Effect of betel chewing, tobacco smoking and alcohol consumption on oral submucous fibrosis: a case-control study in Sri Lanka

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BACKGROUND: Oral submucous fibrosis (OSMF) is a chronic, insidious, disabling potentially malignant condition of the oral mucosa seen predominantly in south and Southeast Asia. No reports are hitherto available on the aetiological factors of OSMF based on Sri Lankan patients.

METHODS: A total of 74 patients with OSMF and 74 controls who consecutively attended the Oral Medicine clinic at the Dental Hospital (Teaching) Faculty of Dental Sciences, University of Peradeniya, Sri Lanka were included in the study. Binary logistic regression analyses were performed to model the influence of betel chewing, smoking and alcohol use and to determine the effects of different combinations of chewing habits on OSMF.

RESULTS: Betel chewing was the only significantly associated factor in the aetiology of OSMF (OR = 171.83, 95% CI: 36.35–812.25). There were no interaction effects of chewing, smoking and alcohol consumption in the causation of OSMF.

CONCLUSION: The present study has shown a strong association of betel quid chewing (including tobacco as an ingredient) with the causation of OSMF.

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Keywords: alcohol; areca nut; betel chewing; case–control; precancer; submucous fibrosis; tobacco

Introduction

Oral submucous fibrosis (OSMF) is a chronic, insidious, disabling potentially malignant condition of the oral cavity seen predominantly in south and Southeast Asia (1–5). It is characterized by excessive production of collagen leading to inelasticity of the oral mucosa and atrophic changes of the epithelium (6, 7). Clinical features of OSMF include burning sensation for spicy food, excessive salivation, dryness of the mouth, defective gustatory sensation and progressive restriction of mouth opening and the protrusion of the tongue (4, 6). These symptoms and signs vary depending on the site affected and the progress of the disease. With the progress of the disease fibrosis may extend from the lamina propria through entire submucosa to the muscle layer. Thick inelastic ropelike fibrous bands appear vertically in the buccal mucosa, along the contours of the faucial pillars and around the entire circle of lips thus leading to difficulty in mouth opening and narrowing of the rima oris. This eventually leads to limited access to the oral cavity that may compromise the oral hygiene and even food intake.

It is generally regarded that the areca nut alkaloids and tannins play an important role in the aetiology of OSMF (1, 8–11). Areca nut is consumed alone or more commonly as an ingredient of the betel quid (2, 10). Betel quid chewing continues to be widespread between south and Southeast Asian populations with a great spectrum of variation in ingredients and method of preparation (12). Betel chewing has deep-seated social and cultural links to modern as well as medieval Sri Lanka (13).

Furthermore, *in vitro* studies also have provided evidence in favour of the aetiological role of areca nut (14, 15). Harvey et al. (16) in an *in vitro* study have shown that areca nut alcaloid, arecoline and its hydrolysed product arecaidine stimulate cultured fibroblast in a dose-dependent manner. Studies on the role of areca nut/betel chewing in the causation of OSMF have been reported from India (17–19), Pakistan (10) and Taiwan (20). However, no case– control studies were reported based on Sri Lankan OSMF patients. Hence, this hospital-based case– control study was carried out to describe demographic and clinical characteristics and to ascertain the association of chewing, smoking and alcohol use in the causation of OSMF.

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Materials and methods

A total of 74 patients with OSMF who consecutively attended the Oral Medicine clinic at the Dental Hospital (Teaching) Faculty of Dental Sciences, University of Peradeniya, Sri Lanka were included in the study. Same number of age- and sex-matched patients who attended consecutively to the same clinic for various other complaints were included as controls.

The diagnosis of OSMF was based on the presence of one or more of the following criteria recommended at the workshop held in Kuala Lumpur, Malaysia (21).

- 1 Palpable fibrous bands.
- 2 Mucosal texture feels tough and leathery.
- **3** Blanching of mucosa together with histopathological features consistent with OSMF (atrophic epithelium with loss of rete-ridges and juxta-epithelial hyalinization of lamina propria).

In the present study, all the cases were confirmed by biopsy. Informed consent was obtained from both the case and control groups before including in the study and doing biopsies. A predetermined data sheet was used to record demographic data, history, clinical findings and details of betel chewing, tobacco smoking and alcohol habits. The following clinical parameters were used to assess the clinical condition of OSMF.

