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Evaluation of Clinically Effective Doses of Triamcinolone Acetonide for Intralesional Injection in Oral Lichen Planus

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Purpose: The aim of this study was to evaluate the optimal doses of intralesional triamcinolone acetonide (TA) in the treatment of oral lichen planus (OLP).

Methods: A randomized clinical trial was performed. Sixty-two lesions of OLP were received 12 mg (group A) or 20 mg (group B) of TA intralesionally weekly for 2 weeks. Subjective symptoms, lesion size, favorable conversion of clinical subtypes, and clinical response were evaluated at weeks 0, 1, 2, and 4.

Results: After two consecutive injections of TA, group B showed significant reduction in burning sensation and reticular area ($p<0.01$). Favorable conversion and complete response were greater in group B. Mild oral candidiasis was developed in group B (10.7%).

Conclusions: A 20-mg injection of TA was much more effective compared with 12-mg injection of TA in the treatment of OLP.

Key Words: Intralesional injections; Oral lichen planus; Triamcinolone acetonide

INTRODUCTION

Lichen planus (LP) is a chronic inflammatory mucocutaneous disease that can affect the skin, the mucosa, or both. The prevalence of oral lesions among patients with LP varies from 50% to 77%, whereas approximately 20% to 30% of patients present oral lesions alone [1,2]. Oral LP (OLP) is estimated to affect 0.5% to 2.2% of the population and is more frequently observed in women between 30 and 60 years of age [3]. The pathogenesis of OLP remains unclear; however, current data suggest that it is a T cell-mediated autoimmune disease in which autocytotoxic CD8+ T cells trigger the apoptosis of basal epithelial cells [4]. All regions of the oral cavity may be affected; however, lesions are most commonly found on the posterior buccal mucosa with a bilateral distribution [5].

Clinically, six variants OLP may develop. These variants are described as reticular, papular, plaque-like, erosive, atrophic, and bullous, and more than one clinical phenotype may be observed simultaneously [6]. In general, reticular lesions are the most frequent type, presenting as fine radiating white striae ('Wickham striae'), and the majority of patients are asymptomatic [3]. Atrophic (erythematous) lesions develop as diffuse erythematous patches surrounded by white striations. Erosive (ulcerative) lesions appear as yellow/white, sloughed inflammatory necrotic tissue with erythema and white striae on the periphery. These unique features help to clinically differentiate OLP from other vesiculo-erosive diseases, such as pemphigus and pemphigoid, which are characterized by isolated areas of erythema and/or erosions [7].

In contrast to the clinical course of the cutaneous form

of LP, which resolves within 2 years, OLP tends to follow a chronic course for up to 25 years, with little tendency toward spontaneous resolution [2,8]. In particular, erythematous and ulcerative lesions are associated with significant symptoms and require therapeutic intervention [4]. Recently, various treatment regimens, such as topical and systemic corticosteroids [9,10], topical calcineurin inhibitors [11], and retinoids [12], have been used to attempt to treat symptomatic OLP. However, none of these treatments resulted in complete or long-term remission, and, topical corticosteroids are currently considered as the mainstay therapy for OLP [9]. Oral corticosteroids, in contrast, are reserved for acute exacerbation, widespread lesions, and conditions that are unresponsive to topical steroids [3,13,14].

Triamcinolone acetonide (TA), one of the mid-potency topical corticosteroids, is a fluorinated prednisolone derivative, and the 9-α fluoridation results in enhanced anti-inflammatory properties [15,16]. An aqueous TA suspension is suitable for intralesional injection, which aims to achieve a sufficiently high steroid concentration locally and remains at the injection site for a longer period of time [15,16]. The beneficial effect of a local steroid injection on OLP has been suggested in the recent literature [17]. Approximately 2 to 20 mg of TA at slightly different concentrations (20 to 40 mg/mL) has been shown to be effective [7,17-23]; however, because there is no current consensus regarding steroid dosage, an evidence-based recommendation cannot be made [3].

Therefore, this study was designed to determine the optimal dose of TA for intralesional injection in OLP by comparing two different doses: 12 mg and 20 mg of TA.

