Lichen planus treatment research study

Aim: Lichen planus is a chronic inflammatory mucocutaneous disease. Its treatment is often symptomatic and includes topical and systemic corticosteroids. Although corticosteroid therapy is usually successful, but because of its side effects, an alternative treatment is favorable. The aim of this study was to compare the efficacy of topical curcumin and triamcinolone on the treatment of oral lichen planus.

Materials & Methods: In this study, 50 patients with the age range of 38 to 73 with oral lichen planus (OLP) were randomly divided into two groups. Each group received 0. 1% triamcinolone or 5% curcumin oral paste 3 times a day for 4 weeks. Measurement of appearance score and severity of pain was done at the baseline and at the end of week 2 and 4 and recorded in the patient’s questionnaires.

Results: In the evaluation of pain reduction in curcumin group, 9 patients (36%) and in triamcinolone group, 8 patients (32%) had complete remission. In the evaluation of appearance score in both groups, one patient (4%) had complete remission. No statistically significant difference was seen between two groups.

Conclusion: Herbal medicines can be a suitable alternative for synthetic drugs, covering their side effects, costs and probable shortages.

Clinical Significance: Application of curcumin because of its desirable anti-inflammatory effects and little side effects is suggested for the treatment of OLP.

Key words: Curcumin, Lichen Planus, Triamcinolone

Aim

Oral lichen planus (OLP) is an immune mediated disease of unknown etiology with the mediacy of T cells (1), in which the symptoms of the patients decrease simultaneously with an increase in (CD4â) counts (2). OLP lesions can be of reticular, papular, plaque-like, bullous, erythematous (atrophic), and ulcerative forms. Ulcerative lesions are the most debilitative forms of OLP (3), which develop painful symptoms and interfere with eating, speaking, swallowing and brushing (4). Corticosteroids are usually successful for controlling the symptoms of the disease (5); but because of frequent side effects of long-term corticosteroid therapy such as: secondary candidiasis , telangectasis, hypothalamic–pituitary–adrenal suppression (6, 7), mucocutaneous atrophy, and increased potential of systemic absorption, it may be better to avoid long-term use of them (8).

Curcuma longa is a perennial plant belonging to Zingiberaceae family (9), which for its anti-inflammatory effects has been used for centuries in Indian traditional medicine (10). Its main ingredients are three curcuminoids including curcumin (the primary ingredient and the one responsible for its yellow color and anti-inflammatory effect), demethoxycurcumin and bisdemethoxycurcumin. Chainani-Wu in a systematic review (11), and others (9, 12-16) confirmed the anti-inflammatory, antioxidant, wound healing, anticarcinogenic effects and safety of curcumin. Clinical studies assessing curcuminoids have evaluated its utilization in inflammatory conditions such as rheumatoid arthritis, postsurgical inflammation, and chronic uveitis.(11)

The curcuminoids, at the same time having anti-inflammatory activity, are safe even in high doses and few side effects were seen (11). Since it seems that oxidative stress may have a role in pathophysiology of OLP (17), and by noting that OLP is a chronic inflammatory disease (18), the herbs which have both anti-inflammatory and antioxidant effect concurrently, may act better in improving the disease process. Antioxidant effect of curcumin against oxidative stress was shown previously (19), Chainani-Wu et al in 2007 and 2011 assessed the efficacy of systemic administration of curcuminoids in treatment of oral lichen planus (10, 20). Efficacious results were obtained in controlling signs and symptoms of oral lichen planus, using high doses of this herb.

Concerning noticeable side effects, reported by patients who consumed corticosteroids (21), chronic nature of OLP, risk of oral candidiasis upon usage of topical corticosteroids, and fewer side effects, safety and anti-inflammatory properties of curcuminoids, we aimed to clinically evaluate the efficacy of curcuminoids in treatment of oral lichen planus, compared with conventional corticosteroid therapy.

