



Efficacy of curcumin in treating palatal changes associated with reverse smoking

Eficácia da curcumina no tratamento de alterações do palato associadas ao fumo reverso

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Abstract

Objectives: To evaluate the efficacy of curcumin preparation on the palatal changes associated with reverse smoking. **Materials and methods:** The study sample was divided into two groups with ten reverse smoking patients each. Group A patients were advised to use curcumin oral gel on an acrylic palatal plate whereas group B patients were instructed about the benefits of smoking cessation. Clinical and cytological smear examinations were performed at the first visit and at the end of the third visit. Data obtained was subjected to statistical analysis. **Results:** Evident improvement with reduction in size and severity of the clinical lesion was observed among the study group at both first and third visits ($p < 0.001$, significant). However, the cytological appearances remained the same in all the cases, except for three cases from the study group, which demonstrated a transition from moderate dysplastic features to milder dysplastic features ($p = 0.28$, not significant). **Conclusion:** Due to its diverse array of molecular targets, curcumin affords great potential as a therapeutic agent for precancerous and cancerous conditions. Results from our pilot study have clearly shown that curcumin is effective in the treatment of the palatal changes associated with reverse smoking.

Keywords: Curcumin. Palatal changes. Reverse smoking.

Resumo

Objetivos: Avaliar a eficácia da curcumina sobre as alterações palatais associadas ao fumo reverso. **Materiais e métodos:** A amostra foi dividida em dois grupos com dez pacientes fumantes cada. No grupo A os pacientes foram aconselhados a usar o gel de curcumina oral em uma placa de acrílico palatina, enquanto os pacientes do grupo B foram instruídos sobre os benefícios da cessação tabágica. Exames de esfregaço citológico e exames clínicos foram realizados na primeira visita e no fim da terceira visita. Os dados obtidos foram submetidos à análise estatística. **Resultados:** Observou-se evidente melhora na redução do tamanho e na gravidade da lesão clínica no grupo de estudo em ambas as visitas ($p < 0,001$, significativo). No entanto, a aparência citológica permaneceu a mesma em todos os casos, exceto em três casos do grupo de estudo, os quais demonstraram uma transição de características displásicas moderadas para leves ($p = 0,28$; não significativo). **Conclusão:** A curcumina, em virtude de seu conjunto diversificado de alvos moleculares, proporciona um grande potencial como agente terapêutico para as condições cancerosas e pré-cancerosas. Os resultados do nosso estudo piloto mostraram claramente que a curcumina é eficaz no tratamento das alterações palatais associadas ao fumo reverso.

Palavras-chave: Curcumina. Alterações palatais. Fumo reverso.

Introduction

Reverse smoking is a prevalent habit among females in certain parts of India and Andhra Pradesh, popularly called “adda poga” in the regional language as stated by Ramulu et al. (1). It is also done by men, but to a lesser extent. Reverse smoking is a specific way of enjoying “chuttas” (homemade cigars) where the smoker puts the burning end of the cigar inside the mouth by cultural custom, in order not to be seen in the dark, or as the chutta will less likely be extinguished by water being splashed on it during household work, or so as to prevent the possibility of hot ashes falling on nursing infants or to prevent the surf of the sea to put out the glow (2). The habit has also been reported from other parts of the world with similar explanations (3). Reverse smoking is also done by men, but to a lesser extent; 25% of the men and 50% of the women are reverse smokers. Preliminary hospital-based studies done by Mehta FS (4) have shown that there is a statistically significant relationship between reverse smoking and carcinoma of the hard palate.

Turmeric is commonly used as a spice in curries, as a food additive and also as a dietary pigment. It has been used to treat various illnesses in the Indian subcontinent from the ancient times (5). Curcumin reportedly possesses several pharmacological properties, including anti-inflammatory, antimicrobial, antiviral, antifungal, antioxidant, chemo sensitizing, radio sensitizing, and wound healing activities (6-8). It

is known to suppress tumor initiation, promotion and metastasis in experimental models, and it can also act as an antiproliferative agent by interrupting the cell cycle, disrupting mitotic spindle structures, and inducing apoptosis and micronucleation (6, 9, 10).

