CHIEF COMPLAINTS	GROUP A		GROUP B	
	% relief	significance	% relief	significance
Burning Sensation in Mouth (<i>Mukhadaha</i>)	83	HS	57.14	HS
Altered Taste (<i>Rasagyan</i>)	50	S	43	HS
Intolerance to Spicy Food (<i>Katu Rasa Asahishnuta</i>)	60	HS	51.9	S
Pain in Mouth (<i>Mukhavedana</i>)	78.79	HS	52.7	HS
Salivation (<i>Lalasarava</i>)	67.86	HS	50.50	HS
Blanching of Oral Mucosa	58.14	HS	54.7	HS
Ulceration in Mouth	82.35	HS	49.01	HS
Consistency of Oral Mucosa	48	HS	45.9	HS
Fibrous Bands	39.02	HS	37	HS
IID	23.73	HS	22.95	HS

Table 2: COMPARISON OF EFFECT OF THERAPY SUBJECTIVE CRITERIA

Chief Complaints	Mean Diff. G - A	Mean Diff. G - B	Mean Diff.	SD ±		SE ±		‘t’	P	Signif.
				A	B	A	B			
Burning Sensation in Mouth (<i>Mukhadaha</i>)	1.71	1.33	0.4	0.6	0.5	0.2	0.1	2.2	0.04	S
Altered Taste (<i>Rasagyan</i>)	1.14	1.14	0.00	0.38	0.38	0.14	0.14	0.00	1.00	IS
Intolerance to Spicy Food (<i>Katu Rasa Asahishnuta</i>)	1.73	1.33	0.40	0.46	0.58	0.12	0.13	2.23	0.03	IS

Pain in Mouth (<i>Mukhavedana</i>)	1.06	0.92	0.14	0.42	0.56	0.10	0.15	0.82	0.42	IS
Salivation (<i>Lalasarava</i>)	1.0	1.0	00	0.5	0.71	0.17	0.32	00	1.0	IS

Table 3: COMPARISON OF EFFECT OF THERAPY: ON OBJECTIVE CRITERIA

Chief Complaints	Mean Diff. G - A	Mean Diff. G - B	Mean Diff.	SD ±		SE ±		‘t’	P	Signif.
				A	B	A	B			
Blanching of Oral Mucosa	1.19	1.38	0.19	0.40	0.50	0.088	0.11	1.36	0.18	IS
Ulceration in Mouth	1.47	1.14	0.33	0.51	0.478	0.118	0.10	2.11	0.04	S
Consistency of Oral Mucosa	1.00	1.11	0.11	0.36	0.32	0.091	0.07	0.94	0.35	IS
Fibrous Bands	0.80	0.62	0.18	0.52	0.50	0.117	0.11	1.14	0.26	IS
IID	0.70	0.71	0.014	0.47	0.46	0.11	0.10	0.10	0.92	IS

TABLE 4:- OVERALL EFFECT OF THERAPY

Assessment of Result	Group A		Group B	
	No. of patients	Percentage (%)	No. of patients	Percentage (%)
Cured	01	4.76	00	00
Marked Improvement	10	47.62	06	28.58
Moderate Improvement	10	47.62	15	71.42
Mild Improvement	00	00	00	00

Unchanged	00	00	00	00
Total	21	100	21	100

EFFECT OF THERAPIES ON CHIEF COMPLAINTS

SUBJECTIVE PARAMETERS:

Group A: Highly significant relief ($p < 0.001$) in Burning sensation of mouth (*Mukhadaha*) (83%), Intolerance to spicy food (*Katu Rasa Asahishnuta*) (78.79%), Salivation (*Lalasarava*) (60%), Pain in mouth (*Mukhavedana*) (67.86%) and significant relief in Altered Taste ($p < 0.05$) (*Rasagyana*) (50%) was noted. All these symptoms are annoying to the patients which make their quality of life very miserable because it is usually seen that patients coming are more worried about these symptoms rather than opening of mouth. Relief of these symptoms also helpful to assess the further diseases progress and prognosis.

Group B: Highly significant relief ($p < 0.001$) in Burning sensation of mouth (*Mukhadaha*) (57.14%), Pain in mouth (*Mukhavedna*) (52.17%), Intolerance to Spicy food (*Katu Rasa Asahishnuta*) (51.9%), Altered taste (*Rasagyana*) (43%) and significant result in Salivation (*Lalasarava*) (50%) ($p < 0.05$) was noted.

OBJECTIVE PARAMETERS:

Group A: In group A highly significant relief ($p < 0.001$) in Ulceration in mouth (82.35%), Consistency of Oral mucosa (48%), Blanching of Oral mucosa (58.14%), Fibrous bands of oral mucosa (39.02%) and IID (23.73%) was noted.