Materials and methods:

In this clinical trial 50 patients (36 women and 14 men) participated with age range of 38 to 73 and mean age of 50. 66 years. The patients had clinical signs of OLP (atrophic and ulcerative forms) which was confirmed by clinical and histopathological examination. Patient exclusion criteria included pregnancy and lactation, current use of anticoagulants or antiplatelet agents (curcumin has inhibitory effects on platelet aggregation) (22), existing orthodontic treatment, history of gastric ulcers, duodenal ulcers, gallstones

(curcumin may induce gastric irritation and stimulate gall bladder constrictions) (23), hepatic diseases (curcumin may cause hepatotoxicity in some mammals including mice and rats) (11), any existing malignancy or viral infection in mouth, receiving any topical treatment for OLP in the past 2 weeks or any systemic treatment for OLP in the past 4 weeks, consuming azathioprine, cyclosporine or receiving PUVA, UVA or UVB in the last month, a history of allergy to corticosteroids or curcumin (6).

The crushed roots of *C. longa* L. were purchased from drug store in Rasht city of Iran and identified by a research fellow. The grounded herbal root (1 g) was extracted with 10 ml of 96% ethanol boiling in water bath for 3 min and the least volume of solvent was added to the given aliquot. Each sample was centrifuged at 8000× *g* for 10 min, then the supernatant was filtered with a syringe filter (0. 45 _m). This mixture included Curcumin, demethoxycurcumin and in less amounts, bisdemethoxycurcumin.

Patients were given complete explanations on their disease and also about curcumin and triamcinolone pastes and then were asked to participate in the study by signing an informed consent and this study was registered at IRCT. ir (IRCT2001105012950N2) which is a Primary Registry in the WHO Registry Network set up. Patients were randomly divided into two groups each group including 25 patients.

The sample size of 25 was based on expected and actual enrollment of study subjects over a 2-month time period. Because of feasibility reasons the enrollment was stopped at 25 subjects.

A blocked randomization (block size of 6) was used. The Guilan University of Medical sciences pharmacy packaged the curcuminoids and triamcinolone in similar oral paste and generated the randomization sequence using the random number generator in Microsoft Excel (Microsoft Corp, Seattle, WA). Both participants and investigators were blinded to the treatment assignment.

All the patients were examined and the age, sex, medical history, smoking, form and location of the oral lesions, duration of the disease, and type of treatments the patient had received, severity of pain and appearance score were recorded. Then patients received triamcinolone 0. 1% or curcumin 5% paste for 4 weeks and asked to apply the drug 3 times a day after eating and brushing, and then they were advised to avoid eating for 20 minutes. Measurement of appearance score and severity of pain was done at the baseline and at the end of weeks 2 and 4 and recorded in the patient's questionnaires.

For determining the severity of pain, we used VAS (Visual Analogue Scale) and subjects ranked their severity of pain on a 10-cm horizontal line marked 0 to 10 which 0 indicated no pain and 10 indicated the most severe pain (24). For determining the appearance score, we also used Thongprasom criteria with the below classification:

0: no lesion, normal mucosa

1: mild white striae, no erythematous area

2: white striae with atrophic area less than $1cm^2$

3: white striae with atrophic area more than 1cm²

4: white striae with ulcerative area less than 1cm²

5: white striae with ulcerative area more than 1cm² (25)

In this work complete remission was referred to the case in which signs or symptoms showed 100% reduction, good response was the case that signs or symptoms showed 50% or more reduction and still less than 100% and in poor responders signs or symptoms had less than 50% reduction. If the status of lesions showed no change, the case was considered as no response.

Data were analyzed by SPSS 17 software, using Mann-Whitney; Fisher exact test and Spearman`s correlation analysis. P value < 0. 05 was considered significant.

