Comparison of therapeutic effect of mucoadhesive Nano-triamcinolone gel and conventional triamcinolone gel on recurrent aphthous stomatitis

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ORIGINAL ARTICLE
Comparison of therapeutic effect of mucoadhesive Nano-triamcinolone gel and conventional triamcinolone gel on recurrent aphthous stomatitis

Objective: Recurrent aphthous stomatitis (RAS) is characterized by recurring ulcers, with well-defined margins. The lesions are confined to the oral mucosa (usually seen in non-keratinized mucosa). The disease manifests in the form of outbreaks, with a chronic and self-limiting course in most cases. Since the cause of the disease is unknown, many drugs have been studied to palliate the symptoms. Treatment used is multifocal and varies according to the predisposing factors. The aim of this study was to investigate the effect of recombinant Nano-based triamcinolone acetonide gel and compare it with conventional triamcinolone gel on RAS.

Material and methods: In this triple-blind randomized clinical trial study, sixty patients with minor aphthous lesions were divided into two groups receiving conventional triamcinolone (CT) and Nano-based triamcinolone (NT). The patients were requested to apply drug four times a day for a week. The severity of pain (through VAS) and the size of the lesions (mean of the largest diameter of the lesions) were evaluated on starting day and days 2, 4, 6 after the intervention. Statistical analysis was performed using chi square and independent t-test. Findings were significant with P < 0.05.

Results: Of the 60 patients enrolled in the study, 5 patients did not continue; 21 (38.2%) cases were female and 34 (61.8%) cases were male (P=0.6). The severity of pain in NT group before and after intervention was significantly lower than CT group (P < 0.05).

Discussion: The results of the present study indicated that Nano-based triamcinolone gel was significantly more effective than conventional triamcinolone gel in the treatment of RAS. This finding is in agreement with previous studies that have demonstrated the efficacy of Nano-based drugs in the treatment of various oral mucosal disorders.

Conclusion: The use of Nano-based triamcinolone gel in the treatment of RAS is recommended due to its superior efficacy compared to conventional triamcinolone gel. Further studies are needed to evaluate the long-term effects of Nano-based drugs on RAS.

ABSTRACT

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Resumo: A estomatite aftosa recorrente (EAR) é caracterizada por úlceras recorrentes, com margens bem definidas. As lesões estão confinadas à mucosa oral (geralmente vista em mucosa não queratinizada). A doença se manifesta na forma de surtos, com um curso crônico e autolimitado na maioria dos casos. Como a causa da doença é desconhecida, muitos medicamentos foram estudados para aliviar os sintomas. O tratamento utilizado é multifocal e varia de acordo com os fatores predisponentes. O objetivo deste estudo foi investigar o efeito do gel acetonido de triancinolona recombinante baseado em Nano e compará-lo com o gel de triancinolona convencional no EAR. Material e métodos: Neste estudo clínico randomizado triplo-cego, sessenta pacientes com lesões aflosas menores foram divididos em dois grupos que receberam triancinolona convencional (CT) e triancinolona Nano (NT). Os pacientes foram solicitados a aplicar droga quatro vezes ao dia durante uma semana. A gravidade da dor (por meio da EVA) e o tamanho das lesões (média do maior diâmetro das lesões) foram avaliados no dia inicial e nos dias 2, 4 e 6 após a intervenção. A análise estatística foi realizada utilizando teste qui quadrado e teste t independente. Os achados foram significativos com P < 0.05.