Apparently, curcumin is a pluripotent pharmacological agent that utilizes multiple molecular pathways to leave its imprint on biological systems (11). Thus, this pilot study aimed at finding the effects of curcumin preparation on the palatal changes associated with reverse smoking in ten patients having the habit and comparison with that of the control patients.

Materials and methods

A sample of 20 subjects with a habit of reverse smoking for more than 25 years and demonstrating evident palatal changes (Table 1) were selected from the outpatient department of our college to be included in the study. The whole sample was divided into two groups comprising ten patients each. Group A with the study patients and group B, having the control patients. The study was approved by the institutional ethics committee of Vishnu Dental College (VDC/1630A/2011, based on ICMR guidelines). All the subjects were explained about the study procedure and written consent was obtained.

Initially, patients from both groups were explained about the harmful effects of reverse smoking and pro-

density of the palatal changes turning into malignancy and further advised to quit the habit.

Group A: An impression was made for fabrication of an acrylic palatal plate (Acrylic resin tray material, manufactured by MP Sai Enterprise, Mumbai-400053) to dispense the medicament so that it remains in contact with the tissue for a longer time and is not washed off in saliva (Figure 1). Patient was instructed to apply the *Curcuma oral gel* (commercially available curcumin preparation having curcuma longa as an active ingredient, manufactured by Piramal Health Care Limited, Piramal tower, Peninsula Corporate Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, India) on the tissue surface of palatal plate 3-4 times daily and place it in the mouth continuously for 2-3 hours.

Group B: Counselling regarding the smoking cessation and oral hygiene instructions was provided to all patients.

All the subjects were advised a recall of three visits at every fifteen day period during which clinical and cytological smear examinations were performed. At every visit, clinical examination was done to evaluate the severity of palatal changes and the lesions were considered to be mildly improved if there was $\frac{1}{4}$ reduction in the clinical presentation (size and severity) of the lesion from the initial appointment, and moderately improved if there was $\frac{1}{2}$ reduction in the clinical presentation (size and severity), fully improved if there was no evidence of the clinical lesion or no improvement if the lesion was persisting as it was. For cytological smear examination, a wooden spatula was used to collect the cells for exfoliative cytology, smear fixed in ethanol and stained using Papanicolaou method. The cytology figures were given different

grades of dysplasia (12) on viewing through a digital research microscope at a magnification of 20 X.

Results

A noticeable change and improvement in the clinical appearance of palatal lesions (Figures 2-7) and histopathological smears was observed on using curcumin with no associated allergy or untoward effects. Evident improvement with reduction in size and severity of the clinical lesion was observed in the study group both at first (Table 2) and third visits (Table 3) with a statistically significant p value of < 0.001 . Cytological smear examinations revealed that majority of cases from both study and control group had a class 2 and class 3 cytology. The cytological appearances remained the same in all the cases of study and control group, except for three cases from study group which demonstrated moderate dysplasia turning to milder dysplasia [$p = 0.28$, not significant] (Figure 8 and Table 4).

Table 2 - Clinical evaluation of palatal changes at the end of second visit in group A and group B (Fisher's Exact Test)

Outcome	Clinical appearance at 2 nd visit	
	Group A n (%)	Group B n (%)
Reduced severity	10 (100)	2 (20)
No improvement	0	8 (80)
Total	10	10

P < 0.001, HS

Source: Research data.



Figure 1 - Maxillary cast with acrylic palatal plate for dispensing the medicament

Table 3 - Clinical evaluation of palatal changes at the end of three visits in group A and group B

Clinical appearance at 3 rd visit		
	Group A	Group B
Outcome	n (%)	n (%)
Mild improvement	0	8 (80)
Moderate improvement	7 (70)	2 (20)
Fully Improved	3 (30)	0
Total	10	10
Chi-Square = 13.77		
P < 0.001, HS		

Source: Research data.

