Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jobcr

Original Article

Comparative evaluation of natural antioxidants spirulina and aloe vera for the treatment of oral submucous fibrosis

Santosh Patil [a,*], Bader Kureyem Al-Zarea [a], Sneha Maheshwari [b], Rohit Sahu [c]

[a] Assistant Professor, College of Dentistry, Al Jouf University, Al Jouf, Sakaka, Saudi Arabia
[b] Dental Practitioner, Jodhpur, Rajasthan, India
[c] Post Graduate Student, Dept of Oral Medicine and Radiology, Chattisgarh Dental College and Research Institute, Rajnandgaon, Chattisgarh, India

ARTICLE INFO

Article history:
Received 11 July 2014
Accepted 30 December 2014
Available online 22 January 2015

Keywords:
Oral submucous fibrosis
Spirulina
Aloe vera
Antioxidant

ABSTRACT

Aim: Oral submucous fibrosis (OSMF) is a high risk premalignant condition predominantly seen in the Indian subcontinent. The aim of the present study was to compare the efficacy of spirulina and aloe vera in the management of OSMF.

Material and methods: 42 subjects with clinico-pathologically diagnosed OSMF were included in the study and divided equally in 2 groups, Group A (spirulina group) and Group B (aloe vera group). Group A was administered 500 mg spirulina in 2 divided doses for 3 months and Group B was given 5 mg aloe vera gel to be applied topically thrice daily for 3 months. Evaluation for different clinical parameters was done at regular intervals and data was analyzed using the Chi-square test. P-value <0.05 was considered to be statistically significant.

Results: The patients in Group A showed significant clinical improvement in mouth opening and ulcers/erosions/vesicles ($p < 0.05$). However, there was no significant improvement in burning sensation ($p = 0.06$) and pain associated with the lesion ($p = 0.04$) among the 2 groups.

Conclusion: Both the drugs showed improvement in the condition; however spirulina can bring about significant clinical improvements in the symptoms like mouth opening and ulcers/erosion/vesicles. Thus, spirulina appears to be more promising when compared to aloe vera for the treatment of OSMF.

* *Corresponding author.*
E-mail address: drpsantosh@gmail.com (S. Patil).
http://dx.doi.org/10.1016/j.jobcr.2014.12.005

1. Introduction

Oral submucous fibrosis (OSMF) is characterized by progressive inability to open the mouth due to inflammation and progressive fibrosis of the submucosal tissues.[1] Susrutha in ancient medicine described a condition similar to OSMF as "vidari".[2] In 1952, Schwartz described a condition of the oral mucosa as "atrophia idiopathica mucosa oris", with the term OSMF coined by Joshi in 1953.[3,4] Pindborg and his associates defined the condition as "an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxtaepithelial inflammatory reaction followed by fibroelastic changes in the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and difficulty in eating".[5] The etiology is believed to be multifactorial and the pathogenesis is not well known. The condition is associated with areca nut and betel quid chewing, being practiced predominately in the Indian subcontinent from a long time.[1]

No successful treatment has been advocated till date, however specific treatment includes administration of steroids, placental extracts, IFN gamma, pentoxifylline, lycopene, surgical excision, etc.[6,7] Many natural plant extracts, synthetic drugs, etc have been introduced and tried for the management of OSMF. One such plant is aloe vera which promotes wound healing, and also has anti-inflammatory, immunomodulatory, and antioxidant properties.[8] Shetty et al recently have evaluated the role of spirulina in the management of OSMF.[9] The blue green algae, spirulina is rich in carotenoids and other micronutrients possessing chemo preventive potential. It has been used to test the clinical activity in reversing the oral precancerous lesions like leukoplakia.[10] No study has been done till date to compare the efficacy of these natural antioxidants. Hence, the present study was carried out to compare the efficacy of spirulina and aloe vera in the management of OSMF.

