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USE OF RETINOIDS IN THE TREATMENT OF ORAL LEUKOPLAKIA: review

Uso de retinoides no tratamento de leucoplasias bucais: revisão

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Abstract

OBJECTIVE: The purpose of this paper is to review the literature regarding the topical use of the retinoids in the treatment of oral leukoplakia, discussing their mechanisms of action, indications, effectiveness, and adverse effects. **DISCUSSION**: Leukoplakia is defined as white lesion in oral mucous membrane that cannot be characterized as any other entity and it has potential for malignancy. It does not present specific histological pattern. Due to its potential for malignancy and high prevalence, dentists should know how to diagnose and treat it correctly. The retinoids are chemopreventive agents derived from the vitamin A. They could be either natural or synthetic and their main role is to suppress cellular mitosis. Retinoid derivatives have been used as agents for chemoprevention of malignant transformation of leukoplakias due to its potential effect on the control of the differentiation and proliferation of the epithelial cells, as well as their induction of apoptosis. **CONCLUSION**: The topical use of retinoids to treat oral leukoplakia is safe, convenient and effective, with minor side effects than the systemic administration.

Keywords: Leukoplakia. Chemoprevention. Vitamin A. Tretinoin.

Resumo

***OBJETIVO**: A proposta deste artigo é revisar a literatura referente ao uso de retinoides no tratamento de lecoplasias bucais e discutir o mecanismo de ação, indicações, efetividade e efeitos adversos. **DISCUSSÃO**: Leucoplasia é definida como lesão branca na mucosa bucal que não pode ser caracterizada como qualquer outra entidade e tem potencial de malignização. Não apresenta padrão histológico específico e, por causa de seu potencial de malignização e alta prevalência, os cirurgiões-dentistas devem conhecer como diagnosticá-la e tratá-la corretamente. Os retinoides têm sido usados como agentes quimio-profiláticos para a transformação maligna das leucoplasias por seu efeito potencial no controle da diferenciação e proliferação da células epiteliais, bem como capazes de indução de apoptose. **CONCLUSÃO**: O uso tópico de retinoides para tratar leucoplasias é seguro, conveniente e efetivo, com efeitos colaterais menores do que na administração sistêmica.*

***Palavras-chave**: Leucoplasia. Quimioprofilaxia. Vitamina A. Tretinoides.*

INTRODUCTION

Oral leukoplakias (OL) are defined by the World Health Organization as "white lesions that can not be characterized as being a result of any other specific disease of the oral mucosa". The etiology and physiopathology are still unclear (1-3) but smoking has been considered one of the main risk factors (1, 2, 4-7). Alcohol consumption, human papillomavirus (HPV) infections, *Candida* sp., traumas, vitamin deficiency and ultraviolet radiation are other factors that could be associated with the disease (1, 4, 7, 8).

The OL is considered to be a pre-malignant lesion without a specific histological pattern (1-11). Histological characteristics may range from increased thickness of the keratin layer to severe epithelial dysplasia or even squamous cell carcinoma (1, 5, 9, 11). It has been found more commonly among men over the age of 50 and its prevalence seems to increase with age (2, 7). A single or multiple lesions may exist and the most common oral sites include lips, jugal mucosa, and gums (7).

Several therapeutic strategies exist such as surgical excision combined with control of risk factors (1, 3, 6, 8, 12, 13). Surgery has been an option only in well defined and accessible lesions. Its use has been limited in cases of extensive leukoplakias that could involve key structures such as the salivar duct and the lingual sulcus or in cases of recurrent lesions after previous surgery which occurs in 10 to 35% of the time (1, 3, 6, 8, 13). Control of risk factors is also mandatory for treatment success (3, 8, 10). In cases of large or multiple lesions or in lesions presenting active epithelial displasia, alternative therapeutic options include cryosurgery, laser surgery, and chemoprevention with retinoids (3, 8, 13).

Chemoprevention may, in theory, reverse the carcinogenesis avoiding the development of invasive tumors or the onset of secondary lesions (8). Retinoids are natural or synthetic chemopreventive agents derived from vitamin A. Their role is to supress cellular mitosis maintaining adequate balance among cellular growth, differentiation, and cellular death, and restore the homeostasis (1, 6) that could have been lost due to disease (10).

The purpose of this review is to describe the application of retinoic acid in the treatment of oral leukoplakias, addressing the mechanisms of action, indications, effectiveness, and adverse effects.

Review of the literature

Leukoplakias can be found in different clinical presentations and tend to change over time (2, 9). Homogenous leukoplakias are usually characterized as uniform, thin white lesions. Their surface could be either smooth or wrinkled, with superficial fissures and consistent texture throughout their extension. The non-homogenous type presents as a predominantly white or reddish-white lesion such as the erosive leukoplakia or the eritroleukoplakia with an irregular, nodular surface (2). Differential diagnosis include the lichen planus, hyperkeratosis, nicotinic stomatitis, leukoedema, and the white sponge nevus (2). Therefore, biopsy should be performed in order to determine the correct diagnosis.

