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Salivary pooling: is it specific to particular regions in oral submucous fibrosis?

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Abstract

Despite extensive research, the pathophysiology of oral submucous fibrosis (OSMF), a premalignant condition that primarily affects the mucosa, is still unclear, although the chewing of areca nut is known to be the primary cause. While a clear association exists between areca nut and OSMF, very little has been published on the reason for its sporadic incidence in the mouth. Many authors have suggested the site where quid is habitually placed, but this fails to explain multiple sites in those who chew on one side. We hypothesised that the pattern of salivary pooling might affect the distribution of OSMF by carrying the chemicals responsible for mucosal damage. In our study of 174 patients, we evaluated the sites where quid was habitually placed and the areas of salivary pooling, and their association with the incidence of OSMF. Most chewers (136/174, 78%) placed the quid in the buccal vestibule, although other sites were also used including the vestibule of the lip, tongue, and floor of the mouth. The standardised residuals suggested significant associations ($p < 0.001$) between salivary pooling and OSMF, and indicated that salivary pooling affects the mucosal surfaces where it occurs. Our results show that the quid is not the only cause of OSMF. Salivary pooling also has an important role and provides a possible mechanism for the sporadic incidence of the condition. To our knowledge this is the first study to evaluate salivary pooling as a contributory factor in OSMF, and it may help to explain the pattern of distribution. Further work is needed in this area to understand the association more fully.

Keywords: Oral submucous fibrosis; Saliva pool; Gutkha; Areca nut; Pathogenesis

Introduction

Oral submucous fibrosis (OSMF) is a complex, debilitating, and precancerous condition that is associated with abnormal metabolism of collagen.[1] Despite more than 3 decades of research, its pathogenesis is still not fully understood,[1,2] and although it is thought to be multifactorial with many influencing factors, areca nut is considered the primary cause.[3–8]

Areca nut contains alkaloids, flavonoids, and copper, which interfere with homeostasis of the extracellular matrix.[1] Many studies provide evidence of a casual association between OSMF and copper in areca nut and drinking water,[3,8–12] and it has been suggested that chewing areca nut substantially raises the concentration of soluble copper in saliva, and as a consequence upregulates local lysyl oxidase activity in the oral mucosa, and promotes fibrosis by the cross-linking of collagen fibres.[8]

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In south Asia, the most commonly used, commercially freeze-dried areca nut products are betel quid and gutkha, the latter having replaced most areca nut preparations. Gutkha contains high concentrations of areca nut along with tobacco,[1] and when chewed, dissolves quickly in saliva and provides central stimulation, which is reported to be more intense than tobacco alone.[1] It is usually placed in the buccal or labial vestibule, and is sometimes placed sublingually, and is chewed for up to an hour until the nut softens and dissolves in saliva. The excess is then spat out or swallowed. Some patients have been known to place it in the buccal vestibule while they sleep. As increased copper concentrations have been found in fibrotic tissue in patients with unilateral OSMF, it has been postulated that chewing at the site where the quid is habitually placed raises the local levels of copper sufficiently to cause fibrosis.[13,14]

While there is a clear association between the chewing of gutkha or areca nut and the incidence of OSMF,[10,11] we know of little that has been published on the cause of its sporadic pattern of distribution in the oral cavity. Persistent chewing of gutkha quid at a specific site has been suggested as the reason for the diverse distribution of OSMF. According to this hypothesis unilateral chewers will have unilateral OSMF. However, this postulation is based on experimental data rather than clinical observation.[9–11]

It has been proposed that proximity of the gutkha or areca quid to the oral mucosa is responsible for the local development of OSMF, and experimentally, exposure of the oral mucosa to saliva containing dissolved products of the quid has resulted in OSMF.[10,11] Based on these findings, it was postulated that gutkha quid and saliva containing its chemicals are the primary cause of OSMF because they enable the chemicals to be absorbed into the oral mucosa.[10,11] However, this fails to explain the incidence of OSMF in multiple sites among unilateral chewers, and why some surfaces are not affected.

The prolonged exposure of the oral mucosa to saliva containing dissolved products of the quid, which occurs when the saliva pools in a specific area, could be an explanation. It could therefore be speculated that the pattern of pooling affects the distribution of OSMF. We recorded the sites where gutkha was chewed and where the saliva pooled to find out whether they were associated with the site of OSMF.

Material and methods

The local ethics committee approved the study which was conducted in the Yadgir district of the Hyderabad–Karnataka region in India. We randomly recruited 174 patients who chewed gutkha or areca nut, and had had OSMF confirmed by clinical examination by one of the authors of the study (GA). We avoided histopathological examination because the pain that results from the biopsy procedure can change the patterns of chewing and salivary pooling. We therefore followed the standard protocol for clinical diagnosis by Khanna and Andrade.[15]

Those previously operated on for OSMF and those who had OSMF but were not currently chewing gutkha, were excluded.

Patients were informed only during the examination to avoid influencing the site of salivary pooling. They were given a detailed explanation about the placement of gutkha quid and sites of salivary pooling in their native language.

Salivary pooling was described as the collection of pooled saliva under pressure in one part of the oral cavity during the process of chewing, and that the surface where this occurred contained a high concentration of the gutkha ingredients. For convenience we divided the oral mucosal surfaces into 6 categories: right buccal mucosa, left buccal mucosa, tongue, lip, floor of the mouth, and back of the mouth.

Each patient (holding the gutkha quid for 5 min) was shown the 6 areas in a healthy volunteer and questioned about where they placed the quid and about the surfaces affected by salivary pooling. These were recorded by one of the authors (GA) and a panel of 3 examiners (medical physiology staff) examined patients repeatedly to assess the sites. Histopathological examination of all the surfaces involved in this large group was beyond the scope and aims of the study.

We recorded the patient's age and occupation, and recorded isolated cases of OSMF separately with the site where quid was placed and surfaces where saliva pooled. Any secondary malignant changes in the mucosal surfaces were confirmed histopathologically and recorded separately for each site involved.

Statistical methods

The nominal (categorical) data were analysed and assessed for association between the site where quid was habitually placed, site of salivary pooling, and clinically affected area. The chi-square test with Yates' continuity correction for 2×2 contingency tables was used to analyse association between groups. The chi square test is an approximate test, and Yates' correction for continuity should make it more exact, specifically in small samples. It makes the result more conservative, which is thought to be beneficial because of the interdependence of the cells in a 2×2 table. The correction subtracts 0.5 from the difference between each served and expected value and therefore reduces the size of the test statistic and increases the probability value. While its use for large samples makes little difference to the outcome of the chi square test, it has been applied here to show that significant associations were identified with the most conservative application of the test. Probabilities of less than 0.05 were considered significant. Data were analysed using SPSS Statistics for Windows (version 20.0, IBM Corp, Armonk, USA).

Results

A total of 174 men, mean (SD) age 26.0 (8) years were included. Quid was most commonly placed in the left buccal