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Original Article

Efficacy of Clobetasol, Ketoconazole and Amitryptiline Mouthwash on Oral Lichen Planus

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Abstract

Oral Lichen Planus (OLP) is a chronic inflammatory disease of oral mucosa, with an immunological origin. Atrophic/erosive OLP needs appropriate treatment, due to the pain and malignancy potential. Topical corticosteroids are the most effective drug therapy and mouthwashes are more effective topical dosage forms for this purpose. However, at present there are no corticosteroid mouthwashes available in Iran. In this study, the efficacy of a new mouthwash containing clobetasol, ketoconasole and amitriptyline was evaluated in comparison to the common treatment.

In this double blind randomized clinical trial study, 50 patients who had inclusion criteria were grouped randomly, with no difference in demographic data. The experimental group was treated using 5ml of mouthwash four times a day for 5 min, while the control group was treated by dexamethasone tablet, nystatin drop and diphenhydramine syrup.

Severity of the lesions and pain were followed as the chief complain and recorded in the initial, 1, 2, 4, 8 and 12 weeks intervals. All the collected data were analyzed with the Chi-Square, Mann-Whitney, student T-test and Mantel-Cox statistical tests, using the SPSS version 13 softwares.

There were significant differences in the pain reduction in the 1st ($P<0.001$), 2nd ($P=0.01$) and 12th ($P=0.025$) weeks between the two groups, but the difference in weeks 4 ($P=0.058$) and 8 ($P=0.131$) were not significant. The lesion reduction was significantly higher in the experimental group ($P<0.001$). Complete resolution of lesions occurred on average after 2.65 and 10.75 weeks for the experimental and control groups, respectively. Also most patients in the experimental group (70.6%) had complete subjective satisfaction (75-100%) of treatment but most patients (43.8%) were mildly satisfied (0-25%) in the control group. Survival analysis showed that the possibility of existence of lesions after 3 months in the experimental group and control groups were 0% and 100% ($P<0.001$), respectively.

In conclusion, it seems that the new mouthwash is more effective in short term, with greater convenience for the patients.

Keywords: Amitriptyline; Clobetasol; Ketoconasole; Mouthwash; Oral Lichen Planus.

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Introduction

Lichen Planus is a chronic inflammatory disease of skin and/or oral muscosa (1-4), that has an immunological origin (5-6). Its clinical features are variable including reticular, papular, plaque- like, atrophic, erosive (7-9) lesions, Among these, erosive and atrophic forms of Oral Lichen Planus (OLP) are painful and interfere with the usual daily activities of the patient (including eating, drinking, talking and maintaining normal relationships) (10).

Malignancy potential of these lesions signifies the importance of appropriate treatment (11). Various treatment regimens have been designed to improve the management of symptomatic OLP, but a permanent cure is not yet possible (12-16).

Numerous treatment strategies have been tried in past, including (but not limited to) topical (10, 12, 17-19) systemic (12, 20-22) and intra-lesinoal corticosteroids (12, 23, 24), topical cyclosporine (12, 14, 25), topical and systemic retinoids (26-28), azathioprine (12, 13), tacromilus (12), photochemotherapy (1, 4) and surgery (12, 29).

The treatment of choice is topical corticosteroids, and among them, clobetasol had been emphasized by many authors (10, 14, 17, 19, 30, 32). However, despite the evident benefits of this topical therapy, it may be difficult for patients with severe and extensive lesions to place the adhesive paste on the whole lesional surface, and a systemic approach is generally adapted in these cases (32). It has also been reported that the grainy texture of the paste is generally disliked, which may affect patient compliance (10). The mouthwash solution provides ready access to all lesional area, and there is an excellent control over the contact time between drug and the lesion (32-34). Since the most common side-effect of oral topical steroid therapy is acute candidiasis (14-17, 30, 35), an antimycotic therapy has been added to this therapy as a prophylaxis against oropharyngeal candidiasis (16).

diphenhydramine is generally used for the reduction of pain and burning sensation of patients, but in this study we used amitriptyline (based on its local anesthesia properties) (36).

The purpose of the present study was to evaluate the efficacy of a new mouthrinse containing clobetasol, ketoconasole, and amitriptyline, in comparison to the treatment strategy with dexamethasone, nystatin, and diphenhydramine.