- 1 The degree of mouth opening (the distance between upper and lower incisors) was measured using a graduated venire gauge and the extent of mouth opening was utilized to determine the stages. Stage I: mouth opening ≥20 mm; stage II: mouth opening 11– 19 mm; stage III: mouth opening ≤10 mm.
- 2 Fibrous banding of the cheeks: the presence or absence of fibrous banding was determined by palpation of both buccal mucosae.
- **3** Mobility of tongue was assessed according to the ability to protrude: (i) beyond the mucocutaneous junction of the lower lip; (ii) only up to vermilion border of the lower lip; (iii) only up to lower incisal edges.
- **4** Status of the tongue papillae: this was assessed by visual examination to find the presence or absence of loss of papillae.
- **5** Burning sensation on spicy food: only the presence or absence was determined and no attempt was made to quantify.
- 6 Leathery feeling of the buccal mucosae: texture of the buccal mucosae was determined by palpation using the index finger.

Data analysis

Different habits and combinations were categorized without overlap. Betel chewing habits were categorized into four groups according to the ingredients used in the quid, i.e. areca nut alone, betel leaves and areca nut without tobacco, betel leaves, areca and lime without tobacco and betel leaves, areca nut, lime and tobacco. Binary logistic regression analyses were performed to model the influence of betel chewing, smoking and alcohol use and to determine the effects of different combinations of chewing habits on OSMF. Two models were fitted: the first fitted chewing, smoking and alcohol consumption. The likelihood ratio was > 0.05 and hence the model fit was considered adequate. As there were no interaction effects the second model was fitted for only the different chewing habits. In calculating the odds ratios (OR) where cell frequencies are zero pertaining to different habits, 0.5 was added to each cell frequency in order it to be possible. Statistical analysis was carried out using sAs V 8 software. The *P*-value below 0.01 was considered to be statistically significant.

Results

The study population consisted of 74 cases and same number of age- and sex-matched individuals as controls. The mean age of cases and controls was 43.9 ± 14.02 years. Table 1 gives the age and gender distribution of cases and controls. The highest number of cases found in the 25-34 years age group was 17 (27.9%). There was a male preponderance with a male to female ratio of 4.6:1. The age range of occurrence of OSMF in the present cohort was 15-76 years in males and 34-68 years in females. There was no statistically significant difference between gender and age of OSMF patients. The mean maximum mouth opening of the OSMF patients was 31.7 mm (SD: ± 10.7). Sixty-four patients (86.5%) had mouth opening ≥ 20 mm and only two patients (2.7%) had the extreme disease with mouth opening < 10 mm. Table 2 summarizes the symptoms and signs of patients with OSMF.

All OSMF patients had at least a single habit whereas 49 (66.2%) in the control group had no habit. Table 3 gives the distribution habits among cases and controls. Betel quid chewing habit was the commonest both in cases and controls. All OSMF patients had chewed betel quid. The distribution of different quid chewing habits in cases and controls are given in Table 4. Odds ratios for OSMF associated with betel chewing, smoking and alcohol habits are presented in Table 5. Betel chewing was the only significantly associated factor in the aetiology of OSMF [OR = 171.83, 95% confidence interval (CI): 36.35-812.25]. There were no interaction effects of chewing, smoking and alcohol consumption in the causation of OSMF. Therefore, the second

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Age group (years)	Male, n (%)	Female, n (%)		
	Case	Control	Case	Control	
14-24	5 (8.2)	3 (4.9)	_	_	
25-34	17 (27.9)	17 (27.9)	1 (7.7)	1 (7.7)	
35-44	13 (21.3)	14 (23.0)	4 (30.8)	5 (38.5)	
45-54	10 (16.4)	11 (18.0)	5 (38.5)	5 (38.5)	
55-64	10 (16.4)	11 (18.0)	1 (7.7)	- '	
≥65	6 (9.8)	5 (8.2)	2 (15.4)	2 (15.4)	
Total	61	61	13	13	

Table 2 Distribution of OSMF patients according to symptoms and signs

	Male		Female		Total	
Symptom/sign	n	%	n	%	n	%
Degree of mouth opening						
≥20	53	86.9	11	84.6	64	86.5
11–19	6	9.8	2	15.4	8	10.8
≤10	2	3.3	-	-	2	2.7
Fibrous banding of the cheeks (right side)						
Yes	21	34.4	6	46.2	27	36.5
No	40	65.6	7	53.8	47	63.5
Fibrous banding of the cheeks (left side)						
Yes	21	34.4	6	46.2	27	36.5
No	40	65.6	7	53.8	47	63.5
Mobility of the tongue						
No restriction	48	78.7	7	53.8	55	74.3
Up to mucocutaneous junction	12	19.7	6	46.2	18	24.3
Up to incisal edges	1	1.6	-	-	1	1.4
Status of the tongue papillae						
Depapillated	54	88.5	11	84.6	65	87.8
Not depapillated	7	11.5	2	15.4	9	12.2
Burning sensation for spicy diet						
Yes	59	96.7	12	92.3	71	95.9
No	2	3.3	1	7.7	3	4.1
Leathery feeling						
Yes	57	93.4	13	100	70	94.6
No	4	6.6	-	-	4	5.4