Results:

Fifty five patients participated in this study. Five patients were missed because of refusing to return for follow up visits. The remaining 50 patients consisted of 36 female and 14 male (female -to-male ratio was 2. 57) with a mean age of 49. 24 years and age range of 38-73 years. The curcumin group consisted of 15 women and 10 men with mean age of 49. 24 years (range 38-73 years), while 21 women and 4 men with mean age of 52. 08 years (range 38-73 years) formed the triamcinolone group. Mean duration of the disease before beginning the study in curcumin group was 23. 96±15. 49 months and in triamcinolone group was 28. 52±15. 72 months. 21 patients had atrophic lesions (42% or 9 patients in curcumin group and 12 patients in

triamcinolone group) and 29 patients had ulcerative lesions (58% or 16 patients in curcumin group and 13 patients in triamcinolone group). All the individuals complained of pain. Mean severity of pain in curcumin group was 5. 84±2. 01 (VAS) and in triamcinolone group was 5. 47 ±3. 12 (VAS) (table 1).

The buccal mucosa was the most common site for OLP followed by the gingiva, tongue, palate, labial mucosa and floor of the mouth (table 2).

Mean VAS score in curcumin group was 5. 84±2. 01 at the baseline which decreased to 3. 08±2. 01 and 2. 64±2. 98 at second and third follow-ups . Mean VAS scores in triamcinolone group was 5. 47±3. 12 at the baseline which declined to 1. 90±1. 58 and 1. 76±1. 78 at second and third visits .

Mean Thongprasom scores in curcumin group was 3. 88±0. 78 at the baseline and decreased to 3. 28±1. 36 and 2. 64±1. 29 at second and third visits. Mean Thongprasom scores in triamcinolone group was 3. 95±1. 07 at the baseline, decreased to 3. 38±1. 07 and 2. 95±0. 97 at second and third visits .

In the evaluation of pain reduction in curcumin group, 9 patients (36%) had complete remission, 4 patients (16%) had good response, 6 patients (24%) had poor response and 6 patients (24) showed no response to the treatment. In triamcinolone group, 8 patients (32%) had complete remission, 8 patients (32%) had good response, 4 patients (16%) had poor response and 5 patients (20) showed no response to the treatment. There is no significant differences between two groups in each of the follow up visits (Mann-Whitney ; P> 0. 05 ; power of analysis = 0. 74). (Table 3).

In the evaluation of appearance score in curcumin group, 1 patient (4%) had complete remission, 6 patients (24%) had good response, 12 patients (48%) had poor response and 6 patients (24) showed no response to the treatment. In triamcinolone group, 1 patient (4%) had complete remission, 2 patients (8%) had good response, 12 patients (48%) had poor response and 10 patients (40) showed no response to the treatment. Two groups had no significant differences (Fisher exact test ; P> 0. 05) (Table 3).

Using Spearman’s correlation analysis, there was no meaningful relation between mean severity of pain and mean appearance score in both groups with age, sex and duration of the disease. (p > 0. 05).

At the end of the study in curcumin group, few patients complained of burning sensation, itching, mild swelling and xerostomia, which was disappeared at the enf of first week of drug consumption. Most of the patients also complained about undesirable yellow color of the drug particularly on the gingiva. In triamcinolone group, only one patient complained about burning sensation in the first week of applying the drug, and one patient complained about mucosal desquamation in the entire duration of treatment.

Discussion

Oral lichen planus, is an chronic autoimmune, mucocutaneous condition, which commonly involves oral mucosa. This lesion can cause oral discomfort and even in some cases, transform into squamous cell carcinoma. Therefore, OLP is considered to be a potentially harmful and malignant disease and attracts many attentions of clinicians.(26)

Most of the previous studies, assessed the effect of corticosteroids (4, 6, 27) and one immunosuppressive drug were compared and in all of them the results in both participating groups were the same and also successful; but since topical use of corticosteroids may lead to oral candidiasis and other side effects and also considering the chronic nature of OLP, it would be better to find an alternative for these types of treatment. Also it has been reported that tacrolimus and pimecrolimus may increase the risk of malignancy in patients using these drugs topically for their cutaneous psoriasis. These medicines should be used in limited situations and their consumption in human is advised to be in minimal doses and limited duration (3, 28-31).