RESUMO

ABSTRACT

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Resumo: A estomatite aftosa recorrente (EAR) é caracterizada por úlceras recorrentes, com margens bem definidas. As lesões estão confinadas à mucosa oral (geralmente vista em mucosa não queratinizada). A doença se manifesta na forma de surtos, com um curso crônico e autolimitado na maioria dos casos. Como a causa da doença é desconhecida, muitos medicamentos foram estudados para aliviar os sintomas. O tratamento utilizado é multifocal e varia de acordo com os fatores predisponentes. O objetivo deste estudo foi investigar o efeito do gel acetonido de triancinolona recombinante baseado em Nano e compará-lo com o gel de triancinolona convencional no EAR. Material e métodos: Neste estudo clínico randomizado triplo-cego, sessenta pacientes com lesões aflosas menores foram divididos em dois grupos que receberam triancinolona convencional (CT) e triancinolona Nano (NT). Os pacientes foram solicitados a aplicar droga quatro vezes ao dia durante uma semana. A gravidade da dor (por meio da EVA) e o tamanho das lesões (média do maior diâmetro das lesões) foram avaliados no dia inicial e nos dias 2, 4 e 6 após a intervenção. A análise estatística foi realizada utilizando teste qui quadrado e teste t independente. Os achados foram significativos com P < 0.05.
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INTRODUCTION

Recurrent aphthous stomatitis is a disorder characterized by numerous symmetrical painful ulcers confined to the oral mucosa. The etiology of RAS is unknown, however some factors including genetic factor, hematologic and immunologic abnormalities, and local factors are considered to cause this disorder. RAS affects approximately 20% of the general population, but when specific ethnic or socioeconomic groups are studied, the incidence ranges from 5 to 50% [1].

RAS is classified according to clinical characteristics: minor, major and herpetiform ulcers. Minor ulcers which comprise over 80% of RAS cases, are less than 1 cm in diameter and heal without scars. Major ulcers are over 1 cm in diameter take longer to heal and often leave the scar. Herpetiform ulcers are considered a distinct clinical entity that manifests as recurring cluster of small ulcers throughout the oral mucosa [2].

The first episodes of RAS most frequently begin during the second decade of life. The buccal and labial mucosae are most commonly involved. The symptoms begin with prodromal burning from 2 to 48 hours before the lesion appears. During this initial period, a localized area of erythema develops. Within hours, a small white papule forms, ulcerates, and gradually enlarges over the next 48 to 72 hours. The individual lesions are round, symmetric, and shallow (similar to viral ulcers), but no tissue tags are present from ruptured vesicles, which helps distinguish RAS from vesiculobullous diseases [2].

The treatment of RAS is mainly symptomatic, and a topical approach is effective in most patients. Nevertheless, systemic treatment should be considered in patients with multiple episodes of minor RAS or patients with major RAS [3]. Local corticosteroids are available in the forms of ointment, cream, lotion and gel [4]. Given that the mucosa is covered with viscoelastic layers, topical drugs such as other foreign substances are did not clog to the mucus with various mechanisms such as hydrophobic and electrostatic adhesion, hydrogen bonding, and washed rapidly in a few seconds to a minute; accordingly, they are unable to penetrate the mucus layers and reach to the epithelial surface [5,6]. For this reason,
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A sustained and effective drug delivery to the mucosa is restricted and mucus is considered as an important barrier to the topical treatment of different oral diseases [7].

The Nano Drug Delivery System (NDDS) is a modern method to cope with the rapid clearance of topical drugs of the mucus and brings sustained and effective drug delivery to the mucosa [7]. Biodegradable nanoparticles can penetrate to mucus layer and reach the epithelium cells [8]. Furthermore, some non-biodegradable nanoparticles containing polyethylene glycol have a greater adhesion to mucus, due to their hydrophilic and non-curable molecules, so less affected by mucus clearance in comparison with non-Nano formulated drugs [9].

The goal of this study was to evaluate the therapeutic effects of Nano-triamcinolone formulation on RAS and compare it with non-Nano triamcinolone formulation. The findings of this study may assist for further evidence about the efficacy of triamcinolone gel with nanoparticle formulation.

METHODS AND MATERIALS

This three-blind randomized clinical trial study (patient, examining physician, and statistic analyst) was conducted at the Isfahan University of Medical Sciences in 2018 after the approval of the Ethics Committee (Code:IR.REC.AJAUMS.2017.66). The study population included 60 eligible patients with minor RAS who referred to the Dental Research Center and Dentistry Faculty at Isfahan University of Medical Sciences.