Table 4 - Cytological Staging in two groups at 1st and 3rd visit (*Mann-Whitney Test)

Cytological Staging	1 st Visit		3 rd Visit	
	Group 1	Group 2	Group 1	Group 2
	n (%)	n (%)	n (%)	n (%)
Stage 2	3 (30)	3 (30)	6 (60)	3 (30)
Stage 3	6 (60)	6 (60)	3 (30)	6 (60)
Stage 4	1 (10)	1 (10)	1 (10)	1 (10)
Total	10	10	10	10
Gr 1 v/s Gr 2 *	P = 1.00, No diff.		P = 0.28, NS	

Source: Research data.

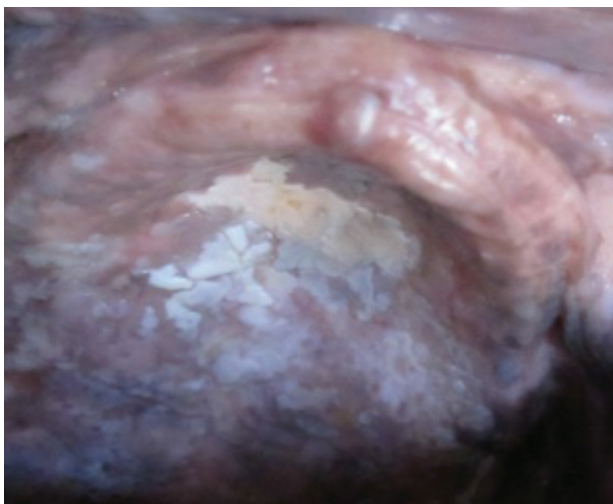
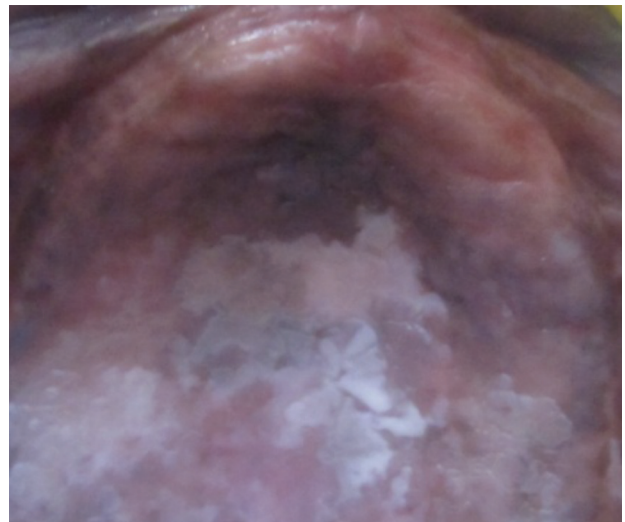
**Figure 2** - Patient 1: multimorphic palatal changes with extensive white patch at first visit**Figure 3** - Reduced clinical presentation at the second visit**Figure 4** - Further improvement at third visit**Figure 5** - Patient 2: multimorphic palatal changes with keratosis, excrescences and hyper pigmentation at first visit



