ARTYKUŁ PRZEGLĄDOWY/REVIEW ARTICLE

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Treatment of symptomatic oral lichen planus: a literature review

Leczenie objawowego liszaja płaskiego jamy ustnej: przegląd literatury

Wkład autorów:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Manuscript Preparation
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F – Funds Collection

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ABSTRACT: Lichen planus (LP) is a relatively common chronic inflammatory mucocutaneous disease. The aetiology is unknown, but appears to be mediated by the immune system. Emotional factors such as stress and anxiety are associated with oral lichen planus (OLP). It affects a higher percentage of middle-aged females. Erosive/ulcerative lesions are accompanied by symptoms such as severe pain and burning sensation, which vary according to the degree of inflammation. The main treatment of symptomatic OLP includes the use of topical corticosteroid drugs. Alternative treatments include immunosuppressants, retinoids, laser therapy, photodynamic therapy, aloe vera and green tea. The objective of this literature review was to describe the effective treatments for symptomatic OLP lesions. It was concluded that topical therapy is the most widely used treatment for symptomatic lesions of OLP. Clobetasol propionate mouthwash was the most used anti-inflammatory drug even though it has the same efficacy as other treatments. There is no stipulated duration of topical treatment for clobetasol propionate and should be used until the complete remission of the symptoms.

KEYWORDS: administration, Topical; Lichen Planus; Mouth mucosa, Adrenal Cortex Hormones

STRESZCZENIE: Liszaj płaski (ang. lichen planus, LP) jest stosunkowo częstą, przewlekłą chorobą zapalną skóry i błon śluzowych. Jego etiologia pozostaje nieznana, ale może mieć związek z funkcjonowaniem układu immunologicznego. Czynniki emocjonalne, takie jak stres i niepokój, odgrywają rolę w liszaju płaskim jamy ustnej (ang. oral lichen planus, OLP) i wpływają na większy odsetek występowania tej choroby wśród kobiet w wieku średnim. Zmianom erozyjnym/wrzodziejącym towarzyszą objawy silnego bólu i pieczenia, które różnią się w zależności od stopnia nasilenia stanu zapalnego. Stosowanie kortykosteroidów miejscowych jest podstawowym leczeniem objawowego OLP. Alternatywne metody stanowią leki immunosupresyjne, retinoidy, laseroterapia, terapia fotodynamiczna, preparaty aloesu i zielona herbata. Celem niniejszego przeglądu literatury było określenie skutecznych metod leczenia objawowego OLP. Stwierdzono, że najpowszechniejszym sposobem postępowania w objawowym OLP jest leczenie miejscowe. Najczęściej stosowanym leczeniem przeciwzapalnym jest płukanie jamy ustnej propionianem klobetazolu, mimo takiej samej skuteczności innych leków. Czas leczenia miejscowego propionianem klobetazolu nie jest określony i powinien trwać aż do całkowitego ustąpienia objawów.

SŁOWA KLUCZOWE: stosowanie miejscowe, liszaj płaski, błona śluzowa jamy ustnej, hormony kory nadnerczy

INTRODUCTION

Lichen planus (LP) is a chronic, inflammatory, mucocutaneous disease with unknown aetiology. It is one of the most common dermatological conditions that affects the oral cavity and is prevalent in 1.27% of the general population [1] and it is more prevalent in middle-aged females [2].

Despite its unknown aetiology, current evidence suggests that the disease is related to a change in cell-mediated immunity, precipitated by exogenous or endogenous factors, resulting in an altered response to self antigens [3]. In oral lichen planus (OLP) the main type of infiltrating cells are T cells, which accumulate in the lamina propria adjacent to the epithelium, and cause rupture of the basal membrane [4].

OLP lesions have been classified as three types: reticular lesions, which include white lines; papules and plaques; atrophic or erythematous lesions; and erosive lesions, which are ulcerative and bullous lesions [5]. They are mainly found on the tongue and buccal mucosa. Erosive OLP is the most painful and severe variant of the disease and is accompanied by chronic inflammation and is usually associated with severe pain and burning sensation [6]. It is the only dysplastic lesion, and therefore requires treatment of the symptoms and long-term clinical follow-up at the dentist [7].