The patients were matched for age, sex and size of lesions in two groups of Nano-based triamcinolone gel (NT) and conventional triamcinolone gel (CT). Inclusion criteria comprised definite diagnosis of minor RAS, the length of time less than 72 hours from the onset of the lesion, and the sign of the written consent. Exclusion criteria included pregnancy and breastfeeding, conditions and diseases that can cause aphthous like lesions (including anemia, inflammatory bowel disease, celiac disease, Behcet’s syndrome, and AIDS), co-administration of any topical drug for the treatment of RAS, usage of systemic drugs for the treatment of RAS within a month ago, usage of immunosuppressive drugs, and sensitivity to corticosteroids.

Drug preparation

Preparation and usage of mucoadhesive gel formulation with 0.1% triamcinolone was performed in the pharmacy faculty of Kermanshah University of Medical Sciences, Iran. For preparation of triamcinolone gel formulation, biocompatible polymers were used by spontaneous emulsification technique. The polymer plus the biocompatibility of the mucous membrane has high adhesion properties (CT). The Nano composition was then added to the triamcinolone and polymer gel(NT). The presence of nanoparticles, its size and morphology were observed with scanning electron microscope (SEM).

In order to count the amount of released drug from NT, a suitable amount of nanoparticles transferred to a receptacle containing 1 ml of phosphate buffer with pH 7.7, and then the buffer and nanoparticles were devided by a dialysis membrane (Mw cutoff = 12,000-14,000 Daltons; Delchimica Scientific Glassware, Milan, Italy). The system was continuously cured at 37°C and centrifuged at 100 rpm. In order to prevent evaporation of the buffer, the receptacle was kept as a sealed container. A certain amount of sample (100 μl) was eliminated at regular intervals from the receptacle and replaced immediately with a fresh buffer solution.

To determine mucosal adhesion of gel used buccal mucosa of sheep. The adhesion durability was calculated about one hour.
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To evaluate the concentration of drug in the receptor phase, UV or High-performance liquid chromatography (HPLC) was used. For this purpose, some of the drug was dissolved in 50 ml of phosphate buffer with 6.6 ph and was shake at 37°C. Then 50 ml of methanol was added to dissolve the drug entirely. After that, the solutions concentration evaluated with UV or HPLC and compared with a standard curve. The concentration of triamcinolone was 0.1%.

**Prescription**

Fifty mg of gels inside the sterile white (NT) and red plastic cans (CT) that was given to the patient without information about the modified formulation of the drug.

For the first time, a physician applied the gels at the site of the lesion(s) in order to patient education. In this way, the oral lesion(s) dried with sterile gas, some of the drug was removed with sterile cotton swab and placed on the lesion(s) and slightly around it. Patients were barred from receiving any food or drink for up to 30 minutes after dipping. Drug using lasted 4 times a day for a week. Patients were requested to mark the daily timetable schedule to ensure regular use of the gels.

**Clinical evaluation**

Demographic information of patients includes age and sex was received one day before study. The size of the lesions and the severity of pain were evaluated on the starting day and days 2, 4, 6 after the intervention. At each day, evaluations were conducted by a trained physician who did not know about the type of administrated drug. The size of the lesions was measured by single-use and graded paper lace. Then, the average length of greater diameter of lesions was recorded in mm per patient (all of lesions in each patient were treated). The severity of pain was measured using the Visual Analogue Scale (VAS), a 100 mm paper ruler. More score shows more pain severity.

In addition, patients with lesions on both sides of their buccal mucosa were administered with both NT and CT. The success of the treatment in this study was the reduction of the severity of the pain to a reasonable amount.

**Data analysis**

Data were analyzed using SPSS 24 software. To describe the quantitative data, the Mean ± SD and for qualitative data, the percentage was used. For between groups comparison, independent t-test or chi-square test was used. Findings were significant with P <0.05.