2. Material and methods

The present prospective study included 42 subjects with clinico-pathologically diagnosed OSMF reporting to the Department of Oral Medicine and Radiology. Patients of either sex with OSMF were included in the study. Ethical clearance was obtained from the Institutional Ethical Committee. A written informed consent was obtained from the patients prior to the inclusion in the study. Those with any evidence of severe psychiatric, cardiac, gastrointestinal or metabolic disorders and pregnancy and lactation were excluded from the study. Detailed family and medical history with a history of associated habits was recorded. A thorough clinical examination was conducted and relevant findings were recorded. The subjects were randomly divided equally in 2 groups, Group A (spirulina group) and Group B (aloe vera group). Group A was administered 500 mg spirulina in 2 divided doses for 3 months and Group B was given 5 mg aloe vera gel (Sheetal Lab, Surat) to be applied topically thrice daily for 3 months and were further followed up for a period of 2 months. Patients were advised not to eat or drink for 15 min after the application of the aloe vera gel. The OSMF was graded on the basis of cheek flexibility as Grade 1 to 5.[11] Mouth opening was measured by measuring the distance between the centre of incisal edges of maxillary central incisors and mandibular central incisor at maximum opened mouth. In edentulous patients, the inter ridge (alveolar) distance along the midline was measured.[12] 3 measurements were recorded consecutively and the average value was calculated and recorded. Evaluation for presence, absence or reduction of other clinical parameters such as ulcers/erosions/vesicles, burning sensation and pain associated with the lesion was done at regular intervals of 1 month, 2 month and 3 months. The clinical parameters such as burning sensation, pain associated with the lesion, difficulty in swallowing and speech were evaluated by using a visual analog scale. The score of 0–1 was considered as absent, score in the range of 1–6 was considered as reduced and a score of 7–10 was evaluated as present. The data was entered using computer software SPSS 12.0 (SPSS Inc., Chicago, USA) and analyzed using the Chi-square test. P-value<0.05 was considered to be statistically significant.

3. Results

There were 24 males and 18 females with a mean age of 31.2 ± 12.4 years. The main causative factors for OSMF included betel nut chewing (60%), tobacco chewing (32%) and spicy foods (39%) (few of the patients had more than 1 habit, hence the total is more than 100%). Clinical improvements in mouth opening and ulcers/erosions/vesicles was significant in the Group A ($p < 0.05$) (Tables 1 and 2). However, there was no significant improvement in pain associated with the lesion ($p = 0.04$) and burning sensation ($p = 0.06$) among the 2 groups (Tables 3 and 4). There were no noticeable side effects of spirulina and aloe vera. There were no dropouts from the study due to any reason during the follow-up. The patients were followed up for a period of 2 months during which 3 patients from Group A and 5 patients from Group B reported ulcers and burning sensation for a period of 7–10 days.

4. Discussion

OSMF is a precancerous condition of the oral cavity and oropharynx seen predominantly in the Indian subcontinent and Southeast Asian countries. The condition is preceded by burning sensation of the oral mucosa, ulceration and pain and characterized by blanching and depigmentation of oral mucosa, reduced movement and depapillation of tongue, and

Table 1 – Effect of spirulina and aloe vera in improving mouth opening (mean values in mm).

	Spirulina	Aloe vera	p-value
Baseline	19.9 ± 2.1	19.1 ± 2.7	<0.05
After 1 month	20.9 ± 2.8	20.4 ± 2.2	
After 2 months	23.4 ± 2.2	22.1 ± 1.5	
After 3 months	25.8 ± 2.5	23.9 ± 1.9	

Table 2 – Effect of spirulina and aloe vera on ulcers/vesicles/erosions.

	Spirulina			Aloe vera		
	Present	Absent	Reduced	Present	Absent	Reduced
Baseline	20	1	–	19	2	–
After 1 month	14	4	3	16	2	3
After 2 months	10	6	5	12	4	5
After 3 months	4	11	6	8	8	5

progressive reduction of mouth opening.[13,14] Nasal twang due to fibrosis of nasopharynx and hearing impairment due to stenosis of eustachian tube may be seen in advanced stages of the condition. The most common etiological factor is areca nut and its products, which induce excessive reactive oxygen species damaging the cell structures. Accompanied with this, vitamin deficiency, iron deficiency anemia, and malnutrition can disturb the repair of the inflamed oral mucosa, leading to poor healing. This results in atrophic oral mucosa which becomes more susceptible to the effects of areca nut. The antioxidant vitamins are thus employed to stabilize and deactivate the free radicals before they attack cells.[6]