Experimental

In this double blind randomized clinical trial 33 patients,19 women and 14 men ranging in age from 20 to 70 years (mean=48.3 years), medically examined at the Oral Medicine Clinic of Mashad university were enrolled.

The inclusion criteria were as follows:

1) Clinical and histological diagnosis of atrophic/erosive OLP on the basis of World Health Organization criteria (16)

2) Naive status (no previous treatment for OLP in the last two weeks)

3) Willingness (written informed consent)

Exclusion criteria included:

1) Histological presence of dysplasia

2) Use of drugs associated with lichenoid reaction

3) Contemporary skin and/or genital lesions

4) Hypersensitivity to corticosteroids and other drugs which were being used

5) Lupus erythematosis, erythema multiform, secondary syphilis,and Graft versus Host Disease (GVHD).

6) Any systemic disorders such as cardiovascular disease, hypertention, etc.

This clinical trial was approved by the local ethics committee.

The sample size was determined based on the study conducted by Carbone. *et al.* (30).

Patient group

Each patient was allocated randomly (based on the random numbering table) to one of the two groups:

The experimental group (group 1) received 5 ml of the new mouthwash [containing clobetasol (Sigma) Ketoconazole (Sigma) and amitriptyline (Sigm)], which was prepared in Razak laboratories, four times a day and each time for a period of 5 min (the patients were instructed not to swallow the solution, nor eat or drink any thing until 1 h).

The control group (group2) three separate

Table 1. Demographic data of the participant patients in this study.

Groups	Mean age (SD)	Gender		Duration of disease (months)	Previous treatment	
		Male	Female		Yes	No
Group 1	49.29 (11.37)	8 (47.1%)	9 (52.9%)	12.88±13.95	11.00 (64.7%)	6.00 (35.3%)
Group 2	47.25 (15.32)	6 (37.5%)	10 (62.5%)	10.25±8.20	9.00 (56.3%)	7.00 (43.8%)
Total	48.30 (13.26)	14 (42.4%)	19 (57.6%)	11.61±11.46	20.00 (60.6%)	13.00 (39.4%)

drugs as described below:

Diluted dexamethasone (0.5 mg tablet in 5 ml water), 30 drops of nystatin 100000 unit, and 1h later a combination of both of them were used for 5 min and then spitted out. 5 ml of Diphenhydramine elixir was used before each meal for 5 min as the mouthrinse and was then spitted out.

After complete resolution of the lesions, the dosage of drugs (in both groups) were tapered and discontinued after 4 weeks (3 times a day for two weeks, 2 times a day for one week and once a day for one week) (10,17, 31).

The participants were blinded and the blind observer, different from the administrator, expert in oral medicine, conducted the survey and the registration of the measurement.

Data collection

Each patient was examined at the beginning of therapy and at this initial visit detailed information (including age, gender, medical history, and the beginning time of their lesion) were recorded. Then each patient was visited at 5 follow-up visits scheduled for weeks 1, 2, 4, 8, and 12 after the beginning of treatment. The clinical data were scored according to the scale used by Piboonniyom (37) as follows:

The oral cavity of each patient was divided into 10 sites (labial mucosa, right buccal mucosa, left buccal mucosa, dorsal tongue, ventral tongue, floor of the mouth, hard palate mucosa, soft palate, tonsillar pillars, maxillary gingiva and mandibular gingiva). The severity of the lesions in each site was recorded based on the presence of reticular/hyperkeratotic, atrophic, erosive/ulcerative lesion (s). For each of of the three clinical signs, a score was derived by summation of the scores of all 10 areas [reticular score=ΣR, atrophic score=ΣA, erosive/ulcerative score= ΣE (RAE score) with a total weighted score of Σ (R×1)+Σ (A×1.5)+Σ (E×2.0)].