**RESULTS**

Sixty eligible patients with RAS were enrolled in the study. Five patients did not complete the study (figure 1). The information of 55 patients is presented below.

The mean age of NT and CT groups was 26 ± 4 and 26.5 ± 5.2 years, respectively (P=0.7). In NT and CT groups, 21 (38.2%) cases were female and 34 (61.8%) cases were male (P=0.6). The severity of pain in NT group before and after the study was 1.4 ± 5.2 and 1.8 ± 1.3 cm, respectively and in CT group was 4.8 ± 1 and 1.8 ± 1.3 cm. The size of the lesions in NT group before and at the end of the study was 0.96 ± 0.1 and 0.18 ± 0.1 mm, respectively and in CT group was 0.93 ± 0.1 and 0.19 ± 0.1 mm. Among the mentioned variables, only size of lesions on the 2nd and 4th days had a significant reduction in NT group in comparison with CT group.

Measuring the severity of pain before the intervention (baseline) and days 2, 4, 6 is showed in Table 1 and Figure 2. In the both groups, the severity of pain showed a decreasing trend compared to baseline. Independent t-test showed a significant difference in pain severity and it was less in NT group than CT on 6th day.
Size of the lesions on 2nd and 4th day was less in NT in comparison with CT group, however they didn't have any significant difference on the final day (Table 2 and figure 3).

### Table 1 - Distribution of pain intensity based on 10 cm VAS scale (independent t test)

| Time (day) | Group | number | mean | Standard. dev | p |
|------------|-------|--------|------|---------------|---|
| 0          | NT    | 27     | 5.2  | 1.4           | 0.3 |
|            | CT    | 28     | 4.8  | 1             |    |
| 2          | NT    | 27     | 3.4  | 1.2           | 0.7 |
|            | CT    | 28     | 3.6  | 1.6           |    |
| 4          | NT    | 27     | 2.6  | 1.2           | 0.1 |
|            | CT    | 28     | 3.2  | 1.5           |    |
| 6          | NT    | 27     | 1.8  | 1.3           | 0.01|
|            | CT    | 28     | 2.8  | 1.5           |    |

### Table 2 - Changes in ulcer size per cm (independent t)

| Time (day) | Group | number | mean | Standard. dev | p   |
|------------|-------|--------|------|---------------|-----|
| 0          | NT    | 27     | 0.96 | 0.1           | 0.3 |
|            | CT    | 28     | 0.93 | 0.13          |    |
| 2          | NT    | 27     | 0.67 | 0.18          | 0.003|
|            | CT    | 28     | 0.81 | 0.14          |    |
| 4          | NT    | 27     | 0.4  | 0.13          | 0.001|
|            | CT    | 28     | 0.55 | 0.15          |    |
| 6          | NT    | 27     | 0.18 | 0.13          | 0.9 |
|            | CT    | 28     | 0.19 | 0.13          |    |

### DISCUSSION

The aim of this study was to compare the effectiveness of triamcinolone acetonide gel with and without nanoparticle combinations on RAS. The findings showed that although Nanotriamcinolone increases the rate of pain relief, and reduces the size of lesions, its difference overall was not significant compared to non-Nano triamcinolone gel.

In the present study, triamcinolone acetonide was polymerized and contained nanoparticles, therefore, it caused more adhesion to the mucus with polymer, and also accumulation and gradual release of the drug at the mucosal surface with nanoparticles (8,9). Gamboa et al figured out that the oral route presents many obstacles for the delivery of biologics. Nanoparticle mediated delivery
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may minimize degradation of the cargo, extend retention time, and enhance transport to the systemic circulation [10]. It seems that the addition of the nanoparticles only accelerate the recovery and decrease symptoms.