Figure 6 - Reduced clinical presentation at the second visit



Figure 7 - Further improvement at third visit

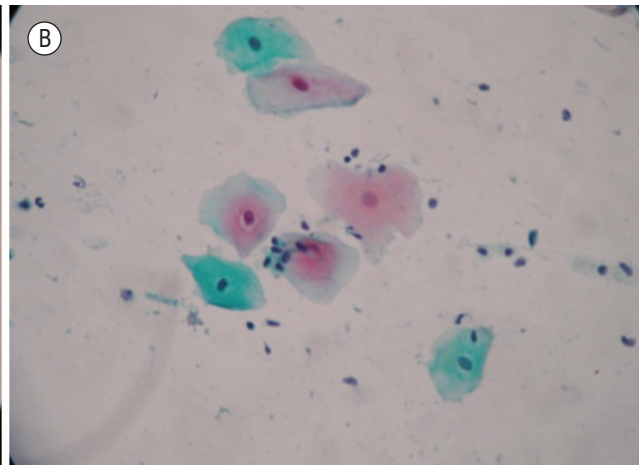
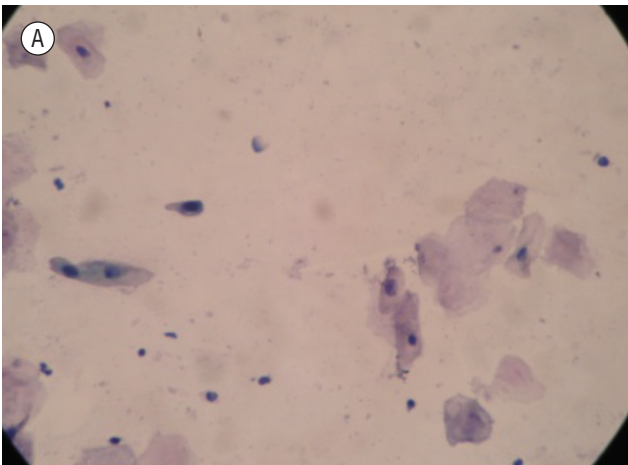


Figure 8 - Histopathological picture of palatal changes. A) Class 3 cytology before application of curcumin (Papanicolaou 20X); B) Class 2 cytological appearance at the end of three visits in the study group (Papanicolaou 20X)

Discussion and conclusion

The term “palatal changes” describes the reaction of the palatal mucosa to reverse chutta smoking. This form of smoking evokes diverse alterations in the palatal mucosa which can be categorized into several interrelated components such as: palatal keratosis, excrescences, patches, red areas, ulcerations, and pigmentation changes (Table 1). They may occur independently or coexist. One component may change into another over time, indicating a single pathogenic mechanism. Therefore, although red areas, patches, and excrescences resemble the lesions of erythroplakia, leukoplakia, and smoker’s palate, respectively, they are not classified in these

terms. Palatal changes occur in up to 46% of the reverse smokers (13).

In reverse smoking the smoke is drawn with the glowing end of the cigarette inside the mouth and the oral tissue is therefore exposed both to the active and passive gas phase of the tobacco smoke. The toxins are furthermore presented to the palatal mucosa located 15-20 mm from the cigarette glow at a temperature of +97 °C. This will raise the temperature of the mucosal surface with +4 °C. The habit is thus known to produce a high frequency of palatal cancer (14, 15). For many years the usual treatment of these potentially malignant lesions was palliative, as quitting the habit of smoking and by using anti-oxidants which are not affordable to this category of

Table 1 - Palatal changes associated with reverse smoking

Changes in palatal mucosa	Clinical aspects
Palatal keratosis	Diffuse whitening of the palatal mucosa. It may be mild, moderate or severe in intensity. Palatal keratosis may occur independently or coexist with other components. Overall, it forms up to 55% of the palatal components.
Excrescences	Excrescences comprise 1-3 mm elevated area, often with central red dots marking the orifices of the palatal mucosa glands. Some 46% of the palatal changes consist of excrescences. Excrescences represent the initial palatal reaction and they are generally transient. The milder forms of excrescence resemble the smoker's palate seen in conventional smokers.
Patches	Patches are well-defined, elevated plaques which could qualify for the clinical term leukoplakia. Palatal patches show characteristics, histologic features that differ from the features of leukoplakia. Patches can be small or large. These account up to 12% of the palatal components.
Red areas	Red areas are well-defined reddening of the palatal mucosa. Clinically, they are indistinguishable from erythroplakias. Red areas form only 2% of the palatal components. Nevertheless, they are the most serious, showing epithelial dysplasia in 52% of the cases. Long-term studies demonstrate a high rate of malignant transformation.
Ulcerated areas	Ulcerated areas are characterized by crater-like ulcerations with deposits of fibrin often surrounded by keratinization. Ulcerations form only 2% of the palatal components. They represent a "burn" type reaction of the palatal mucosa from the intense heat of the lighted end of chutta.
Hyperpigmentation	Pigmentation changes that include hyperpigmentation and loss of pigmentation occur in almost all reserves chutta smokers. Hyperpigmentation manifests in various forms, such as the spotted, linear, patchy, diffuse, and reticular types. Palatal pigmentation in reverse smokers is perhaps a protective reaction to the heat and smoke; it is not known to predispose to a melanoma or any other pathology.
Nonpigmented areas	Nonpigmented areas indicate areas of palatal mucosa which are clinically devoid of melanin pigmentation. Nonpigmented areas result following the regression of red areas. Loss of pigmentation may render the palatal mucosa more vulnerable to the action of carcinogens in tobacco. Epithelial dysplasia was observed with increased frequency in nonpigmented areas.
Multimorphic lesion	Various palatal components may coexist and they also occur in association with non-palatal lesions.
Non-palatal lesions	About 5% of the palatal changes are associated with non-palatal lesions; the most common of them is leukoplakia, which occurs on the dorsum of the tongue that is otherwise an uncommon location.