MATERIALS AND METHODS

1. Patients

Patients were selected according to the inclusion criteria, which were based on a modified version of the criteria of the Asian LP Group [24]: (1) all patients had clinically or histologically confirmed OLP based on the World Health Organization's diagnostic criteria (2003) [25], which state that clinically, erythematous or ulcerative lesions should be accompanied by the 'classic' reticular form on the buccal mucosa, with bilateral lesions; (2) patients receiving topical or systemic medication for OLP were included in this trial only after a wash-out period of 2 or 4 weeks, respectively; and (3) patients with secondary infection of their OLP lesions were first treated with antimicrobials. The exclusion criteria were as follows: (1) the presence of other mucosal or skin lesions; (2) histopathological signs of dysplasia; (3) systemic diseases, such as autoimmune diseases, chronic liver or renal diseases, hematological diseases, and diabetes mellitus; and (4) pregnancy and lactation. A total of 36 patients from the Department of Oral Medicine at Pusan National University Dental Hospital met all the eligibility criteria and were enrolled in the study.

This study was approved by the Institutional Review Board of Pusan National University Dental Hospital (IRB no. PNUDH-2013-034) and informed consent was obtained. The entire process, potential side effects, and alternative treatments were explained before the procedure, and the trial was conducted with the participants' agreement.

2. Study Design and Interventions

The 36 patients were randomly divided into two groups of 18. Patients in the two groups, designated A and B received 12 mg (0.3 mL) or 20 mg (0.5 mL) of TA via injection (40 mg/mL; Tamceton; HanAll BioPharma, Seoul, Korea), respectively. In group A, 30 lesions were used as targets, whereas 32 lesions were used in group B. Each lesion was given a number based on the sequence of enrollment of the patients. When a bilateral lesion satisfied the criteria, the lesion on the right was assigned the preceding number. That is, lesions on the right and left buccal mucosa were evaluated separately, as independent objects. One week after the first injection, both groups received an additional 0.5 mL of TA via injection, followed by a 2-week follow-up period. The TA was injected using a 31-gauge insulin syringe (DM Ject; Shinchang Medical, Gumi, Korea) that was directly placed into the submucosa immediately underlying the lesion on the buccal mucosa. The injection was given at two central points in each half of the lesion, with a distance of at least 1 cm between injections. The ulcerative area was avoided as much as possible.

3. Clinical Assessment

Baseline parameters were measured and recorded on the

day of the first visit (week 0). Clinical symptoms and signs were evaluated at weeks 0, 1, 2, and 4 after initiating treatment. Clinical photographs were taken at each visit.

1) Subjective assessment

Pain or a burning sensation was scored via self-administered assessment using a numeric rating scale (NRS). The patients were instructed to point to a number from 0 (no pain) to 10 (extreme pain) that best described their discomfort at the moment when their erythema and/or ulceration area was brushed gently with a sterile cotton swab. The improvement in each patient's symptoms was also recorded as 'improved', 'same', or 'worse' since the initial visit.

2) Objective assessment

The lesion size was determined based on the mean length of the clinical diameter and the maximum width perpendicular to the diameter using a sterile, flexible, transparent ruler that was calibrated to 2 mm square. Reticulation, erythema, and ulceration were calculated independently (Fig. 1). Changes in the clinical form from ulcerative OLP (U-OLP) or erythematous OLP (E-OLP) to reticular OLP (R-OLP) or normal mucosa were also recorded at every visit, as shown in Fig. 2. The clinical response to TA injection was evaluated based on resolution in the erythema area, which was present in both groups. This resolution was classified as a complete response (CR; a lack of detectable erythema and/or ulceration, with the absence or regression of reticulation and no symptoms), a partial response (PR; a reduction in the erythema diameter of at least 30%), or no response (NR; a reduction in the erythema diameter of less than 30%) according to the modified version of the 'lesion responses' proposed by Kuo et al. [18]. Once a CR was confirmed, no additional injections were administered. At each visit, side effects that were directly observed by the investigator and/or disclosed during patient interviews were recorded. Any patient who developed adverse drug reactions or whose symptoms appeared worse at any visit during the trial was shifted to alternative therapy.