In order to determine the reduction in severity of the lesion in each visit (improvement of the lesion), the following formula was used:

$$\frac{100\times(\text{total score of lesion before the start of treatment-total score of lesion in each visit})}{\text{Total score of lesion before the start of treatment}}$$

The patients' pain experience was measured by means of the Visual Analogue Scale (VAS) (38), as follows:

Score 3 = 7 <VAS≤ 10

Score 2 = 3.5 <VAS≤ 7

Score 1 = 0 <VAS≤ 3.5

Score 0= no pain

The reduction in pain suffered (improvement of the pain) was calculated as shown below:

$$\frac{100\times\ (\text{total score of pain before the start of treatment-total score of pain in each visit })}{\text{Total score of pain before the start of treatment}}$$

At the end of study, patients were asked about their overall satisfaction of the treatment strategy and their views were recorded as shown:

4=75 %< complete satisfaction≤100%

3=50 %< high satisfaction≤75%

2=25 %< moderate satisfactio≤50%

1=0 %< mild satisfaction≤25%

0=no satisfaction

All the collected data were analyzed with the Chi-square, Mann-Whitney, student T-test and Mantel-Cox statistical tests, using the SPSS version.13 software.

Results

Demographic data of patients has been shown in table 1. Based on the statistical tests

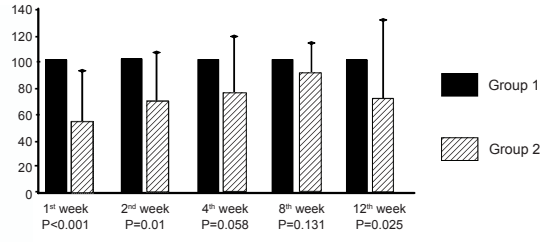

Figure 1. Mean improvement of pain in different visits in two groups.

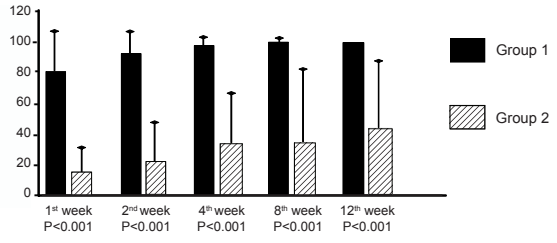

Figure 2. Mean of improvement of lesions between two groups at different follow up visits.

conducted, gender, age, duration of disease before our treatment, location of the lesions, and the severity of pain and lesion (total scores at first visit) had no significant difference between the two groups this showed homogeneity of the two groups at the beginning of the study. The mean reduction in the severity of burning and pain (improvement of pain) was 100 % in group 1 at one week after initiation of treatment and continued until the 12th week, but it was 54.55% for group 2 at the end of first week and 71.21% at the end of 12th week. This showed that some patients had pain after 12 weeks of treatment in group 2 (Figure 1).

The-Whitney test showed that improvement of pain resulted in a significant difference between the two groups at first (Z=-3.487, P value<0.001) and second (Z=-2.562, P value=0.01) weeks but without any significant difference at the 4th (Z=-1.893, P value=0.058) and the 8th (Z=-1.50, P value=0.131) weeks. Again, a significant difference after the 12th (Z= -2.236, P value=0.035) weeks was observed.

The mean improvement of the lesions has been shown in Figure 2.

T-test showed significant differences in improvement of the lesions between the 2 groups at first, second and fourth weeks [(1st week: t=6.821, p value<0.001), (2nd week: t=10.541, p value<0.001), (4th week: t=8.069, p value<0.001)].

Also, the Mann-Whitney test showed that there were significant differences at 8th (Z=-5.165, P value<0.001) and 12th (Z=-5.272, P value<0.001) weeks. Furthermore, the mean time of drug use for complete resolution of lesions were 2.65±3.02 weeks for the experimental group (group 1: minimum of 1 week and maximum of 12 weeks, in which only one patient who had very severe lesions took drug until the 12 weeks). The 10.75±2.41 weeks for the control group (group 2: 12 patients took drug until 12th week) and Mann-Whitney test showed that there was a significant difference between the two groups (Z=-4.613, P <0.001). As represented in Figure 3. The frequency of patients' satisfaction is shown in Figure 4, and Mann-Whitney test showed significant intra-group differences. It no side effect due to drug administration was noted in this study.