Source: Research data.

patients who earn their livelihood by depending on daily wages. So a medicament that can relieve the signs and symptoms of these palatal changes with a long proven history of safety is warranted.

Turmeric (called Haldi in India) named by British as curry spice, is the dried rhizome powder of *Curcuma longa*, a perennial herb of the *Zingiberaceae* family, a valuable cash crop, widely cultivated in India, China, and other tropical countries. In spite of not possessing any nutritive value, it has been in constant use by humans as turmeric powder since Vedic times or even earlier, and considered as pharmacologically safe (6). Ammon HP et al. (16) stated that human consumption of curcumin as a dietary spice ranges up to 100 mg/day and recent phase I

clinical trials indicate that humans can tolerate a dose of curcumin as high as 12 g/day, without any toxic side effects. The latest report by Siwak DR et al. and Lao CD et al. (9, 17) has indicated a safe dose of curcumin up to 12 g/day in humans.

Curcuma species contain turmerin (a water-soluble peptide), essential oils (such as turmerones, atlantones and zingiberene) and curcuminoids including curcumin [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3, 5-dione] which exhibit profound, anticarcinogenic and antimutagenic activities (18). Two well defined eukaryotic transcription factors nuclear factor - Kappa B (NF-Kappa B) and activator protein (AP-1) have been implicated in the pathogenesis of many human diseases, including

cancer; turmeric exerts antitumor promotional effects through suppression of tumor promoter induced activation of transcription factors, NF-Kappa B and AP-1 (19). Others are of opinion that the anti-precancerous effects of curcumin are mediated through an antioxidant mechanism, by increasing levels of vitamins C and E, and by preventing lipid peroxidation and DNA damage (20). The anti-carcinogenic activity is also thought to be mediated by inhibition of AK-5 tumor growth and induced apoptosis in AK-5 cells. In addition, turmeric induced tumor cell death is caused through generation of reactive oxygen intermediates, which is inhibited by N-acetyl cysteine (21).

In our study, the study group demonstrated evident improvement in the clinical picture when compared to the control group signifying the efficacy of curcumin in treating the palatal lesions associated with reverse smoking. However, the absence of cytological differences between treated and not treated lesions may probably be attributed to the varying practices of the habit (duration and frequency) among those subjects.

Many people are familiar with turmeric as a spice but very few know of its medicinal values (22). Curcumin due to its diverse array of molecular targets affords great potential as a therapeutic agent for precancerous and cancerous conditions. In the present pilot study, we made an attempt in using this holistic gift of nature in curing the palatal changes associated with reverse smoking habit. Based on our results, we conclude that the palatal changes associated with reverse smoking can be effectively treated using the curcumin preparation. Further, long-term studies with larger samples in the form of randomised controlled trails are required to determine the relationship between curcumin, biomarkers and oral cancer, and to advocate its utility in cancer chemoprevention and chemotherapy. There is need to explain its maximum potential in the field of medicinal and pharmaceutical science for novel and fruitful applications in near future.

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