Group B: In group B highly significant relief ($p < 0.001$) in Blanching of oral mucosa (54.7%), Ulceration in mouth (49.01%), Consistency of oral mucosa (45.9%), Fibrous bands of oral mucosa (37%) and in IID (22.95%) was noted.

Overall Effect of Therapy: In group A, cured improvement was seen in 4.76% (1 patient), Marked improvement was found in 47.62% of patients (10 patients) in group A, while 28.58% relief (6 patients) was found in group B. Moderate improvement was found in 47.62% of patients (10 patients) in group A, while 71.42% relief (15 patients) was found in group B.

DISCUSSION

1. Probable Mode of Action of *Madhupippalyadi Yoga Pratisarana*:-

As understood by the general pathology of OSMF, development of fibrous bands below the mucosal layer cause for many of the symptoms of the disease. Dissolution or reducing the stiffness to some extent can provide the patient a great relief in mouth opening difficulty. Applying the *Pratisarana Dravya* with a gentle pressure exerts some pressure to the fibrous bands that may eventually get dissociated or loosen up.

Gentle pressured application of the medicine also improves local circulation of the mucosa and sub mucosa. Atrophication of the oral mucosa and sub mucosa triggered by fibrous cross linking may

get reverted eventually by such regular, gentle pressurized medicine applications, which eventually provides *Rasa Rakta Prasadana* in these sites.

Overall, most of the drugs are *Lekhana, Shothahara, Vranasodhana, Vranaropana* and *Srotovishodhana*. They are also with anti-inflammatory, antioxidant, wound healing and cleaning properties. Usage of *Madhu* as medium for application gives the extra effects such *Chedana, Rookshana, Sandhana*. It also provides summative effects on *Vranasodhana, Vranaropana*. Unique property of *Madhu* as *Yogavahi Dravya* also increases the potency of *Pratisarana Dravya*.

By all these properties, *Pratisarana* with *Madhupippalyadi Yoga* results in predominantly *Mamsa Dhatu Prasadana*, which can be understood as the reduction fibrous band effects and promotion in nourishment and thus reduction of atrophy of mucosa and sub mucosa.

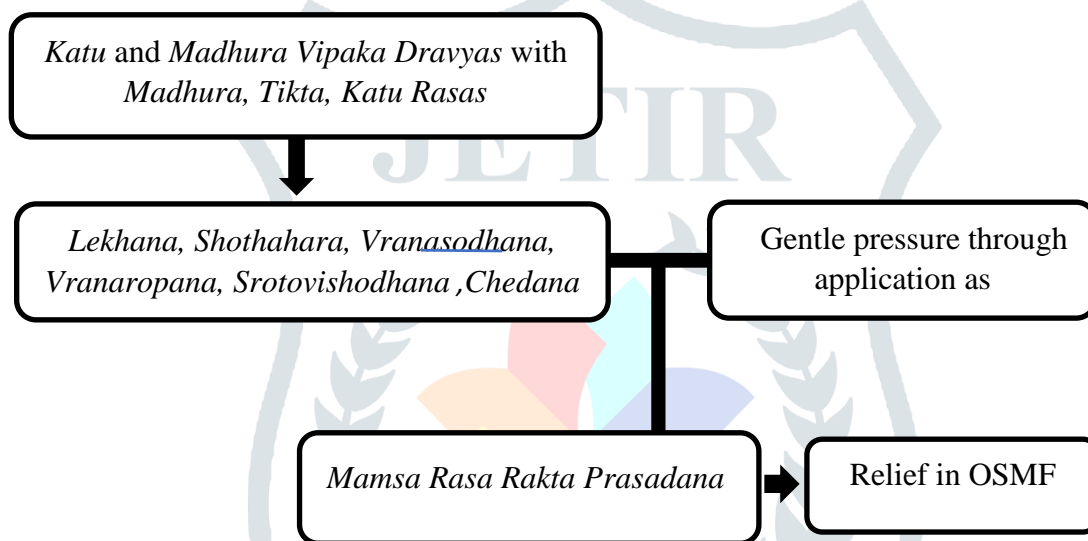


Chart 2- Mode of action of *Madhupippalyadi Yoga*

2. Probable mode of action of *Nishadi Taila Kavala*

Mode of action of *Kavala* with *Nishadi Taila* can be understood grossly in two ways;

- i. Effects achieved by specificity of procedure
 - *Poorva Karmas* done prior to procedure i.e, *Swedana* and *Mardana* over *Lalata, Kapola, Skandha* helps in stimulating these areas probably by means of increasing circulation. This may amplify the local interaction of *Kavala Dravya* with mucosa
 - The procedure of *Kavala* that involves purposeful movements of cheek with to and fro movements and sideways movements can be regarded as way to achieve loosening of the muscles that has become stiff due to the fibrosis. This useful physiotherapeutic measure cannot be attained through *Gandusha Dharana*. As a complimentary benefit above all these mentioned effects, procedure of *Kavala Dharana* rinses of all the impacted food debris in between the teeth and gums and aids in maintaining fair oral hygiene.