4. Statistical Analysis

The results were analyzed as per protocol. The baseline characteristics of the two groups were compared using an independent t-test and a chi-square test. Differences in subjective discomfort (the NRS pain score) and the lesion size were ascertained using repeated-measures analysis of variance with Bonferroni multiple comparisons. The participants' discomfort (improvement), the clinical response, and the conversion of clinical subtypes were compared using a chi-square test. The data were presented as means±standard deviation for quantitative variables and % for qualitative variables. A probability value of <0.05 was considered to be statistically significant for all tests performed in the present study, as determined using IBM SPSS Statistics ver. 20.0

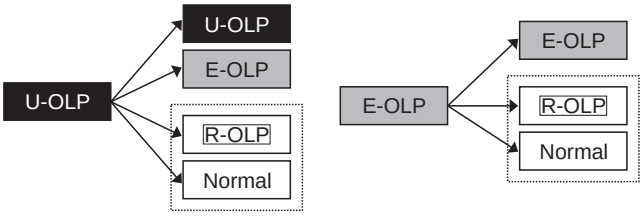

Fig. 2. The favorable clinical forms of U-OLP and E-OLP. Changes in the clinical form from U-OLP or E-OLP to R-OLP or normal mucosa were recorded. U-OLP, ulcerative oral lichen planus (OLP); E-OLP, erythematous OLP; R-OLP, reticular OLP; Normal, normal mucosa.

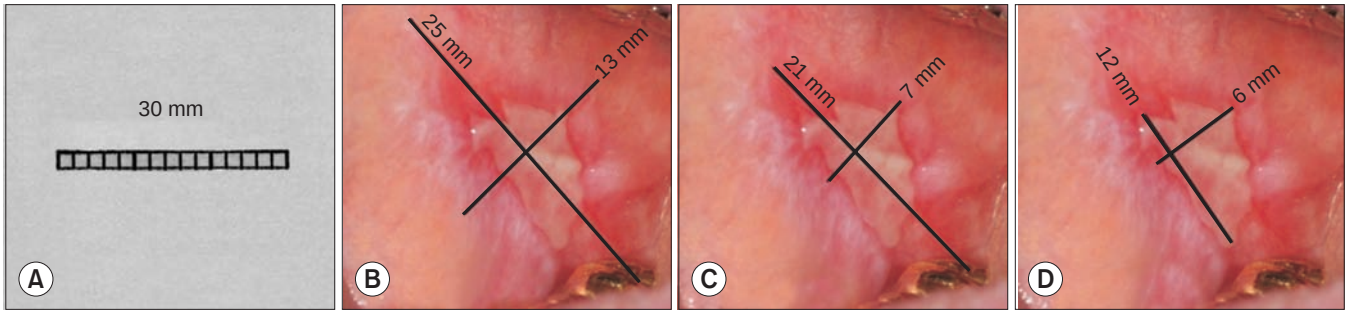

Fig. 1. A method to determine the size of oral lichen planus lesion on buccal mucosa. (A) A Flexible, transparent ruler as measuring tool for lesion size. (B-D) The lesion size was measured at the lesion periphery of the (B) area of reticulation, (C) erythema, and (D) ulceration, independently. The lesion sizes are 19 mm, 14 mm, and 9 mm for reticulation, erythema, and ulceration, respectively, based on this method.

software (IBM Co., Armonk, NY, USA).

RESULTS

A total of 36 patients (29 females and 7 males, mean age 57.22±10.95 years) were enrolled in this study. The patients were divided into groups A and B, with a total of 30 and 32 sites in the buccal mucosa, respectively. Fig. 3 illustrates the complete profile of the study. There were no significant differences between the two groups regarding the clinical and symptomatic baseline characteristics of the lesions (Table 1).

1. Subjective Symptoms

The NRS scores for pain or burning sensation were significantly decreased in both groups (p=0.000), and there were no intergroup differences at each follow-up visit (p=0.058), as presented in Fig. 3A. At 1, 2, and 4 weeks, the NRS scores in group A were 30%, 50%, and 60% reduced, respectively, while in group B, the scores were 34%, 53%, and 67% reduced, respectively. In addition, after the first injection, the symptoms were recorded as 'improved' in 70.0% of cases, 'the same' in 23.3% of cases, and 'worse' in 6.7% of cases in group A, whereas 90.6% cases were 'improved', 9.4% of cases were 'the same', and 0.0% of cases