Finally, survival analysis of the disease showed that probability of the remaining disease after 1 week was 47.1%.These probabilities were 23.5% after 2 weeks, 11.8% after 4 weeks, 5.9% after 8 weeks and 0% after 12 weeks in the experimental group. Despite the use of drug until the 12th week, the probability of remained disease was 100% in the control group. Mantel-Cox (Log rank) test showed a significant difference between the probabilities of the remaining disease (χ^2= 37.082, P<0.001) (Figure 5).

Discussion

Absence of any significant difference between the two groups in confounding variables such as age, gender, duration of the disease and etc, shows good homogeneity between the two groups.

Although some types of OLP are asymptomatic, but atrophic or erosive types are painful, and can interfere with eating or speaking (10). Also these types have the possibility of recurrence and transformation to a malignancy. Hence, medical treatment is necessary (11, 39, 40).Yet with the above limitations, corticosteroid therapy remains the first choice in the management of

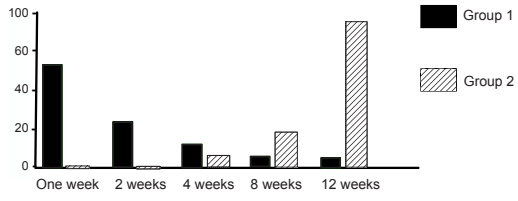

Figure 3. Frequency percent of patients at different drug using time to complete resolution of lesions.

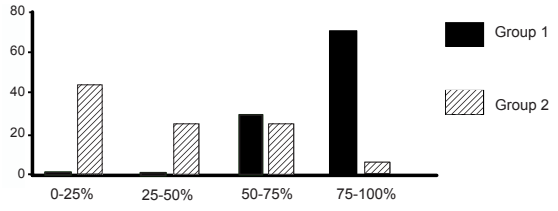

Figure 4. Mean satisfaction of patient in two groups.

atrophic/erosive forms of OLP (17, 31), among them clobetasol is recommended by a number of researcher (10, 14, 17, 19, 30, 31, 32). Therefore, used was in this study.

Although longitudinal studies did not show any systemic side effect in the usage of topical corticosteroids (41) but psendomemberanus candidiasis has been their sole side effect in the oral cavity (12, 18, 21, 31, 41). Hence, we used ketoconazole as an antifungal agent, due to it's stability in combination form in the designed formulation.

Based on the topical anesthetic properties of amitryptiline (36), and the possibility of combining amitryptiline with clobetasol and ketoconazole, it was used instead of diphenhydramine in this study.

We tried to prepare this combination dosage form (mouthwash) of drugs, since there were several drawbacks in the use of steroidal preparations in orabase. It is difficult to apply the grainy gel to the oral mucosa, it adheres rather poorly and it is difficult to apply it to large areas or posterior areas of the mucosa (34). These problems in addition to the unpleasant taste sensation which these type of drugs could produce for patients, may result in patient dissatisfaction and can also adversely influence improvement of the disease. However, the use of mouthwash could be more comfortable and also patients could benefits from a more intimate contact with the lesions and the problem of using separate drugs would be solved,

Based on the results obtained, most of the patients (70.6%) in group 1 whom used mouthwash had complete (75-100%) satisfaction but most patients (43.8%) in group 2 whom used separate drugs (in form of tablet, drop and syrup) had moderate (0-25%) satisfaction and only 6.2% of patients had complete (75-100%) satisfaction.

The scoring system which we used was a quantitative scoring system for monitoring OLP, easy to use, reproducible, objectively measuring the severity of disease in its different clinical forms, and correlates well with the clinical finding of healing (37). Because each type of lesion causes a different degree of discomfort and pain, we weighted each type of lesion accordingly. Reticular lesions were weighted 1, because this presentation tends to be asymptomatic. Atrophic lesions were weighted 1.5, since they tend to cause some degree of discomfort. Erosive/ ulcerative lesions were weighted 2.0, since they tend to be the most painful. The scores for each site were then totaled. Comparison of this system with another system used by Thongprasom et al (18) that was later modified by Kaliakatsou et al (42), showed that this scoring system could allow each site of involvement, in the mouth to be scored individually, and the scores of all sites to be totaled, giving a more accurate picture of the severity of the disease. The grid system (43) allows for accurate measurement of area of involvement but it is time-consuming and may be difficult to perform in patients with extensive ulcers.