Treatment of OLP aims to reduce the symptoms of ulcers, facilitating their healing and reducing the potential risk of malignant transformation [8]. Traumatic factors in close proximity to the lesion and local irritants such as alcohol and tobacco should be first eliminated.

The drugs that are often recommended are corticosteroids due to their ability to modulate inflammatory and immune responses, hence restoring the function of T suppressor lymphocytes. The use of topical corticosteroids are the principal chosen form of treatment. Systemic corticosteroids and other immunosuppressive drugs are sometimes used, however are limited due to adverse effects from long-term usage [9]. In addition to the corticosteroids, treatments with immunosuppressive agents [10], retinoids [11] low level laser therapy [12], photodynamic therapy [13], *aloe vera* [14] and green tea [15] are also administered.

Pharmaceutical preparations for the treatment of OLP are presented as gels, ointments, creams, orabase, solutions, suspensions, emulsions and sprays. The administration route may be topical or systemic depending on the extension and severity of the lesion [16] and the dosage varies according to the type of drug used. Thus, the aim of this literature review is to identify the most used treatment for OLP.

LITERATURE REVIEW

TOPICAL AND SYSTEMIC ANTI-INFLAMMATORIES

Drugs often indicated for the symptomatic treatment of OLP lesions are high- potency topical corticosteroids vehicled as mouthwashes, ointments or orabase pastes (ointment in orabase), applied twice or three times a day [3].

The creams are not indicated for use on the oral mucosa while the orabase pastes, are used exclusively for intra-oral lesions. Lesions located on the vermilion of the lips should be treated with ointments. Dental surgeons rarely use oral or intralesional corticosteroids for the treatment of intra-oral lesions. The therapeutic target (inflammatory infiltrate) is easily treated with topical treatment, considering that only erosive lesions will be treated [17].

Corticosteroids are the first therapeutic choice for symptomatic OLP lesions. Its effectiveness is not always clear where the remission of lesions is concerned [17]. Clobetasol propionate is mainly indicated for the atrophic, erosive and ulcerative variants of OLP. It may be presented as a solution, ointment or orabase paste [18] and is effective for the remission of symptomatic OLP lesions [17,19].

One of the disadvantages of topical oral medication is the difficulty of application in posterior regions and obtaining total coverage of the affected area [17].

Notwithstanding, clobetasol propionate stands out as a safe and effective option for the treatment of erosive OLP lesions. It may be associated with an antifungal agent to prevent the consequential development of candidiasis as a result of prolonged treatment [19]. Triamcinolone acetonide 0.1% is presented as a mouthwash and paste. When the two forms were compared, the mouthwash proved to be better accepted by the patients as the latter presentation was difficult to apply due to its sticky consistency. There were, however, no statistically significant differences between both presentations where therapeutic efficacy was concerned [20].

Patients who used 5 mL of 0.1% of mometasone furoate microemulsion mouthwash for 30 days had statistically significant reduction in pain, erythema and ulceration of erosive OLP lesions [21]. Fluticasone propionate spray and betamethasone sodium phosphate mouthwash were both evaluated for acceptability and efficacy. Both drugs showed efficiency for short-term management of OLP lesions, however fluticasone propionate was better accepted by patients due to the convenience of its spray form [22].

The best results were obtained with the use of clobetasol propionate as a mouthwash, based on its comfortable application, easy accessibility to oral lesions and contact time with lesions [17]. Another advantage of its topical use is that systemic corticosteroid therapy and immunosuppressants may be maintained during its administration [23].

The systemic use of corticosteroids is probably the most effective treatment modality for patients with diffuse erosive OLP or multiple lesions in different areas. However, the literature is limited to non-randomized clinical trials for its use. Methylprednisolone and prednisone have been employed in cases of severe recalcitrant erosive OLP [24]. Additionally, systemic corticosteroids may be indicated for patients who do not respond to topical steroids or in individuals with mucocutaneous disease. They can be administered in high doses (1.5-2.0 mg/kg/day), but adverse effects are likely to occur even if the treatment is administered for a short period. Prednisone is generally used for systemic treatment, administered in a dose of 30 to 60 mg once a day for 2 to 3 weeks. Prolonged use of systemic corticosteroids is limited due to its high toxicity and common adverse effects [23].

