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Research paper

Efficacy of 0.1% triamcinolone with nanoliposomal carrier formulation in orabase for oral lichen planus patients: A clinical trial

Arash Azizi[a,*], Orkideh Ghorban Dadras[b], Mohamadreza Jafari[c], Nahid Moezi Ghadim[d], Shirin Lawaf[e], Donia Sadri[f]

[a] Associate professor of Oral medicine department, Islamic Azad university, Dental Branch, Tehran, Iran
[b] Assistant professor of Pharmacology department, Islamic Azad university, Tehran, Iran
[c] Professor of Pharmacology department, Mashhad university, Mashhad, Iran
[d] Assistant professor of Oral medicine department, Islamic Azad university, Dental Branch, Tehran, Iran
[e] Assistant professor of Prosthodontics department, Islamic Azad university, Dental Branch, Tehran, Iran
[f] Associate professor of Pathology department, Islamic Azad university, Dental Branch, Tehran, Iran

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ABSTRACT

Introduction: Lichen planus (LP) is a chronic mucocutaneous disease, with different clinical subtypes. The erythematous-ulcerative type is accompanied by pain and burning sensation. Topical or systemic corticosteroid therapy is among the common treatments. No evidence is available supporting the superiority of any specific type or dose of treatment. Nano-drugs have recently been used for the management of oral lesions. This study sought to compare the anti-inflammatory effects of 0.1% triamcinolone acetonide in Orabase® with and without nanoliposomal carriers on oral lichen planus (OLP).

Methods: This randomized clinical trial was performed on 60 patients with erythematous-ulcerative OLP. Formulations of 0.1% triamcinolone acetonide with and without nanoliposomal carriers in Orabase were used 3 times a day for a month in case and control groups, respectively. Pain intensity by linear Visual Analog Scale [0–10] and cross sectional area of the lesions by a grid paper (mm^2) were measured before and one, two and four weeks after treatment. Data were analyzed using *t*-test, chi-square, Fisher's Exact, Mann–Whitney and Wilcoxon Singed-Rank tests.

Results: The pain intensity and size of oral lesions decreased statistically by each drug formulation ($P \leq 0.001$). Also there were significant differences between the two formulations after two and four weeks of treatment ($P < 0.05$).

Conclusion: Based on the results, the efficacy 0.1% triamcinolone acetonide with nanoliposomal carrier formulations was more effective than 0.1% triamcinolone acetonide without nanoliposomal for OLP.

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1. Introduction

Lichen planus is an immunologic, chronic, mucocutaneous disease with an unknown etiology and a wide spectrum of clinical manifestations [1,2]. It can affect the skin, oral mucosa, nose, esophagus and anogenital area simultaneously or independently [3]. Oral mucosa is commonly involved and in some cases is the only site of involvement [1,3].

Corticosteroids are the most commonly used medication for treatment of OLP; they can regulate the inflammatory and immunological responses via decreasing the lymphocytic exudate and stabilizing the lysosomal membrane [4]. Topical steroids are the first line treatment of this condition; but no evidence exists regarding the superior efficacy of a specific type or dose of steroids over others [5,6]. The most important side effects of steroids include secondary candidiasis infection, bad taste, nausea, xerostomia, oral mucosal swelling and sore throat [7,8]. Long-term administration of strong steroids (i.e. Clobetasol) is associated with a high risk of tachyphylaxis and adrenal insufficiency. If left untreated, OLP especially the erosive type, can cause significant pain and discomfort and decrease the quality of life of patients [6]. Also, it may turn into a precancerous lesion with 0–20% risk of malignant transformation [1].

According to Farshi et al. study that compared the anti-inflammatory effects of liposomal formulations of dexamethasone with those of the conventional formulation on oral mucosal ulcers

* Corresponding author. Fax.: +98 2122886039.
E-mail addresses: drarashazizi@yahoo.com (A. Azizi), dadras.o@iaups.ac.ir (O.G. Dadras), jafarimr@mums.ac.ir (M. Jafari), nahid_mg@yahoo.com (N. Moezi Ghadim), drshlawaf@yahoo.com (S. Lawaf), donia1351@yahoo.com (D. Sadri).

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of rats, they found that liposomal carriers accumulate in the upper layer of epidermis due to their structural similarity with liposomes and confer benefits such as protection against metabolic degradation of drugs, increasing the half-life of drugs, increasing their topical efficacy, decreasing their side effects, regulating their dosage, slow-release of drugs, the ability to store the medication, prolonging drug effects, the ability to carry hydrophilic and hydrophobic drugs, biocompatibility and biodegradability [9,10]. Also they showed liposomes increase local and decrease systematic drug concentration [9]. Use of liposomal carriers has resulted in promising advances in local drug delivery to the oral mucosa [11].

The efficacy of the formulation of triamcinolone with liposomal carriers has not yet been evaluated for human OLP lesions. Thus, this study sought to assess and compare the anti-inflammatory effects of this new formulation (triamcinolone with liposomal carrier) with those of the conventional formulation on OLP.

2. Methods

2.1. Patients and recruitment

This double blind randomized clinical trial was conducted from March 2013 to June 2014 (a total of 15 months) on all patients who were referred to the Tehran Islamic Azad University of Dentistry and had symptomatic oral lesions suspected of lichen planus erosive which, clinically can be spotted as a red and white areas with papules or reticular texture of Wickham striae in the periphery.