ii. Effects of medicine used for *Kavala*

- Predominantly, the ingredients of the medicine are having *Madhura Rasa, Snigdha Guna, Sheeta Veerya, Madhura Vipaka* and *Vata Pitta Shamaka* and *Daha Shamaka Balya* properties, which are suitable for any kind of ulcerations in oral cavity and atrophy of mucosa. Moreover the *Kavala Dravya* selected for procedure is *Taila*, which being a *Sneha* will provide much needed *Snigdha Guna* to reduce the *Rookshata* in the oral cavity, reduce the stiffness in mouth opening and counteracts for the atrophy of mucosa.

Advantage of selecting *Taila* over other forms of *Sneha Dravyas* in using for *Kavala* in this particular condition is that it won't aggravate the *Kapha Dushti*.

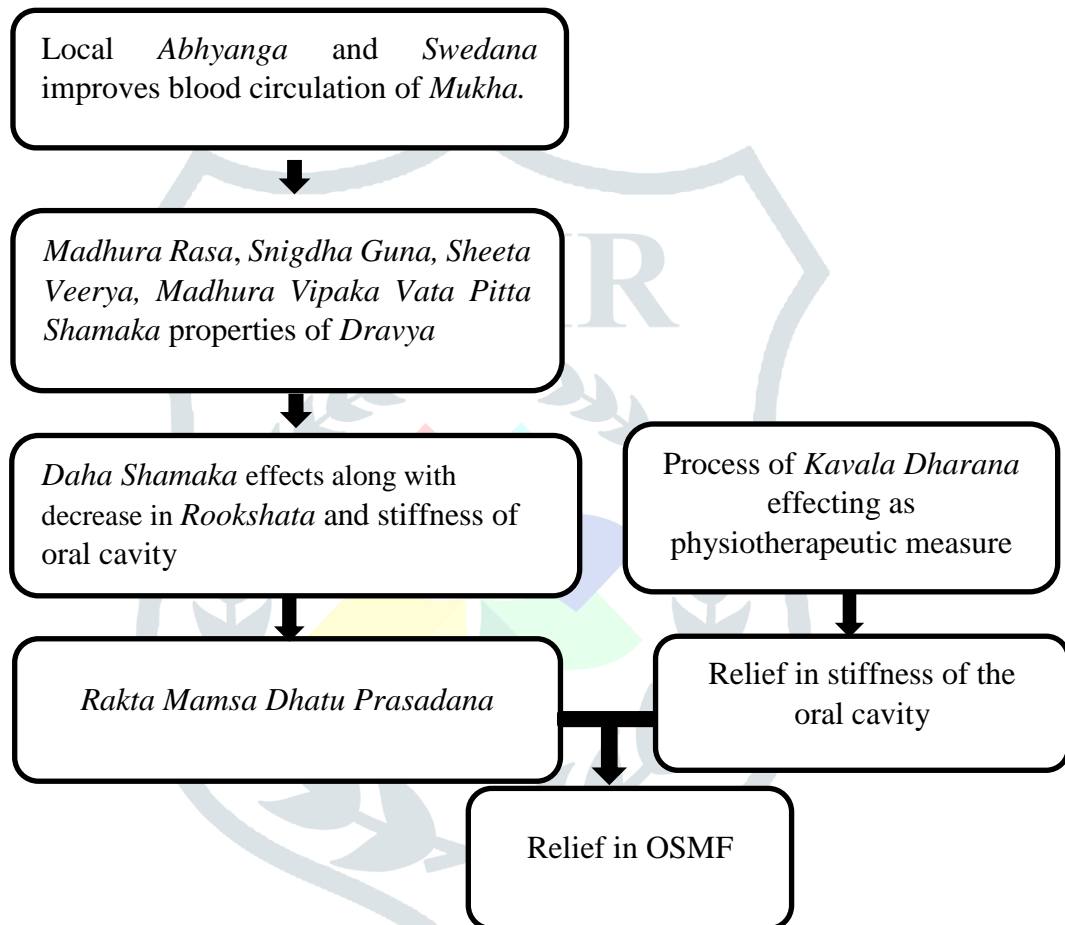


Chart 3- Mode of action of *Nishadi Taila*

3. Probable Mode of Action of *Rasayana Yoga*:

Probable mode of action of *Rasayana Yoga* can be:

Drugs in the *Rasayana Yoga* are predominantly with *Madhura Tikta Rasas, Guru Snigdha Gunas, Sheetha Virya, Madhura Vipaka* and *Tridosha Shamaka* properties, more specifically being *Vata-Pitta Shamaka*. While both *Madhura* and *Tikta Rasas* have *Ropana* actions, additionally, *Madhura Rasa* is *Snehana, Brimhana, Balya, Preenana, Dahashamaka, Vata-Pitta Shamaka* and *Tikta Rasa* is *Vishagna, Prasadana* and *Pitta- Kapha Shamaka*. It can be assumed that *Katu Rasa* predominance of drugs like *Haridra* in this formulation act as a controlling factor to avoid excessive *Snehana* and *Brimhana* which may cause *Agnimandya* that will not be favourable for this condition.