Solid lipid nanoparticles (gel) have been applied locally with a good therapeutic effect on oral aphthous [11]. Karavana et al showed that the bioadhesive gel formulation containing cyclosporine A solid lipid nanoparticles (CsA SLNs) that was reported in their study is a promising candidate for the topical treatment of recurrent aphthous stomatitis. By texture analysis, the developed formulations were shown to have an appropriate consistency, with high adhesiveness and cohesiveness values. This study also demonstrated a rapid decrease in ulcer size with the application of the ideal gel containing cyclosporine A-loaded solid lipid nanoparticles. In the experimental standard mucosal wound animal study, the gel containing CsA-loaded SLNs showed a statistically significant increased rate of mucosal repair. When lesions were covered with the gel formulation containing no active agent, moderate improvement was observed, compared with untreated animals, suggesting that the gel base provided a protective layer over the lesion. Thus, the above-mentioned novel bioadhesive gel formulation containing CsA-loaded SLNs appears to be a candidate for the topical treatment of RAS [12].

Altenburg et al through a review of relevant articles stated that if combination therapy with topical anesthetics and anti-inflammatory agents is not effective, topical corticosteroids should be employed. Also, the especially painful, deep ulcers can be treated with intralesional triamcinolone suspension 0.1-0.5 ml per lesion. They concluded that the treatment of chronic recurrent oral aphthous ulcers is symptomatic, mainly with topically applied agents. It is tailored to the severity of the problem in the individual case, i.e., the frequency of ulcers, the intensity of pain, and the responsiveness of the lesions to treatment. Effective treatment relieves pain, lessens functional impairment, and lowers the frequency and severity of recurrences [13].

When topical corticosteroids are used regularly, one should be alert to the possibility of increased numbers of oral yeast infections [13].

If systemic therapy is needed for RAS, corticosteroids are the first choice. They are usually used as rescue therapy in patients with acute severe RAS outbreaks [14]. The drug can produce long-term adverse effects; as a result, its efficacy has been compared with other drugs in order to search of alternative therapies. According to Femiano et al. compared the efficacy of prednisone prescribed at a dose of 25 mg/day via the oral route during 15 days, 12.5 mg/day during 15 days, 6.25 mg/day during 15 days, and then 6.25 mg on alternate days during 15 days, in comparison with montelukast (a leukotriene receptor antagonist used as an antiasthma drug) at a dose of 10 mg via the oral route each night, followed by administration on alternate days during the second month [15]. The authors found both treatment modalities to be effective in reducing the number of lesions, affording pain relief and accelerating healing of the ulcers. As regards adverse effects, montelukast was found to be safer, and therefore should be taken into account as an option when systemic corticosteroids are contraindicated.

In another study, Pakfetrat et al. compared prednisolone 5 mg/day versus colchicine (a drug that interferes with different pathways of the inflammatory process) 0.5 mg/day. Both treatments were seen to be equally effective and significantly reduced the lesion outbreaks, though colchicine produced more side effects. Thus, 5 mg/day of prednisolone seems to be a better option in reducing the signs and symptoms of the disease [16].

Limited studies have been conducted on the evaluation of Nano-based triamcinolone on improving oral lesions. Azizi et al. compared the anti-inflammatory effect of 0.1% triamcinolone in Orabase with and without nanoliposomal carriers on OLP lesions. They concluded that both drugs reduced the severity of pain and size of the lesions; however, the efficacy 0.1%
triamcinolone with nanoliposomal carrier was more effective than 0.1% triamcinolone without nanoliposomal [17].

In the present study, although the lesion was different from Azizi’s studied lesion (however, both RAS and OLP are of inflammatory nature), the same variables and similar drugs were assessed, and finally, in both studies, almost identical results were obtained from comparing the effect of the drugs on the variables studied.

In conclusion, the findings of study showed that Nano-based triamcinolone gel promoted better healing compared to non-Nano-based triamcinolone; the size of lesions showed a significant reduction on the 2nd and 4th days in NT group in comparison with CT group, therefore NT has a better impact on RAS in comparison with CT.

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