IMUNOSSUPRESSANTS, RETINOIDS AND OTHER AGENTS

Topical cyclosporine solution and tacrolimus 0.1% have been found to be effective for reducing symptomatology of lesions [6,9,10]. The most frequent adverse effect reported was burning of the mouth, which was self-limiting and mild to moderate [25].

Pimecrolimus is another immunosupressant whose mode of action is similar to that of tacrolimus. Pimecrolimus cream 1% applied twice a day for a month to erosive OLP lesions showed a significant decrease in pain scores [25]. However, its immunosuppressing capacity when compared to tacrolimus is substantially lower.

Topical retinoids may be used as an alternative to corticosteroids in the orabase form, as this presentation allows for longer contact with the oral mucosa. Isotretinoin is the most commonly used retinoid for the treatment of OLP lesions [11]. Treatment with isotretinoin ameliorated the clinical and histopathological aspects of symptomatic OLP, with minimal and transitory side effects such as burning and erythema following application and sensitivity to hot foods [26].

Low level laser therapy (LLLT) is a non-pharmacological and non-invasive modality that causes biostimulation of the tissues, which leads to intracellular biological reactions and regeneration of tissues without adverse effects. LLT was applied using a 980-nm diode with a fluence of 4 J/cm^2 per lesion. A significant reduction in pain and clinical scores for unresponsive refractory symptomatic OLP lesions was reported [12].

Photodynamic therapy (PDT) has also been used as an alternative treatment for symptomatic OLP with improvement of the signs and symptoms over an extended period of time. PDT was applied using a xenon arc lamp of 630 ± 5 nm wavelength, with a total dose of 120 J/cm2 and methylene blue as a photosensitizer [13].

Ultraviolet radiation (UV) combined with psoralen modulates the function of cells of the immune system and improves OLP lesions. However, there were several adverse effects such as nausea, dizziness and sensitivity to the sun [15].

Aloe vera was shown to be more effective in clinical amelioration when compared to triamcinolone acetonide [14]. *Aloe vera* and green tea are another non-pharmaceutical mode of OLP treatment. Sixty percent of the 64 patients treated with doses of 0.4 mL of *aloe vera* (70% concentration) had complete resolution of pain at 12 weeks with no adverse effects [15]. Green tea has anti-inflammatory and chemopreventive properties and reduces the incidence of OLP by regulating the factors that are involved in the pathogenesis of the disease [15].

DISCUSSION

The patient's medical history (history of diabetes, hypertension, liver disease), psychological state, adherence to treatment and possible drug interactions should be considered when assessing the cost-effectiveness of any chosen treatment [16]. Also, drug administration should be interrupted when the appearance of the lesion is related to the usage of a drug [27]. Most studies on the treatment of OLP suggest that the best option is the use of high-potency topical corticosteroids, while systemic corticosteroids may occasionally be indicated for severe, erosive, recalcitrant OLP or for patients with diffuse mucocutaneous involvement [16,17,18,23].

Systemic use is indicated for exacerbated cases of OLP, with multiple lesions or in cases of widespread disease. In these cases, systemic corticosteroids are combined with topical corticosteroids [23]. The use of systemic corticosteroids produces a number of adverse effects, even if administered short-term, such as hyperglycemia, diabetes, osteoporosis, cataract, depression, hypertension, hypothyroidism, and amenorrhea. The adverse effects of topical corticosteroids are less severe than those of systemic corticosteroids, but may include opportunis-

tic candidiasis, mucosal atrophy, and, in cases of high-potency corticosteroids, adrenal suppression [28].

Clobetasol propionate as a topical anti-inflammatory agent [18], when compared with systemic treatment proved to be easier and more cost-effective than being succeeded by systematic therapy [16].

In this review, amongst all the anti-inflammatories researched, the most frequent topical application of OLP lesions in solution form, such as mouthwash/oral rinses, was clobetasol propionate 0.05%. Clobetasol propionate is the most used topical corticosteroid in oral mucosal lesions in stomatology. This is justified because of its minimal side effects when used properly. Proper use does not cause suppression of the hypothalamic-pituitary-adrenal axis. It is a potent corticosteroid and also presents low gastric absorption [18].