In the course of OSMF, nutritional deficiency is most commonly seen in its sequel. Due to early symptoms such as burning sensation of mouth, intolerance to spicy foods, ulcerations in mouth, pain in mouth etc., normal food intake becomes difficult. In such patients and further nutritional issues may arise. Also, due to the ongoing pathology, there occurs atrophy of buccal mucosa, which otherwise should be understood as *Dhatukshaya*. In efforts of reversing the pathology and counteracting the complications of the disease, there should be interventions with above said objectives. In this perspective, *Rasayana Yoga* can be considered as an ideal intervention.

- *Tridosha Shamaka* properties seen in most of the drugs helps the body to attain *Dosha Satmya*. Such drugs often show *Rasayana Gunas* in association as it is evident in this formulation. This ensures proper *Dhatu Nirmana* and thus its *Poshana*. Indirectly, it is also right to assume that proper *Dhatu Poshana* also ensures *Samyak Ojo Nirmana* which is the essence of *Prana*. Thus, this systemic medicine support is crucial in quick management of condition and as *Shareera* itself is a byproduct of what we ingest.
- All the effects of the formulation is catalysed by the *Anupana* indicated for it, i.e, *Madhu* and *Ghrta*. Both being *Yogavahi* are suitable for increasing the potency of the formulation. Also, ghee itself has *Rasayana* property. Thus they are helpful in increasing the outcome of the intervention.

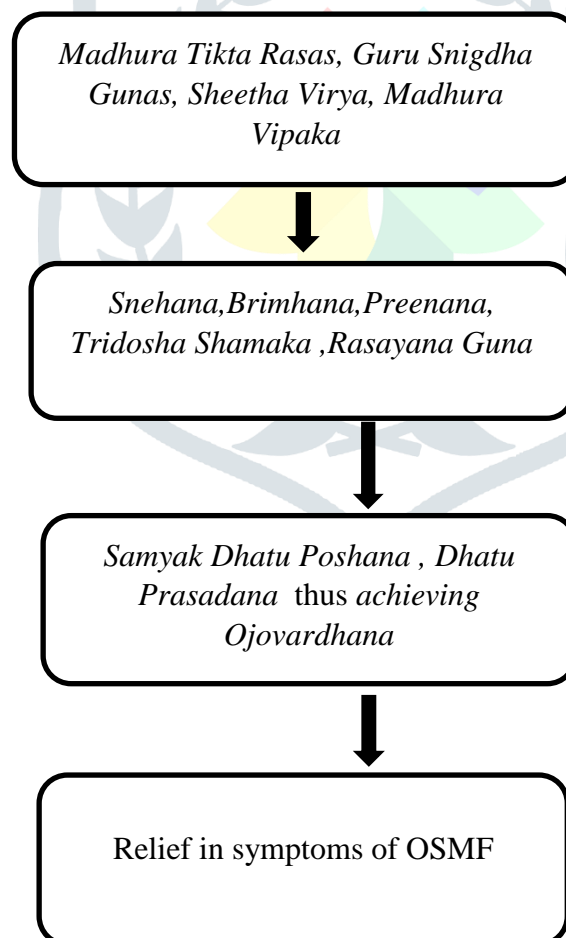


Chart 4- Mode of action of *Rasayana Yoga*

CONCLUSION

Thus it can be now concluded that group A shows statistically significant result than that of group B, hence on the basis of outcomes of the study null hypothesis i.e. ‘Administration of *Madhupippalyadi Yoga Pratisarana, Nishadi Taila Kavala* with and without *Rasayana Yoga* orally is equally effective in the management of Oral submucous fibrosis was rejected and alternate hypothesis i.e. ‘Administration of *Madhupippalyadi Yoga Pratisarana, Nishadi Taila Kavala* with *Rasayana Yoga* orally is more effective than that of Administration of *Madhupippalyadi Yoga Pratisarana, Nishadi Taila Kavala* without *Rasayana Yoga* orally in the management of Oral submucous fibrosis was accepted. So Ayurvedic line of management for OSMF must include *Rasayana* medicines at systemic level rather than relying solely on local therapies.

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Conflicts of interest : There are no conflicts of interest

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