Histologically, leukoplakias have been classified as simple orthokeratosis; parakeratosis with epithelial hyperplasia and minimum inflammation; and hyperkeratosis with different degrees of dysplasia (16% of the cases). Epithelial dysplasia has been categorized as mild, moderate, and severe; the latter known as *in situ* carcinoma due to its location within the layer of epithelial cells (1, 10, 12).

Regarding the molecular histopathological aspect of the disease, the p53 protein has been considered a marker of early cellular transformation, working as a preceptor of lesion progression to dysplasia and carcinomas. The accumulation of inactive p53 protein on the basal layer may be an early sign of cancer (1, 4). Studies of the DNA from OL cells helped in the prediction of malignant transformation of dysplasic lesions as well as in changes in the tumor gene supressor WWOX (5). The accumulation of beta-catenin found in the nucleus of cancerous epithelial cells has been related to the progression of the dysplasia in OL cases (9).

Oral leukoplakias have the tendency to malignization. However, only 10% of leukoplakias progress to dysplastic lesions and 17.5% to carcinomas, depending on the severity of the dysplasia (1). In non-homogenous lesions, malignization occurs in 15% to 40% of the cases. On the other hand, lesions free of atypical cells may resolve spontaneously although it could be difficult to determine which lesions could resolve or evolve to malignancy. Therefore, all individuals with such lesions should be followed closely in order to detect early changes (4, 8, 14).

Treatments for OL are indicated according to the extension of the lesion and its histological subtype. Surgical removal has been indicated in localized and accessible lesions. Its use has been limited in cases of extensive leukoplakias that could involve key structures or in cases of recurrent lesions after previous surgery (10 to 35% of the time) (1, 3, 6, 8, 13). Control of risk factors such as smoking and alcohol consumption is also mandatory for the treatment success (3, 8, 10). In lesions presenting active epithelial dysplasia, alternative therapeutic options include cryosurgery, laser surgery, and use of retinoids (3, 8, 13).

Chemoprevention is the administration of one or more agents in order to suppress or reverse the carcinogenesis before it reaches invasive stages. However, chemoprevention may also be effective after the onset of carcinogenesis in avoiding the development of secondary tumors. Chemotherapeutic agents can be classified as blocking or suppressing agents. The former acts as a barrier against carcinogens, preventing them from reaching and interacting with the target organ or tissue and the latter decreases the susceptibility of organs and tissues to the action of carcinogens (6, 8).

Retinoids, a new class of medications derived from vitamin A, are included in this type of therapy with lower toxicity and a more specific therapeutic effect. Vitamin A is necessary for cellular growth and epithelial cell differentiation, modulating cellular gene expression. This vitamin can be obtained from carotene and animal products such as meat, eggs, and milk. Retinoids are antioxidant compounds and they are responsible for maintaining the balance among cellular growth, differentiation, and death. The balance of cellular homeostasis has been shown to be effective in the prevention of primary and recurrent oral leukoplastic lesions, secondary tumors, and in the regression of potentially malignant lesions (1, 6). Retinoids induce apoptosis, supressing cellular growth and carcinogenesis (15, 16).

Among the more than 1500 synthetic vitamin A analogous, the 13-cis retinoic acid (isotretinoin) is of great interest due to its potential action in preventing the development of secondary tumors (1).

The mechanisms of action of retinoids are related to the retinoic acid receptors (RAR). Studies have been done to explain the mechanisms of action of retinoids and their therapeutic effects using biomarkers (1, 6, 17). Retinoids bind to their receptors, enter the cells and, after metabolization, are transported to the nucleus by cytosolic proteins. The discovery of a nuclear RAR contributed to the development of retinoic molecules with higher specificity. These receptors are connected to regions in genes that are sensitive to the activation of retinoids. Further, proteins are synthesized by ribossomes after transcription of DNA to messenger RNA. These proteins could be structural or act in several nuclear processes such as the production of keratine, growth hormone, and apoptosis and, as a consequence, participate in cellular differentiation, embryological morphogenesis, and carcinogenesis (1, 6).

The literature shows that retinoids can be administered systemically or topically for the treatment of OL. In addition, retinoids could also be used for the treatment of acne vulgaris, folliculitis, and psoriasis (5).

The systemic administration of vitamin A may lead to a complete or partial remission of the oral lesion, but recurrence may occur after discontinuation of its use (1, 6, 8, 10, 18). In some patients, adverse effects may cause more damage than the disease itself. Potential complications due to the use of retinoids include cutaneous and mucous alterations (dryness, mucositis, and epistaxis), muscular-skeletal disorders, dyslipidemia, liver dysfunction, and teratogenicity limiting its use in high doses (1, 2, 10).