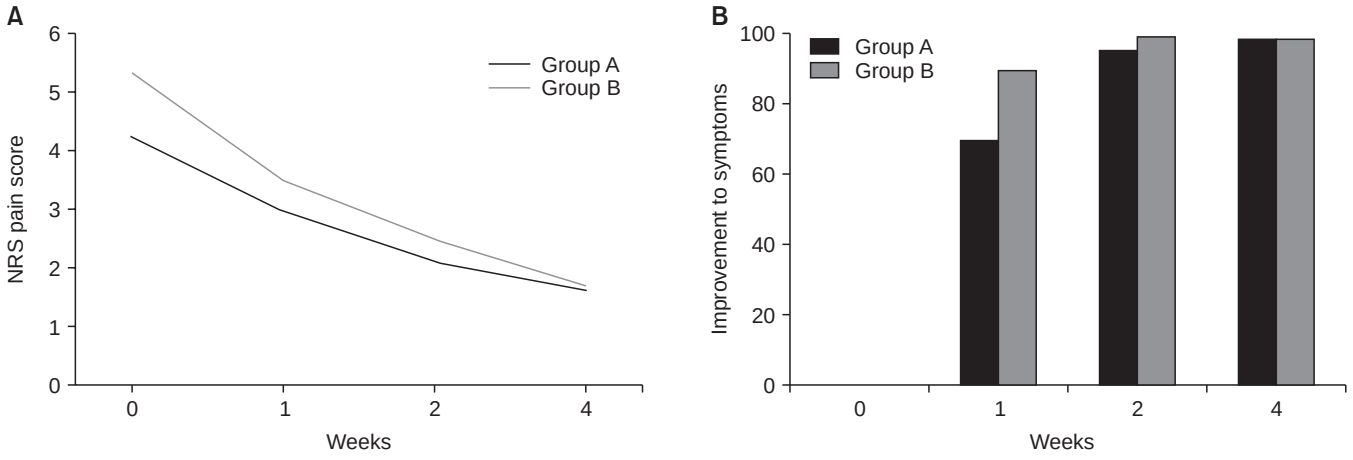

Fig. 3. Comparison of subjective symptoms. (A) The numeric rating scale (NRS) scores for pain or burning sensation were significantly decreased in both groups (p=0.000), and there were no intergroup differences (p=0.058). (B) After the first injection, the improvement of symptoms was significantly greater in group B (p=0.002).

Table 1. Baseline characteristics of the study lesions

Characteristic	Group A	Group B	Total	p-value
Number of target sites	30	32	62	[a]
Duration of lesions (mo)	21.11±20.01	41.60±51.37	30.42±38.40	0.163
Past steroid treatment				
No treatment	6 (20.0)	8 (25.0)	14 (22.6)	0.700
Treatment	24 (80.0)	24 (75.0)	48 (77.4)	0.700
Type of lesion				
Reticular form	30 (100.0)	32 (100.0)	62 (100.0)	[a]
Erythematous form	30 (100.0)	32 (100.0)	62 (100.0)	[a]
Ulcerative form	16 (53.3)	20 (62.5)	36 (58.1)	0.480
NRS pain score	4.43±1.70	5.03±1.73	4.74±1.73	0.175
Lesion size, mm				
Reticulation	24.42±9.79	23.55±6.55	23.97±8.22	0.685
Erythema	14.80±7.60	13.39±5.85	14.07±6.73	0.415
Ulceration	7.38±6.65	7.43±4.54	7.40±5.62	0.978

NRS, numeric rating scale.
Values are presented as number only, mean±standard deviation, or number (%).
[a]No statistics computed as this is a constant value.

were 'worse' in group B. The improvement was significantly greater in group B, as shown in Fig. 3B (p=0.002).

2. Objective Signs

1) Lesion size

The areas of reticulation, erythema, and ulceration were significantly decreased during the 4-week study period in both groups, as shown in Fig. 4 (p=0.000). Whereas erythema and ulceration did not significantly differ between the groups (p=0.595 and p=0.497, respectively), reticulation in group B was significantly decreased in each follow-up visit compared with reticulation in group A (p=0.002). After groups A and B had undergone 1 week of treatment, the groups respectively showed 11.9% and 24.2% reductions in reticulation size, 32.2% and 32.9% reductions in erythema size, and 37.5% and 48.2% reductions in ulceration size.