In current study we used curcumin, which its safety, anti-inflammatory and antioxidant effects have been confirmed in many studies (9, 11-16). Clinical efficacy of curcumin is compared with topical corticosteroid, which is the standard treatment for OLP. It was concluded that in addition to effectiveness of curcumin in the treatment of OLP, its effects are similar to topical corticosteroid, and can be an alternative for it.

Chainani-Wu et al. in 2007 (10) used curcumin for the treatment of OLP in placebo controlled study. Curcuminoids were prescribed as tablets, at dose of 2000mg/day for 7 weeks. They concluded that systemic administration of curcumin wasn’t a successful treatment in managing OLP lesions. Systemic administration of curcumin in Chainani-wu’s study is different with topical administration in present study, which increases the topical efficacy of the drug. Chainani-Wu et al. Administered a primary dose of systemic prednisone (60 mg/day for the first 1 week) in both groups that was not done in our

study which could affect the final result. Long periods of observation not only could interfere with patient compliance in less subject retention until the end of study, but also can affect treatment outcomes, as they concluded to design next studies in shorter periods of follow-ups. In the present study, last observation session was at week 4.

Chainani-Wu et al. in 2011.(20) used higher dose of cucrumin in treatmen of OLP. They implemented systemiccurcumin, with a dose of 6000mg/d. This dose is higher than the one in their previous study (2000 mg/d). Interestingly, they found curcumin efficacious in controlling signs and symptoms of oral lichen planus. It was well tolerated by the patients and safety was confirmed at this dose. Observation period was reduced to two weeks, which our study is more harmonious with, compared to 7 weeks of their previous study. Sample size of the present study is similar to this study, as they enrolled 20 patients. Concerning their findings, erythema, mucositis, ulceration of the OLP patients were significantly reduced, after using curcuminoids. The other thing we can add about current study was the little difference between two groups in patients' responses to the reduction of pain and appearance score (There was no statistically significant difference between two groups (P> 0. 05)). The number of patients responding to the reduction of appearance score in curcumin group were more than triamcinolone group (76% in curcumin group versus 60% in triamcinolone group); but the number of patients with reduction in severity of pain in triamcinolone group were more than curcumin group (80% in triamcinolone group versus 76% in curcumin group). This difference may be explained as:

_ Some of the patients complained of burning sensation while applying the curcumin that might affect the pain and burning sensation during the treatment.

_ Half of the patients which didn’t respond to pain reduction by applying the curcumin, had the same problem with triamcinolone paste in their history, this might be due to the topical form of the drugs, because the same patients didn’t have any problem with corticosteroid mouthrinse.

At the end of the study, we asked the patients of curcumin group if they had used corticosteroid in orabase or mouthrinse, to compare the efficacy of them with curcumin. 20 patients (80%) preferred triamcinolone in orabase to curcumin. seven patients (35%) had only problems with undesirable yellowish color of curcumin particularly on gingival or other exposed areas. The other 13 patients (65%) had experienced burning sensation while applying curcumin.

Larger sample size, using the drug in the form of mouthrinse and using the novel curcumin derivatives (curcumin-carboxy derivative, and curcumin protein conjugate) that improve the biological activity of natural curcumin (32), may be used in future studies.

Conclusion:

Corticosteroids as conventional therapy of this chronic disease, may lead to noticeable side effects and develop other conditions like oral candidiasis. Herbal medicines can be a suitable alternative for these synthetic drugs, covering their side effects, costs and probable shortages. Topical curcumin can be suggested for the treatment of OLP. It is recommended that a larger

sample size and using the drug in the form of mouthrinse may be used in future studies.

Clinical Significance: Application of curcumin because of its desirable anti-inflammatory effects and little side effects is suggested for the treatment of