The topical administration of retinoids allows the use of higher doses with less adverse effects (1, 5). One study reported that all 26 patients using topical 0.05% tretinoin gel four times a day for 3.5 years showed signs of clinical improvement. However, 27% showed total remission and 40% of these patients had recurrence of the disease after the discontinuation of the treatment (10). Lesions were compared histologically before and after treatment. None of the lesions classified as "moderate" presented changes but a decrease in severity was observed for those classified as "severe" before the treatment (10). In another study, 0.1% 13-cis retinoic acid gel was applied 3 times a day in 10 patients for four months. Only one patient had total remission of the lesion and all others had partial remission. No adverse effects were observed (18). Studies indicate that low doses of 13-cis retinoic acid (0.5 mg/kg/day) administered for longer periods are less toxic and are related to lower recurrence rates after treatment discontinuation (1).

Topical use requires high patient compliance in order to apply the medication on the same site, in addition to the difficulties in reaching the right location and the dilution of the agent by the saliva (1).

DISCUSSION

Clinical aspects of OL can vary and, therefore, the correlation between clinical and histopathological information is important for the final diagnosis. Molecular characteristics of the lesion may predict its progression to carcinoma allowing early detection and treatment including chemoprevention.

The chemoprevention is indicated for patients with leukoplakia with any other premalignant epithelial lesion that cannot be surgically removed, or for those who developed new lesions during the post-operatory period.

The systemic use of retinoids may lead to severe adverse effects, especially in individuals who need high doses of medication or long-term treatment. The toxicity seems to be dose-dependent and recurrences are common after the discontinuation of its use (1, 2, 10). Therefore, a close follow-up of these patients is mandatory. On the other hand, the topical administration of retinoids allows the application of higher concentrations of the drug directly on the lesion but with less adverse effects (1, 5). It is important to note that recurrences may occur even with the topical use and results can vary (1, 5, 10, 18).

Recurrence is common after surgical excision and one option would be the use of topical retinoic acid with or without bleomycin (10).

Of all studies reviewed, none reported the reversal of dysplasia (3, 10) and only one reported a decrease in the severity of dysplasia classified as "severe" before treatment (10). There is no consensus regarding the dose of retinoid for the treatment of OL.

Lower concentrations of retinoids combined with other antioxidant agents could be alternatives with less adverse effects but same chemopreventive action (16).

Figure 1 shows one confirmed case of leukoplakia treated with daily applications of 0.05% 13-cis retinoic acid during 3 months with significant clinical improvement (Figure 2). This patient is still under follow-up in our service.

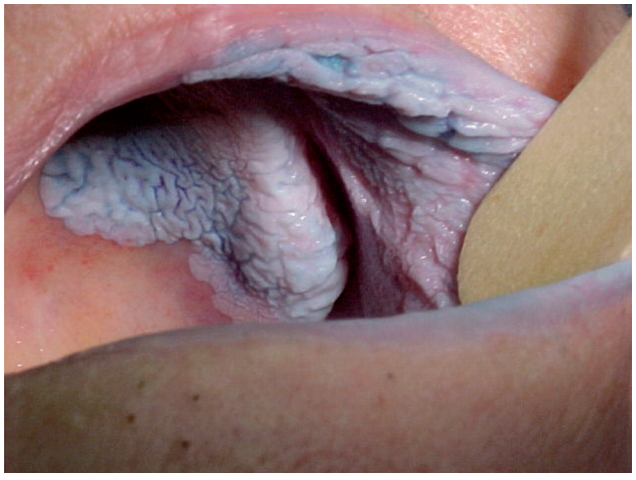

Figure 1 - Extensive verrucous leukoplakia in palatine, jugal, and labial mucosa, and edentulous alveolar ridge

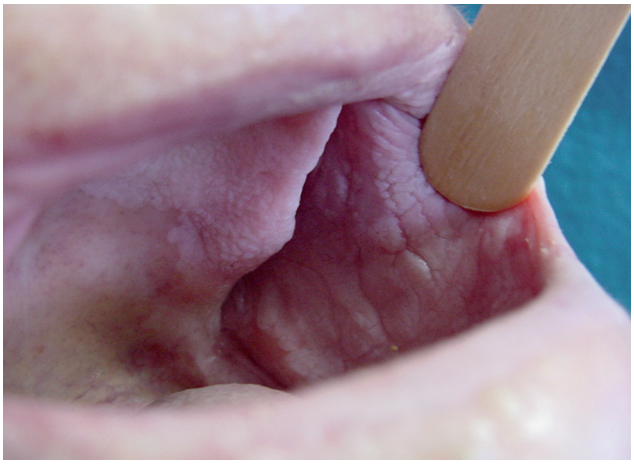

Figure 2 - Reduction of the leukoplastic hyperkeratosis after application (3 month) of retinoic acid

CONCLUSIONS

Therapeutic guidelines for the use of retinoids and other vitamin A derivatives have not been established yet. The use of this agent has been described in case reports or small case series. Its use is still controversial because it does not decrease the risk of oral cancer. The topical use of retinoids has advantages when compared to the systemic administration although recurrence may occur in both cases. Controlled clinical trials are necessary to determine the safety and effectiveness of the retinoic acid in the treatment of oral leukoplakias.

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