The overall prevalence rate in India is believed to be about 0.2%–0.5% and prevalence by gender varying from 0.2 to 2.3% in males and 1.2–4.57% in females.[15,16] It is considered to have a high degree of malignant potential, which ranges between 2.3% and 7.6%.[17] Majority of OSMF patients present with irreversible moderate-to-severe condition and may be associated with oral leukoplakia and other potentially malignant disorders such as squamous cell carcinoma. The precancerous nature of OSMF is still unanswered, however it has been proved by, higher occurrence of OSMF in oral squamous cell carcinoma patients, histological diagnosis of cancer without any clinical suspicion in OSMF, high frequency of epithelial dysplasia and higher prevalence of leukoplakia among OSMF.[16,18] The pathology is suggested to develop within the epithelium due to intraoral trauma and various other irritational factors and poor oral hygiene.[19]

Various treatment modalities have been advocated with no significant success, for relieving the symptoms. The first and foremost preventive measure should be in advising the patient to discontinue the associated habit, which can be encouraged through patient education and counseling. Medical treatment is symptomatic and aimed at improving mouth movements. According to Canniff et al the medical management of OSMF is both empirical and unsatisfactory.[17] According to Rehana et al multiple minerals and micronutrients showed significant improvement in mouth opening of 41% of the patients.[20] Whereas, Borle et al showed improvement in symptoms of OSMF but insignificant improvement in mouth opening with vitamin A.[21] Singh et al have shown significant improvement in mouth opening, hyperkeratosis, pain in mouth and size of the lesion with oxitard capsules.[7] Rajendran et al found significant results with mouth opening and burning sensation with pentoxifylline, although results with tongue protrusion were not significant.[22] Lycopene has also showed significant improvement in mouth opening in the study by Karemore et al.[23] Sudarshan et al have shown significant improvement in the mouth opening with aloe vera.[24] Shetty et al recently have shown that spirulina can bring about significant improvement in mouth opening and tongue protrusion in the management of OSMF.[9] The present study is the first to compare the efficacy of the 2 natural antioxidants spirulina and aloe vera in the improvement of clinical parameters such as, moth opening, ulcers/erosions/vesicles, pain associated with the lesion and burning sensation.

Spirulina is a microalgae with rich natural source of proteins, carotenoids and other micronutrients and used in daily diet of African and American natives. It contains phenolic acid, tocopherols, and betacarotene which are known to exhibit antioxidant properties.[9] Spirulina has been used for the treatment of several oral mucosal lesions with successful results. It has been primarily assessed in treating leukoplakia with promising results.[8] However, its effects on OSMF are not well documented. Recently Shetty et al have evaluated the role of spirulina as an adjuvant therapy in the management of OSMF.[9]

Aloe vera is a mannoprotein containing many amino acids known as 'wound healing hormones'. Aloe vera has been used for a very wide range of conditions. The polysaccharides contained in the gel of the leaves, promote wound healing, and have anti-inflammatory, immunomodulatory, antioxidant properties and gastro protective properties. Further, sterols in the Aloe vera have strong ability to inhibit inflammation similar to the action of cortisone without any side effects. It can be found easily and is of low cost in India.[24] It has been said that topical application of the aloe vera gel can be used as a preventive or treatment modality for radiation-induced skin reactions. Anthraquinones present in the latex also have cytotoxic, radioprotective as well as antiangiogenic

Table 3 – Effect of spirulina and aloe vera on pain associated with lesion.

	Spirulina			Aloe vera		
	Present	Absent	Reduced	Present	Absent	Reduced
Baseline	19	2	–	20	1	–
After 1 month	15	3	3	16	2	3
After 2 months	11	5	5	12	5	4
After 3 months	6	9	6	8	8	5

Table 4 – Effect of spirulina and aloe vera on burning sensation.