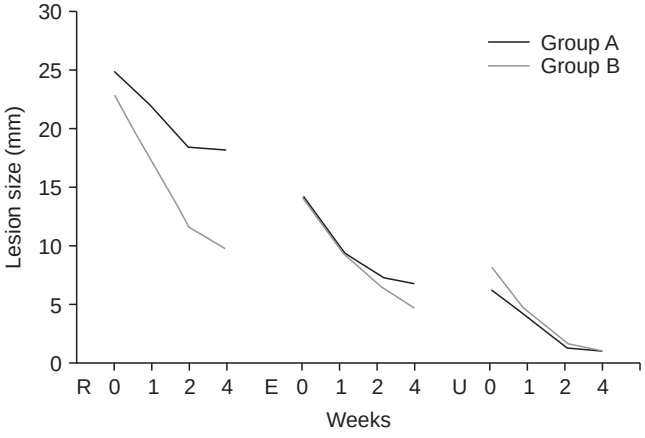

Fig. 4. Comparison of lesion size by the clinical type of oral lichen planus. The areas of reticulation, erythema, and ulceration were significantly decreased in both groups (p=0.000). Whereas erythema and ulceration did not significantly differ between the groups (p=0.595 and p=0.497, respectively), reticulation in group B was significantly decreased in each follow-up visit compared with reticulation in group A (p=0.002). R, reticulation; E, erythema; U, ulceration.

2) Favorable conversion of clinical subtypes

In group A, U-OLP lesions were converted into a more favorable type (R-OLP or normal mucosa) in 0%, 0%, and 7% of cases at weeks 1, 2, and 4, respectively; however, in group B, favorable conversions were noted in 15%, 25%, and 38% of cases. In group A, E-OLP lesions were converted into more favorable types in 7%, 29%, and 33% of cases at weeks 1, 2, and 4, whereas in group B, favorable conversion were noted in 0%, 25%, and 58% of cases. The percentage of favorable conversion into R-OLP or normal mucosa was greatest in group B at week 1 for U-OLP lesions and week 4 for E-OLP lesions (p=0.001 for E-OLP) (Fig. 5).

3) Clinical response

The percentage of NR was decreased and the percentage of CR was increased in both groups. These changes were significantly greater in group B (p=0.000) than in group A (p=0.269). After 4 weeks of treatment, 5 patients (19.2%)

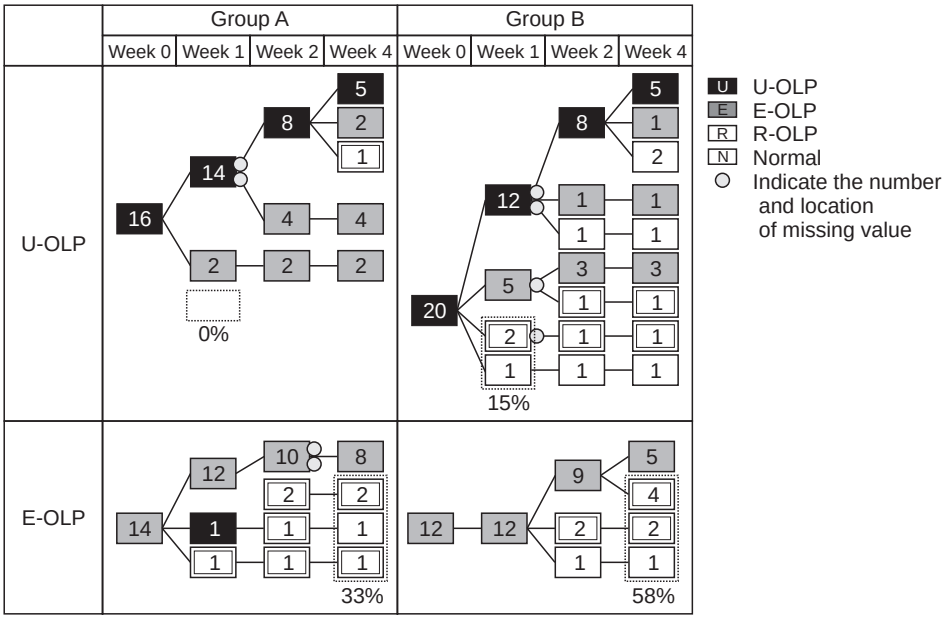

Fig. 5. The favorable conversion of clinical form of U-OLP and E-OLP. The percentage of favorable conversion into R-OLP or normal mucosa was greatest in group B at week 1 for U-OLP lesions and week 4 for E-OLP lesions (p=0.001 for E-OLP). U-OLP, ulcerative oral lichen planus (OLP); E-OLP, erythematous OLP; R-OLP, reticular OLP; normal, normal mucosa.

showed a CR, 16 patients (61.5%) had a PR, and 5 patients (19.2%) showed NR in group A. In contrast, in group B, there were no cases of NR, 15 patients (53.6%) showed a PR, and 13 patients (46.4%) had a CR (Fig. 6).