Table 3 Distribution of habits in cases and controls

Habits	<i>Case, n (%)</i>	Control, n (%)
No habit	_	49 (66.2)
Betel chewing only	52 (70.2)	10 (13.5)
Tobacco smoking only	-	5 (6.8)
Alcohol only	-	3 (4.1)
Smoking + alcohol	-	4 (5.4)
Chewing + alcohol	4 (5.4)	2 (2.7)
Chewing + smoking	7 (9.4)	1 (1.3)
Chewing + smoking + alcohol	11 (14.8)	-

regression model was fitted only for the different chewing habits according to the ingredients used. The use of all ingredients in the quid (betel leaves, areca nut, lime and tobacco) was significantly associated with the occurrence of OSMF (OR = 16.24, 95% CI: 5.88-44.86). Association of chewing areca nut alone (OR = 11.79, 95% CI: 0.64-217.21) was not statistically significant (Table 6).

Discussion

In Sri Lanka, oral and pharyngeal cancers are the commonest out of all body site cancers with an incidence 10.99/10 000 for men and 4.37/100 000 for women (22). Some of these cancers are preceded by potentially malignant lesions and conditions. Tobacco, the most important causative factor for oral cancer is consumed mainly in the form of betel quid chewing in south and Southeast Asia including Sri Lanka (23). Betel quid chewing habit also can lead to pre-cancer such as leukoplakia and OSMF in the oral mucosa (24–27). Given this scenario the present study was performed to ascertain the effect of betel chewing, tobacco smoking and alcohol use on OSMF, which had hitherto not been studied in Sri Lanka. Although the present study does not conform to the strict criteria of population-based study it has provided very useful information being the first in Sri Lanka to ascertain the effects of such habits on OSMF.

 Table 4
 Distribution of betel chewing habit in cases and controls according to age groups

Age group (years)	B + A, n (%)		B + L + A, n (%)		B + L + A + T, n (%)		A, n (%)		No habit, n (%)	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
14-24	1 (20)	_	_	_	3 (60)	_	1 (20)	_	_	3 (100)
25-34	-	1 (5.6)	1 (5.6)	-	15 (83.3)	-	2(11.1)	-	-	17 (94.4)
35-44	1 (5.9)	- ` `	1 (5.9)	-	14 (82.3)	1 (5.3)	1 (5.9)	-	_	18 (94.7)
45-54	- ` `	-	1 (6.7)	3 (18.8)	12 (80)	3 (18.8)	2 (13.3)	-	-	10 (62.5)
55-64	-	1 (9.1)	1 (9.1)	2 (18.2)	10 (90.9)	1 (9.1)		_	_	7 (63.6)
≥65	2 (25)	-	- ` ´	-	6 (75)	1 (14.3)		-	-	6 (85.7)
Total	4 (5.4)	2 (2.7)	4 (5.4)	5 (6.8)	60 (81.1)	6 (8.1)	6 (8.1)	-	-	61 (82.4)

B, betel; L, lime; A, areca; T, tobacco.

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 Table 5
 Logistic regression analysis for OSMF associated with different habits

Habits	Case, n (%)	Control, n (%)	Odds ratio	95% CI	P-value
Smoking ^a	0	5 (6.8)	2.77	0.54-14.05	0.2184
Alcohola	0	3 (4.1)	0.932	0.20-4.330	0.9282
Chewing alone	52 (70.2)	10 (13.5)	171.83	36.35-812.25	0.000 ^b

^a0.5 added to each cell frequency to calculate OR.

^bSignificant at 1% level of significance.

 Table 6
 Logistic regression analysis for OSMF associated with different betel chewing habits

Habits	Case, n (%)	Control, n (%)	Odds ratio	95% CI	P-value
Areca nut only ^a	5 (6.8)	0	11.79	0.64-217.21	0.058
Betel leaves + areca	3 (4.1)	1 (1.4)	3.08	0.31-30.36	0.62
Betel leaves + areca + lime	4 (5.4)	4 (5.4)	1	0.24-4.16	1.00
Betel leaves + areca + lime + tobacco	40 (54.1)	5 (6.8)	16.24	5.88-44.86	0.000 ^b

^a0.5 added to each cell frequency to calculate OR.