After the biopsy procedure did take place from the mentioned lesions, patients who had no dysplasia histologically, were selected in regards of the histological symptoms of OLP which contains areas of hyperkeratosis, liquefaction degeneration of basal cell layer, dense band like infiltration of chronic inflammatory cells in the upper parts of connective tissue and a confirmed diagnosis of atrophic or erosive OLP.

Patients were recruited sequentially to the oral medicine department of dental school of Islamic Azad University were entered into the study and with systematic randomization and based on the sequence of referral, from each two individuals, the first one was placed in the case group and the second person was placed in the control group.

Biopsies were carried out for all patients with clinical diagnosis of erosive lichen planus. Considering the possibility of dysplastic changes in erosive lichen planus, a biopsy was obtained from all patients with a clinical diagnosis of erosive lichen planus to confirm the diagnosis and assess possible dysplastic changes.

The exclusion criteria were dysplasia on histological examination, pregnancy, nursing, immunosuppression (organ transplantation, lupus erythematous, ulcerative colitis), hematologic diseases, and systemic diseases, history of systemic or topical corticosteroid therapy for treatment of OLP in the past one month and lichenoid reactions related to drug use or restorative materials. All patients signed a written informed consent .This clinical trial was approved by the Ethics Committee of Islamic Azad University and registered in Iranian Randomized Clinical Trial. The number of registration was IRCT2014080416090N5. All patients reported pain and burning sensation due to OLP. Biopsy samples were taken in the Oral Medicine Department of the university and sent to the Pathology Department of the University for Microscopic Examination. A total of 12 patients in the two groups quit treatment and failed to attend any follow up sessions and therefore were excluded from the study. Of these dropouts, 7 were in case group and 5 were in control group. Given this dropout rate further patients were selected for this study. Finally, 30 patients were included in the case group and 30 patients in the control group.

Triamcinolone acetonide (0.1%) in Orabase was purchased from Raha Pharmaceuticals (Tehran, Iran) and the ingredients required for making 0.1% triamcinolone acetonide with nanoliposomal carriers in Orabase (triamcinolone and Orabase) were purchased from Iran Daru (Tehran, Iran). In this study the nanoliposomal formulation was manufactured in the Pharmacy and Biotechnology Research Center of Mashhad University of Medical Sciences. The medications were poured into uniform bottles by someone other than the researcher and randomly coded from 1 to 60 by a statistician.

Subjects recruited into the study were sequentially and randomly divided into two groups-cases (0.1% triamcinolone acetonide with nanoliposomal carriers in Orabase) and controls (0.1% triamcinolone acetonide in Orabase). For each group of patients, a data form was filled out. Subjects underwent oral examinations and their pain intensity was assessed using linear visual analog scale [0–10]. To assess the objective patient symptoms, an area of oral mucosa with the most severe and extensive erythematous or erosive OLP lesion was outlined with a copying pencil and measured in mm^2 using a grid paper (transparent paper sheet with 5 mm^2 square cells). Figs. 1 and 2 [12,13].

Size of lesions and the intensity of pain were measured by an oral medicine specialist. The medication assigned for each group was then administered three times a day after meal for one month and the patients were requested to refrain from eating, drinking, or smoking for 30 min after taking the medication. Also, nystatin mouthwash (100,000 IU) was prescribed once a day for all patients for the entire treatment course. Nystatin mouthwash was used for all of patients for the prevention of overgrowth candida albicans in OLP lesions [5].

The patients were recalled after one, two and four weeks to assess the efficacy of medications. At each recall session, all measurements were repeated as described earlier and the results were recorded. If the lesions resolved completely during the follow up period, the drug was used for one month and then discontinued. In case of not achieving a full recovery, the treatment and follow-ups continued.

2.2. Preparation of triamcinolone with liposomal carriers

Phosphatidylcholine, cholesterol and triamcinolone were dissolved in an organic solvent (methanol and chloroform with a volume ratio of 2/1). The solvent was then vaporized using a rotary vaporizer (Heidolph, Germany) yielding a thin layer of a lipid compound on the internal wall of the lowest part of the balloon. To eliminate the residual solvent, the lipid layer was frozen at −70 °C and placed in a cold dryer for 4 h. During the hydration process, phosphate buffered saline at a temperature above the melting

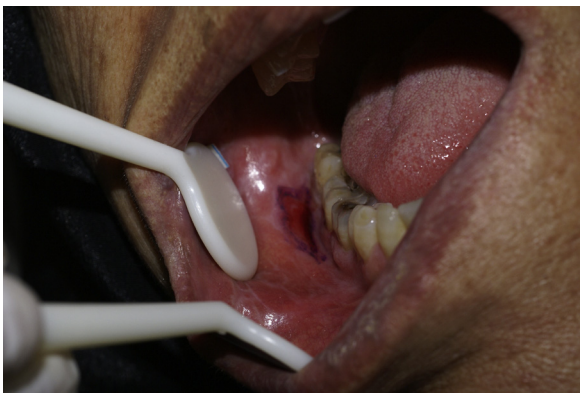

Fig. 1. Highlighting border of lesion.

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