As evidenced in the clinical photographs of ulcerative lesions, a CR was achieved in group B after a 0.5-mL TA injection. Reticulation, erythema, and ulceration were clearly resolved, and this condition was maintained at week 4 (Fig. 7).

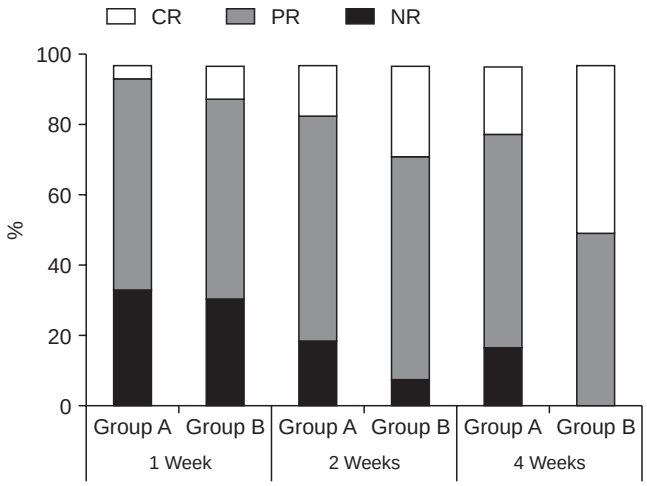

Fig. 6. Comparison of clinical response. The percentage of NR was decreased and the percentage of CR was increased in both groups. These changes were significantly greater in group B (p=0.269 and p=0.000 for group A and group B, respectively). CR, complete remission; PR, partial remission; NR, no response.

3. Adverse events

Whereas three lesions (10.7%) in group B developed oral candidiasis, which was identified by the KOH smear method, no candidiasis was observed in group A. All three lesions had localized fungal colonies adjacent to the injection site at week 2, which were resolved with or without topical antimycotics (PMS-Nystatin suspension; Pharmascience Inc., Montreal, QU, Canada) at week 4 (Fig. 8).

DISCUSSION

Topical corticosteroids have been used as the mainstay of OLP treatment [3]. Many different formulations, including mouthwashes, gels, pastes, and patches, are used to effectively deliver steroids into the oral mucosa. The permeability barrier of the mucosa is not as extensive as the skin's stratum corneum; thus, steroids are easily absorbed through the mucosa [26]. However, compounding the problem of

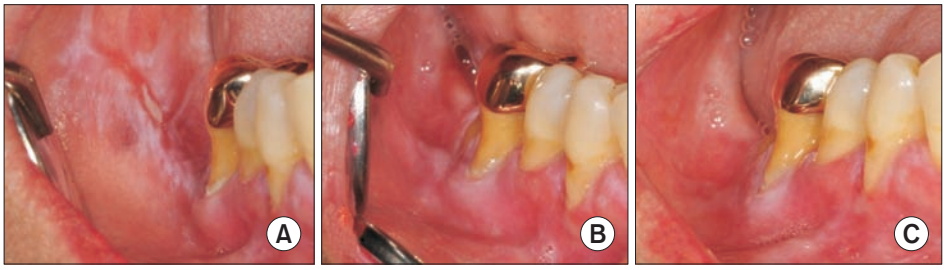

Fig. 7. Clinical photographs of oral lichen planus lesions. (A) An ulcerative lesion at the right buccal mucosa of a 54-year-old female patient. (B) The same patient after the 1-week treatment with 0.5 mL of triamcinolone acetonide injection showed complete response. (C) The condition of normal mucosa was maintained at week 4 without additional injection.