^bSignificant at 1% level of significance.

In accordance with the other studies, the present study has also shown male preponderance (17, 18). However, a case-control study in Pakistan reported female preponderance (10). In the present study, the highest number (n = 17, 27.9%) of cases was found in a relatively younger age group and also the mean age of the cases and controls of the present study was younger $(43.9 \pm 14.02 \text{ years})$ than the mean age (58.6 ± 12.1) reported in a previous clinical study based on Sri Lankan patients (4). Furthermore, males were affected at a relatively younger age compared with females and this finding was similar to previous studies (9, 10). In the present study, there were no cases of OSMF without chewing habit. A case without betel chewing habit was reported in a recent study conducted in Chennai, south India (18).

Quid has been defined as 'a substance or mixture of substances, placed in the mouth or chewed and remaining in contact with the mucosa, usually containing one or both of the two basic ingredients, tobacco and/or areca nut in raw or any manufactured or processed form' (21). There is a great spectrum of variation of ingredients included in quid among consumers in the south and Southeast Asian countries (12). The commonest form consumed in Sri Lanka is a combination of betel leaves, areca nut, lime and tobacco. The present study shows that the majority of cases (81.8%) with OSMF consumed the above combination. All the patients in the study group had at least a single habit (betel chewing, smoking or alcohol consumption) whereas 49 (66.2%) had no habit in the control group and betel quid chewing habit was the commonest both

in cases and controls. Logistic regression has shown that the betel chewing has the highest risk in developing OSMF with OR = 171.83 (95% CI: 36.35–812.25). Ranasinghe et al. (28) in 1993 reported that betel quid chewing habit with tobacco was the most common habit (84%) among Sri Lankan patients with oral cancer. Furthermore, it was revealed that 63% of oral cancer patients used to smoke tobacco and 55% had both betel chewing and smoking habits. Interestingly there were no consumers of tobacco in the form of smoking as the only habit in the present cohort of OSMF patients. However, a small proportion of OSMF patients (9.4%) in the present cohort had both betel chewing and smoking habits.

Areca nut chewing alone was practiced by six (8.1%) patients with OSMF. The rest of the OSMF patients consumed areca nut as an ingredient in their quid. This shows that areca nut was an essential ingredient of the betel quid consumed in the present cohort with OSMF. Areca nut is the seed of the oriental palm tree *Areca catechu* that is freely grown in many parts of Sri Lanka. Areca nut is one of the main ingredients incorporated in the betel quid consumed in Sri Lanka. Areca nut alcaloid, arecoline (1,2,4,5-tetrahydro-1-methyl-pyridinecarboxylic acid) induces the collagen synthesis leading to submucous fibrosis (8).

When the ingredients of the quid were taken into consideration the highest risk was found to be associated with all ingredient chewing (betel leaves, areca nut, lime and tobacco). The role of areca nut chewing alone was not found to be significant and similar results were found in south India (18). Role of tobacco smoking and alcohol consumption also was not found to be associated with causation of OSMF. Previous studies (9, 17) also found similar results with regard to the smoking habit. Although tobacco consumption was found to have strong relationship in causing oral cancer and precancer such as leukoplakia (24, 29) to date there is no evidence of its role in causing OSMF. The present study is also in favour of this. However, a hospital-based casecontrol study in south India has shown that the concomitant use of tobacco and alcohol with areca nut habit increases the risk of OSMF (18). No significant interaction effects were found in the present study although there were 11 (14.8%) individuals in the OSMF group who had all three habits.

It is a unique feature in the present cohort that females were neither smokers nor alcohol users. This may be due to the strong social and cultural influences on females in the medieval and modern Sri Lanka. Similar result with regard to smoking was found previously in another study based on Sri Lankan oral cancer patients (28).

The present study provided somewhat different results in terms of the role of areca nut chewing in causing OSMF compared with studies in India and Pakistan (10, 17, 18). This may be due to the fact that the number of individuals chewing areca nut alone in the present cohort is limited.

In conclusion, the present study has described the clinical and demographic data of Sri Lankan OSMF

patients and shown further evidence on the role of betel quid chewing in the aetiology of OSMF. Given this scenario and considering the role of tobacco use in the aetiology of oral cancer, pre-cancer and its malignant transformation, lack of successful treatment for OSMF, this study shows a dire need of preventive strategies in this community where there is high risk of oral cancer.

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