	Spirulina			Aloe vera		
	Present	Absent	Reduced	Present	Absent	Reduced
Baseline	21	–	–	21	–	–
After 1 month	14	3	4	16	2	3
After 2 months	8	7	6	11	5	5
After 3 months	3	12	6	5	9	7

effects and inhibit angiogenic and metastatic regulatory processes.[25] Also, it may enhance cisplatin antineoplastic activity in B16–F10 melanoma cells.[26]

There was significant improvement in mouth opening and ulcer/erosions/vesicles in patients who were given spirulina when compared to aloe vera ($p < 0.05$). This was similar to the findings of Shetty et al, who showed significant improvement in mouth opening with spirulina.[9] Similarly Karemore et al. and Kumar et al. observed significant improvement in mouth opening with lycopene.[23,27] Singh et al also observed similar findings with oxitard capsules.[7] However, Sudarshan et al showed significant improvement in the mouth opening and burning sensation of the patients who were given aloe vera.[24] Both the groups showed improvement in burning sensation and pain associated with the lesion, but this was not statistically significant ($p > 0.05$). The relief from burning sensation in patients treated with spirulina is probably due to betacarotene, phenolic acid, tocopherols, and various micronutrients present in spirulina.[28] Administration of betacarotene – systemically and topically improves the epithelial integrity and also induces redifferentiation of dysplastic epithelium.[29] There were no noticeable side effects of spirulina and aloe vera.

The results of the present study show that spirulina significantly improves mouth opening and ulcers/erosions/vesicles in OSMF patients. Both the drugs were equally effective in improving the pain and burning sensation of the patients. Thus, spirulina can be thought to bring about relatively more positive outcomes for the patients with OSMF, when compared to aloe vera. The improvements in both the groups should also be related with the quitting of the associated habit, as this has also has a considerable effect in the regression of the disease. A larger sample size, with longer period of treatment follow-up, and a multi-institutional double-blind prospective study for assessment of effects of both the drugs is recommended to draw further conclusion on their utility in the treatment of OSMF.

5. Conclusion

Treatment of OSMF has been a challenge ever since its discovery. Newer drugs have been constantly evolving for the management of this complex disease. The results of the present study showed that both spirulina and aloe vera were found to be effective in the management of OSMF, though spirulina was found to be relatively more effective. Quitting of the habit alone as an intervention may have a significantly greater effect, on the symptoms of OSMF. Hence, intervention studies and public health campaigns at the community level must be encouraged, as they may prove to be the best way of controlling OSMF.

Conflicts of interest

All authors have none to declare.

REFERENCES

1. Cox SC, Walker DM. Oral submucous fibrosis. A review. *Aust Dent J*. 1996;41:294–299.
2. Gupta SC, Yadav YC. "Misi" an aetiological factor in oral submucosal fibrosis. *Indian J Otolaryngol*. 1978;30:5–6.
3. Schwartz J. Atrophia idiopathica mucosa oris. In: *Demonstrated at the 11th International Dental Congress: London*. 1952.
4. Joshi SG. Fibrosis of the palate and pillars. *Indian J Otolaryngol*. 1953;4:1.
5. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. *Oral Surg Oral Med Oral Pathol*. 1966;22:764–779.
6. Chole RH, Gondivkar SM, Gadbail AR, et al. Review of drug treatment of oral submucous fibrosis. *Oral Oncol*. 2012;48:393–398.
7. Singh BP, Mittal N, Sharma V, Palani. Evaluation of role of oxitard capsules in the treatment of oral submucous fibrosis. *Antiseptic*. 2009;106:103–107.
8. Ramadass T, Manokaran G, Pushpala SM, Narayanan N, Kulkarni GN. Oral submucous fibrosis – new dimensions in surgery. *Indian J Otolaryngol Head Neck Surg*. 2005;57:99–102.
9. Shetty P, Shenai P, Chatra L, Rao PK. Efficacy of spirulina as an antioxidant adjuvant to corticosteroid injection in management of oral submucous fibrosis. *Indian J Dent Res*. 2013;24:347–350.
10. Babu M, Rengaswamy S, Padmanabhan P, Varghese C. Evaluation of chemoprevention of oral cancer with Spirulina fusiformis. *Nutr Cancer*. 1995;24:197–202.
11. Patil S, Maheshwari S. Proposed new grading of oral submucous fibrosis based on cheek flexibility. *J Clin Exp Dent*. 2014;6:e255–e258.
12. Mathur RM, Jha T. Normal oral flexibility – a guideline for SMF cases. *J Indian Dent Assoc*. 1993;64:139–143.
13. More CB, Das S, Patel H, Adalja C, Kamatchi V, Venkatesh R. Proposed clinical classification for oral submucous fibrosis. *Oral Oncol*. 2012;48:200–202.
14. Tilakaratne WM, Klinikowski MF, Saku T, Peters TJ, Warnakulasuriya S. Oral submucous fibrosis: review on aetiology and pathogenesis. *Oral Oncol*. 2006;42:561–568.
15. Khan S, Chatra L, Prashanth SK, Veena KM, Rao PK. Pathogenesis of oral submucous fibrosis. *J Cancer Res Ther*. 2012;8:199–203.
16. Yoithapprabhunath TR, Maheswaran T, Dineshshankar J, Anusushanth A, Sindhuja P, Sitra G. Pathogenesis and