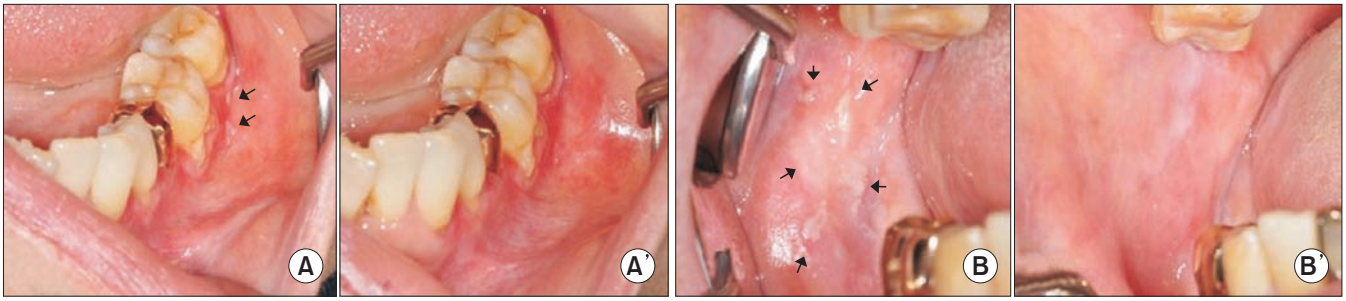

Fig. 8. Secondary candidiasis in group B. (A, B) The fungal colonies appeared after two consecutive injections of 0.5 mL of triamcinolone acetonide (arrows). (A', B') Underlying mucosa after wiping off the fungal colonies.

achieving contact between steroids and lesions is the difficulty of adherence to moist mucous membranes, causing formulations to dislodge easily and reducing the concentration of steroids.

An intralesional injection method improves upon the limited value of topical preparations. Local injection allows the introduction of a high concentration of steroids directly into a lesion for an enhanced immunosuppressive effect with less systemic toxicity [15,27]. Injectable corticosteroids can be classified into five categories according to their solubility [28]. Among these categories, an aqueous TA suspension is generally the preferred preparation because it is a fluorinated compound that has enhanced anti-inflammatory properties, and its insoluble character produces a more prolonged effect [15,16].

Intralesional TA injection is known to be an effective treatment for alopecia areata [29], keloids [30], hemangiomas [31], and central giant cell granuloma [32]. This approach also has a beneficial effect in OLP treatment. Xia et al. [17] proposed that TA injection itself had excellent treatment efficacy in OLP. Kuo et al. [18] demonstrated that a combination of steroid injection and oral administration accelerated the healing of OLP, and Zegarelli [33] suggested another combination approach, including topical and intralesional corticosteroids. Lee at al. [19] evaluated the clinical effects of TA injection (20 mg) and a TA mouth rinse (0.4%). In our study, an intralesional injection of 20 mg of TA (0.5 mL) was more effective in relieving the symptoms and signs of OLP compared with an injection of 12 mg of TA (0.3 mL).

Patients reported an "improved" response significantly more frequently after the first 0.5-mL injection of TA ($p=0.002$), although there were no significant intergroup differences in NRS scores for pain. Thus, 0.5 mL of TA was much more effective than 0.3 mL for dramatically reducing a patient's discomfort within 1 week, a short-term period.

The rate of conversion into R-OLP or normal mucosa was significantly higher in the group receiving 0.5 mL of TA. In particular, U-OLP lesions were converted to more favorable forms after the first injection, and E-OLP lesions were converted more slowly (by week 4). Our finding that the rate of size reduction was greater in ulcerations than in erythemas suggested that U-OLP changed clinical forms faster than E-OLP. These findings were differed from those of Xia et al. [17], who found that a similar degree of size change occurred in erythemas and ulcerations in response to 0.5 mL of TA (40 mg/mL). From our point of view, intralesional steroids are recommended for patients with the ulcerative form of OLP. In previous studies, researchers have also noted that local steroid injections have benefits in the management of ulcerative OLP [22,23].

The current study included the erythematous type and broadened the spectrum of symptomatic OLP, although most research has focused on the ulcerative type of OLP [18,34]. Earlier studies used the area of ulceration and/or erythema to evaluate lesion size [17,18]. in addition to these parameters, the present study also measured the reticulation size. At each follow-up visit, the rate of reduction in reticulation in response to 0.5 mL of TA was significantly decreased (by approximately two-fold) compared with the response to 0.3 mL of TA. Thus, reticulation also has the potential to undergo a significant size decrease, depending on the steroid dose. No studies have concentrated on the remission of R-OLP because of its asymptomatic character. Xia et al. [17] reported that reticular lesions tend to persist after an intralesional TA injection over a short time, which was a finding based on a specific dose. In contrast to these results, the outcome of our study was achieved by comparing two different doses of steroids. Thus, it is reasonable to assume that reticular lesions can significantly change depending on the dosage of steroids. To promote the remission of a reticular lesion (due to a patient's anxiety or the discomfort of mucosal tension), it is worth considering the administration of a higher dose of steroids to the lesion.

