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Anticancer Property of Incudent Tooth Paste Formulation

Review Article

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Abstract

Oral leukoplakia which is a major problem in countries with prevalent tobacco use, has been closely linked with inflammation. Twenty patients with oral leukoplakia along with 20 normal healthy control subjects who satisfied all inclusion and exclusion criteria, were included in the study. All subjects brushing twice per day with new tooth paste formulation. Tooth paste formulation induced the disappearance of clinical sign and symptoms. Levels of inflammatory cytokine in serum and saliva were examined just prior to start brushing with new tooth paste and after clinical improvement of precancerous lesions. In contrast to normal healthy subjects, levels of TNF-alpha, IL-6, and IL-8 in serum and saliva showed statistically significant increased in patients with oral leukoplakia. These levels significantly decreased in all groups after brushing. Pain scores and size of lesion in oral leukoplakia improved significantly. Based on these results we conclude that new formulation active ingredient mediates its beneficial effects in patients with oral leukoplakia through the suppression of proinflammatory cytokines.

Keywords: Herbal Formulation; NF-kappa B; Precancerous Lesions; Serum; Salivary; Anticancer.

Introduction

Oral cancer is the sixth commonest cancer in the world [1]. Its incidence is predominantly high in India specially north India, some other countries in Asia, and in certain places in the western hemisphere. It has been reported that 90% of oral cancers in India among men were attributable to chewing and smoking habits. In India, the age standardized incidence rate of oral cancer is 12.6 per 100 000 population [2]. Oral squamous cell carcinoma develops through a multi-step process of genetic, epigenetic and metabolic changes resulting from exposure to carcinogens [3]. The initial presence of a precursor subsequently developing into cancer is well-established in oral cancer [4]. Oral leukoplakia, submucous fibrosis, lichen planus are major known precursor lesions. Only 8-10% of these lesions ultimately turn into malignancy [5]. Ability to clinically predict malignant transformation is limited and routine histopathological diagnosis has limited its prognostic value. Inspite of advances of technologies in early detection of oral precancerous and cancerous lesions, there are limitations for its use such as, the diagnosis is essentially subjective, all lesions exhibiting dysplasia do not eventually become malignant and some may even regress, and carcinoma can develop from lesions in which epithelial dysplasia was not diagnosed in previous biopsies [6, 7]. Therefore, it is necessary to develop other methods for predicting the malignant potential of pre-malignant lesions and preventive measures [7].

Recently, strong evidences have been suggested that the nuclear factor-κB (NF-κB) signaling pathway plays a critical role in carcinogenesis, protection from apoptosis and chemoresistance in a number of cancer types, including head and neck cancer, breast cancer, hepatocellular carcinoma and gastric cancer [8-12]. Recently, accumulating evidence suggested that the NF-kappa B dependent cytokine levels in saliva and tissue specimens of patients with oral premalignant lesions are elevated [13]. So, an agent that can target NF-kappaB dependent cytokine of attention for prevention and treatment of oral precancerous lesions. Various dentifrices have available in market for prevention of oral diseases. Recently , one formulation of anticancer tooth paste has been proposed. This study was planned to study the find the anticancer properties by using salivary biomarkers nuclear factor-κB (NF-κB)in oral leukoplakia.

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Materials and Methods

The patients clinically and histopathologically confirmed as oral leukoplakia and Oral sub-mucous fibrosis were recruited for this study based on the definition of oral cancer and precancerous by the World Health Organization. Healthy normal served as the control group. All subjects neither had smoking history and detectable gingival and/or periodontal inflammation, nor any visible oral lesions under careful examination; moreover, they had not received any treatments for the oral lesions within 90 days prior to the specimen collection, and had no history, symptoms and/or signs of systematic infections and other diseases. The conventional histopathological diagnosis was made by one oral pathologist. This study was approved by the Ethical committee of diagnostic study and informed consents were obtained from all subjects. This was a nonrandomized and phase II trial of herbal tooth paste formulation known as Incudent, Denmark and we are treating on the 20 oral leukoplakia who satisfied all inclusion and exclusion criteria. Patients brush daily and keep the semisolid of paste in mouth for 2-3 minutes till clinical sign and symptoms disappeared. Systemic and local adverse events were assessed using the National Cancer Institute expanded Common Toxicity Criteria version 3.0. Pain control and lesion healing were the 2 main clinical variables for evaluating of oral leukoplakia. we used a visual scale analog ranging from 0.5 (very mild pain) to 5 (severe pain). Clinical and histopathological examinations were conducted, along with collection of serum and salivary samples prior to starting brushing with this formulation. Clinical and histopathological examinations were again performed and along with collection of serum and salivary samples. For each sample, 1.0 ml of supernatant was used for the enzyme-linked immunoassay (ELISA) cytokine assays by using the human ELISA kit for TNF-a, IL-6, and IL-8 (R&D Systems Inc., Minneapolis, MN, USA), according to the manufacturer's instructions.

Results and Discussion

The patient characteristics were showed in Table-1. No difference in TNF-alpha, IL-6, and IL-8 levels in serum and salivary were found in vegetarian and non-vegetarian (data were not shown). Also, further no difference in TNF-alpha, IL-6, and IL-8 levels in serum and salivary were found in females and males (data were not shown). The value of serum and salivary TNF-alpha, IL-6, and IL-8 showed statistically significant increased in oral leukoplakia in contrast to normal healthy subjects; while it significantly decreased in all groups after formulation (Table-2-7, $P<0.05$). Serum and salivary correlation analysis revealed strong and highly significant correlation for TNF-alpha, IL-6, and IL-8 in all groups ($r=0.64$, $r=0.61$, $r=0.62$, $P<0.001$) respectively. Furthermore, the values were statistically significant after clinical improvement of diseases. Pain scores and size of lesion in oral leukoplakia improved significantly ($p < 0.05$). The oral leukoplakia was significantly improved 234+/-15, days respectively after using new formulation. The goal of this study is to determine whether the anticancer effects of new formulation are mediated through inhibiting NF-kappa B dependent cytokine. Our results suggest that formulation significantly increased the local and systemic inhibiting NF-kappa B dependent cytokine, decreased levels of TNF-alpha, IL-6, and IL-8 in all groups after brushing and rinsing mouth with new formulation in precancerous lesions. Furthermore, the values were statistically significant after clinical improve of diseases. Pain scores and size of lesion in oral leukoplakia improved significantly. We did not record any treatment-related toxic effects, even brushing more than twice a day of keep it for more than two minutes. The significant correlation was observed in serum and salivary markers in all groups. Since, saliva can be easily collected; measurement of biomarkers of diseases may prove useful in early detection of oral cancer risks. Moreover, the salivary analysis for oral diagnosis may prove a cost effective method for screening large populations.

Table 1. Patient Characteristics.

Oral leukoplakia	20
Controls	20
Median age of patients	44 years
Median time of treatment	209 days
Number subjects evaluable for toxicity	65
Number subjects evaluable for response	50

Table 2. Effect of Formulation on Serum and Salivary Levels of Proinflammatory Cytokines in Leukoplakia Patients.

	No Treatment			formulation Treated		
	TNF	**IL-6**	**IL-8**	**TNF**	**IL-6**	**IL-8**
Saliva	3.94 ± 0.34	16.07 ± 3.63	20.05 ± 7.05	2.04 ± 0.60	10.89 ± 1.94	13.52 ± 4.18
Serum	18.25 ± 6.50	39.80 ± 10.69	930.61 ± 120.74	12.19 ± 3.90	27.22 ± 6.63	673.39 ± 148.28

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