therapeutic intervention of oral submucous fibrosis. *J Pharm Bioallied Sci*. 2013;5:S85–S88.
17. Canniff JP, Harvey W. The aetiology of oral submucous fibrosis: the stimulation of collagen synthesis by extracts of areca nut. *Int J Oral Surg*. 1981;10:163–167.
18. Pindborg JJ. Is submucous fibrosis a precancerous condition in the oral cavity? *Int Dent J*. 1972;22:474–480.
19. Dayal Reddy R, Anuradha Bhat K. Malignant potential of oral submucous fibrosis due to intraoral trauma. *Indian J Med Sci*. 2000;54:182–187.
20. Maher R, Aga P, Johnson NW, Sankaranarayanan R, Warnakulasuriya S. Evaluation of multiple micronutrient supplementation in the management of oral submucous fibrosis in Karachi, Pakistan. *Nutr Cancer*. 1997;27:41–47.
21. Borle RM, Borle SR. Management of oral submucous fibrosis: a conservative approach. *J Oral Maxillofac Surg*. 1991;49:788–791.
22. Rajendran R, Rani V, Shaikh S. Pentoxifylline therapy: a new adjunct in the treatment of oral submucous fibrosis. *Indian J Dent Res*. 2006;17:190–198.
23. Karemore TV, Motwani M. Evaluation of the effect of newer antioxidant lycopene in the treatment of oral submucous fibrosis. *Indian J Dent Res*. 2012;23:524–528.
24. Sudarshan R, Annigeri RG, Sree Vijayabala G. Aloe vera in the treatment for oral submucous fibrosis – a preliminary study. *J Oral Pathol Med*. 2012;41:755–761.
25. Suboj P, Babykutty S, Valiyaparambil Gopi DR, Nair RS, Srinivas P, Gopala S. Aloe emodin inhibits colon cancer cell migration/angiogenesis by downregulating MMP-2/9, RhoB and VEGF via reduced DNA binding activity of NF-kappaB. *Eur J Pharm Sci*. 2012;45:581–591.
26. Tabolacci C, Rossi S, Lentini A, et al. Aloin enhances cisplatin antineoplastic activity in B16-F10 melanoma cells by transglutaminase-induced differentiation. *Amino Acids*. 2013;44:293–300.
27. Kumar A, Bagewadi A, Keluskar V, Singh M. Efficacy of lycopene in the management of oral submucous fibrosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2007;103:207–213.
28. Miranda MS, Cintra RG, Barros SB, Mancini FJ. Antioxidant activity of the microalga Spirulina maxima. *Braz J Med Biol Res*. 1998;31:1075–1079.
29. Varghese IP, Hari S. *Role of Beta-carotene in the Management of Oral Submucous Fibrosis*. Published in the 27th Kerala State Dental Conference; Calicut. 1994.