Most studies have monitored changes in lesion size according to the total surface area of a lesion [34,35], the surface area of a single ulcerative lesion [36], or the diameter of an ulceration area [18,37]. We utilized another method to evaluate lesion size, in which the lesion area was measured based on the mean length of the clinical diameter and the maximum width perpendicular to the diameter. This measurement was clinically convenient for determining the lesion size and reflected the entire morphology of a lesion.

According to the clinical response at week 4, some lesions were still classified as NR following treatment with 0.5 mL of TA (19.2%), whereas all the lesions treated with 0.3 mL

of TA exhibited a PR or CR. That is, the effect of 0.5 mL of TA was longer lasting than that of 0.3 mL of TA during the post-treatment period. Although the percentage of CR was as much as 2.5 times higher in the group treated with 0.5 mL of TA, 56.3% of cases still exhibited a PR, not reaching a CR. Thus, further assessment of higher doses of steroid will be needed to determine the optimal steroid dose for intralesional injection in OLP.

Our study noted oral candidiasis in three patients who received a 0.5-mL injection of TA. This result corresponds well with the findings of an earlier study that reported that the most frequent side effect of steroid injection in the oral mucosa was oral candidiasis [38,39]. Lee at al. [19] reported that fungal infection was found in 5.0% of lesions in response to injection with 0.5 mL of TA (40 mg/mL); however, Xia et al. [17] showed no candidiasis with the same concentration and volume of TA. The prevalence rate of oral candidiasis following steroid injection is relatively lower than that observed with topical steroids (11% to 47% rate of candidiasis) [38,40-42]. Moreover, patient's discomfort is relatively improved when fungal colonies arise. Therefore, it is reasonable to suppose that secondary candidiasis due to intralesional injection is mild and transient. Furthermore, because the fungal colonies appeared after two consecutive injections of 0.5 mL of TA in the current study, we recommend a follow-up check after at least 2 weeks of local injection, especially when using doses over 0.5 mL of TA.

For the oral mucosa is under chronic inflammation in OLP, one of most adverse reactions related to topical steroid treatment is fungal infection. As we have seen in our study, there was no candidiasis was observed in 12 mg TA group, however it was developed in 3 patients (10.7%) in 20 mg TA group as the steroid dose increasingly.

Therefore the possibility of secondary oral candidiasis after intralesional steroid therapy as much as it after topical or systemic steroid therapy should be considered. Also in all OLP patients, it is important to remove local exacerbating factors and should be instructed in thorough oral hygiene. When the candida albicans superinfection is suspected, it should be controlled with topical antimycotics.

Other reported localized adverse effects of steroid injection are mucosal atrophy [43,44] and a tingling or burning sensation [45] at the injection site. However, these adverse effects were not observed in our 4-week period. Several studies have mentioned that the pain associated with injection is one of the reasons why intralesional injection is not used [7,23]. However, most of the patients in our study experienced only a tolerable pricking sensation and heaviness at the site. This finding was consistent with another report of little to no discomfort following the injection [21]. Thus, local anesthesia is not an essential consideration for intralesional injection, particularly for non-keratinized epithelium, such as the buccal mucosa. Pre-application of a topical anesthetic or aqueous mixture containing lidocaine can be used, if necessary [17,46]. In this study, bleeding arising at the site of injection was easily controlled within seconds by gentle digital pressure. Additionally, TA injection was well accepted by the patients due to the simplicity and efficacy of this treatment procedure.

One of the limitations of this study was the fact that the intervention and measurements were performed by a non-blinded researcher. However, potential bias was minimized by the random assignment of the participants and the use of a standardized protocol. Several subjects did not have histologically confirmed OLP; therefore, our study used the buccal mucosa as the target location, which has a relatively lower risk of dysplasia and malignancy, and we selected lesions that showed typical manifestation, with bilateral distribution.

In conclusion, intralesional steroid injection was a simple and effective method for treating localized OLP. A 0.5-mL injection of TA was much more effective in maximizing the early remission of symptoms and signs of OLP compared with a 0.3-mL injection of TA. In particular, the former dose is indicated for U-OLP, whereas the higher dose of intralesional steroids or an additional approach might be considered to promote the healing of E-OLP. Mild candidiasis can result after two consecutive 0.5-mL injections of TA; thus, a follow-up check will be needed after at least 2 weeks of treatment.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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