The severity of pain and burning had no significant difference before the start of treatment, between the two groups, but there was a significant difference at 1st and 2nd weeks after the start of treatment being due to the more rapid improvement of lesions in group one compared to group 2. There was no significant difference at 4th and 8th weeks, because patients in group 2 got better. However, there was a significant difference again at 12th week because some patients in group 2 got worse (despite taking

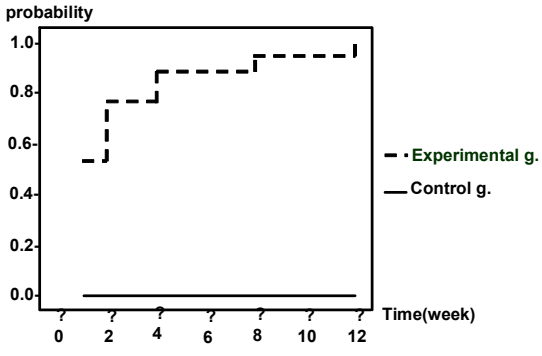

Figure 5. The probability of improvement of disease at different time intervals of drug use in the two study groups

medication). Patients in group one whom used mouthwash had no burning and pain, right from the start of taking the mouthwash. Conrotto (14)concluded that clobetasol was more effective than cyclosporine,and has reported the improvement of burning and pain soon after the therapeutic effect of clobetasol started. Also, Campisi (31) and Moles (32), similar to our study, have reported improvement of pain as soon as the treatment with clobetasol starts.

In this study we observed 95% improvement of mouth lesions in group1 after the 4th week, but Conrotto (14) reported this healing after the 8th week.This could be due to the use of mouthwash in this study instead of ointment which they used. In another study, Conrotto (14) reported complete resolution of lesions, although the keratotic steria was remained But we reported complete resolution without any keratotic steria, which shows that our mouthwash could be more effective in the resolution of lesions, even hyperkeratosis. Gonzales-Moles (32) reported treatment of severe chronic oral erosive lesions with clobetasol propionate in aqueous solution. They showed 90% complete resolution at the 6th week, while we noted this result after the 2nd week in group one. This difference seems to be the result of heterogenity of their samples (in the Moles study only 83% of patients had OLP and 17% had other types of chronic oral erosive lesions). They also used their mouthwash 3 times a day, whilst our patients used the mouthwash 4 times a day.

Carbone (30), Campisi (31), Lozada-Nur (10) and Lo Muzio (19) evaluated the effect of different formulations of clobetasol in comparison to other corticosteroids in the treatment of OLP, and all of them emphasized that clobetasol had better effect, like our results.

One of the important issue in the treatment of OLP is prevention of recurrence of the lesions. So, Gonzales (32) suggested that the use of drugs after complete resolution should be tapered Hence in different studies (10, 17 and 31)which tapered, stable results (did not have any recurrence)were observed. However, Conrotto (14) did not explain this gradual dose reduction, and saw some recurrence. In our study, we used tapering after complete resolution of the lesion, and observed no recurrence.

In Using ketoconazole as an antifungal drug, we did not observe any side effect. However. in a study conducted by Lozada-Nur (10), that did not use any antifungal drug, 12.5% of their patients had pseudomembranus or erythematosis candidiasis.

The mean time of drug use for complete resolution of lesions were 2.65 weeks in group 1 (experimental) and 10.75 weeks in group 2 (control). While, 70% of patients in group 2 did not have complete resolution,even after the 12th week.This kind of evolution has not been reported in any study.

Based on the survival analysis of the disease, the probability of the disease remaining until 12th week was 0% in the experimental group and 100% in the control group. This means that all patients whom used mouthwash, showed complete resolution after the 12th week. We did not find such analysis in thepublished literature.

Conclusion

Based on our results, we suggest that a mouthwash containing clobetasol, ketoconazole and amitryptiline could be significantly more effective than common combination therapies using the dexamethasone tablet, nystatin drop and diphenhydramine syrup in the treatment of OLP. In addition, pain relief and lesion resolution were achived quicker and more recognizable in the mouthwash treated group. Also, mouthwash was significantly more satisfiable and resulted in a reduction in the drug administration period.

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