The different forms of presentation whether ointment, gel, oral solution, spray, orabase paste (ointment in orabase) of clobetasol propionate are all effective. However, solutions in the form of mouthwash are to be given preference based on their easy application and overall acceptance by patients, and are therefore more practical for daily use [17].

The ointment in orabase and gel presentations is also indicated as they both allow for the slow release of anti-inflammatory lesions in the mucosa [18,19]. However, the clinician cannot guarantee that the patient applies the orabase or ointment correctly to the lesions nor for the desired contact time the drug requires. Although the ointment in orabase is an adhesive carrier, the movements of the mouth and the saliva can rapidly displace it from the lesion. It has also been reported that patients generally reject the grainy texture of the ointment in orabase, which affects treatment compliance [17].

The number of applications depends on the potency of the corticosteroids. Therefore, those corticosteroids of low or medium strength should be applied, on average, 5 to 6 times per day. On the other hand, the corticosteroids of high-potency should be applied on average, 2 or 3 times a day. Once the evolution of symptoms and the clinical aspect is favourable, the dosage should be gradually reduced [29].

Regarding the duration of treatment, Gonzalez-Moles et al. reported that more than 85% of patients had no pain nor ulcerations with full recovery of daily activities at 6 weeks of treatment, and 93.3% showed complete remission of symptoms at the end of the 48th week when administered 0.05% clobetasol mouthwash [17].

Lo Muzio et al. showed that the group that received the combination of bioadhesive paste with clobetasol propionate had complete clinical remission of erosive OLP lesions in 6-13 days. The group that used clobetasol propionate in the form of ointment attained the same clinical results in 10-14 days. The group that received clobetasol propionate mixed with an oral analgesic base (Orabase-B®), showed absence of symptoms in 7-10 days. Henceforth, duration of treatment varies depending on the presentation of the drug and is normally administered until remission of signs and symptoms are attained [18].

Currently, high-potency topical corticosteroids are considered the first line of treatment for symptomatic OLP in whichever area. However, prolonged use of topical corticosteroids may result in drug tolerance or secondary candidiasis, these being their principal disadvantages.

There are alternative therapies for those patients who do not respond adequately to treatment with corticosteroids or are allergic or insensitive to topical glucocorticoids. These therapies include topical retinoids, immunosupressants, laser, photodynamic therapy, ultraviolet treatment, *aloe vera* and green tea. Retinoids may cause burning and erythema after application and recurrence of lesions [11]. Immunosuppresants such as tacrolimus may increase the risk of development of malignant tumours and pimecrolimus requires long-term follow-up in order to maintain results obtained [2]. LLLT, PDT and UV therapy require additional training in order to administer therapy to patients. *Aloe vera* and green tea require a larger number of controlled studies to verify their effectiveness.

In addition to drug and palliative therapy, oral hygiene care is important. Calculus and accumulation of biofilm can cause local inflammation and exacerbate lesions and should be removed by the dentist when observed. The replacement of metal restorative materials is indicated when allergic reactions to these substances are suspected (lichenoid lesion). Improvement occurs most commonly in those cases where all lesions are located in areas closest to the fillings [3]. The correct diagnosis of OLP is fundamental for treatment and should be based on clinical and also histopathological examination.

Follow-up sessions should be done periodically in order to gradually reduce medication and to principally observe the evolution of the atrophic scar-like lesions [3]. Patients with OLP must be accompanied throughout their lives, given the chronic nature of the disease and frequent relapses. During recurrence, for better control of symptoms (burning sensation, pain and functional disability observed in erosive lesions), we suggest topical use of clobetasol propionate solution, three times a day until reduction of symptoms and remission of the lesion. Af-

terwards, the use of the medication should be discontinued.

According to a systematic literature review about interventions for erosive LP in the mucosa, treatment of these lesions is difficult and usually aimed at palliation rather than cure. Even though several topical and systemic agents have been used with varying results, there is no definitive evidence for the efficacy of a single treatment, including topical steroids, which are the widely accepted first-line therapy for erosive LP [5].

CONCLUSION

Based on the literature reviewed, it can be concluded that topical therapy in the form of solution is the presentation most frequently used for the treatment of symptomatic OLP lesions and presents greatest ease of application with the least adverse effects. Duration of treatment is relative and is normally administered until there is reduction symptomatology and remission of the lesion.

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