Greater therapeutic efficacy of prednisolone plus medicinal herbs than prednisolone or medicinal herbs alone in patients with oral lichen planus

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Abstract

Background/purpose: Various treatment regimens have been attempted to improve oral lichen planus (OLP) lesions; however, a complete cure has not been found. The most commonly employed and useful agents for treating OLP are topical corticosteroids. The aim of this study was to determine if the use of prednisolone plus traditional medicinal herbs could improve OLP symptoms, reduce recurrent severity, and prolong the time to flare-up, thus providing evidence for future prospective randomized clinical trials.

Materials and methods: A retrospective study of 78 patients with OLP was conducted. The resources of 2 hospital departments (Oral and Maxillofacial Surgery and Chinese Medicine) were combined to treat these patients. Thirty OLP patients (group A) were given a low dose (20 mg/d) of prednisolone plus 3 medicinal herbs (gan-lu-yin, jia-wei-xiao-yao-san, and zhi-bai-di-huang-wan), 26 OLP patients (group B) were administered prednisolone alone, and 22 OLP patients (group C) were administered the medicinal herbs only. Differences among the patient groups were compared after a 4-week treatment course and after follow-up observations which occurred at 6 and 12 months.
Results: The 24 patients (87.7%) in group A experienced no symptom recurrence of OLP within 6 months of follow-up, and neither did 10 patients (38.5%) in group B nor 8 patients (36.4%) in group C. Likewise, 17 patients (56.7%) in group A had no recurrence of OLP at 1 year, and neither did 7 patients (27.8%) in group B nor 6 patients (27.3%) in group C. The average time to flare-up for group A (within 1 year) was 30.9 ± 7.4 weeks, while those for groups B and C were 19.5 ± 5.7 and 20.8 ± 5.0 weeks, respectively. The times to flare-up for groups A versus B and A versus C significantly differed. With the exception of 2 patients with mild oral candidiasis in group A (6.7%), no other obvious side-effects or complaints were reported. The recurrent OLP severity also significantly differed for groups A versus B and A versus C.

Conclusion: Our results suggest that treatment consisting of prednisolone plus traditional medicinal herbs can improve OLP symptoms, relieve pain, reduce recurrent severity, and increase the disease-free period. The benefits of combined therapy for OLP should be investigated by conducting a prospective randomized clinical trial in the future.

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Introduction

Oral lichen planus (OLP) is a T cell-mediated chronic inflammatory disorder affecting the stratified squamous epithelium. The most common type of OLP lesions observed is atrophic-erosive (89.7%). The atrophic and erosive forms can cause symptoms ranging from a burning sensation to severe pain, and can interfere with life. Various treatment regimens were attempted to improve refractory atrophic-erosive OLP lesions, but a complete cure has not been achieved. The most commonly employed and useful agents for treating OLP are corticosteroids, among which prednisolone is widely available. However, one-third of OLP patients treated with topical corticosteroids develops secondary candidiasis which necessitates treatment. The potential toxicity of prednisolone requires that it be used only when necessary, at the lowest dose possible, and for the shortest duration.

Use of alternative medicines or unconventional medicines is on the rise worldwide. Therefore, interest in the use of such alternative medicines for managing symptoms of OLP has also increased. Chinese herbal medicines are generally considered to be capable of greater improvements in immune function with fewer side-effects. In East Asia, especially in China and Taiwan, traditional medicines are often used to treat ulcers and chronic inflammation of the oral mucosa, among which gan-lu-yin, jia-wei-xiao-yao-san, and zhi-bai-di-huang-wan are widely available (Table 1). These 3 commercial herbal formulas have been used by numerous patients for many years with no obvious adverse effects, and have also been used to enhance or modulate cell-mediated and humoral immunities. The use of both traditional and Western medicines may reduce the side-effects of the latter and may intensify the medicinal effects. Several papers compared (1) herbal medicine, (2) steroid, and (3) combined-therapy efficacies for separately treating OLP; however in this study, we compared 3 treatment modalities, and also demonstrated a unique analysis that focused on the severity and duration of OLP recurrence. The aim of this study was to determine if the use of prednisolone plus medicinal herbs could improve OLP symptoms, reduce recurrence severity, and prolong the time to flare-up. Few studies have researched these issues.

Materials and methods

Data collection and definitions

A retrospective study of 78 patients with the atrophic or erosive type of OLP was carried out in the Department of Oral and Maxillofacial Surgery, and Department of Chinese Medicine between 2004 and 2007. All patients had been clinically and pathologically diagnosed with atrophic or...
erosive-type OLP, and all patients had symptoms such as roughness, a burning sensation, and pain. In order to ensure a proper diagnosis and prevent inter- and intra-observer differences, we developed a proposal for the clinical-pathological diagnostic criteria for OLP. A set of clinical and histopathologic diagnostic criteria, with both inter- and intra-observer agreement, was validated for this study. If patients were only clinically diagnosed with OLP, but it was not proven pathologically, then they were not included in the study. Patients were fully instructed about the treatment procedures, care, follow-up examinations, and alternative treatment options. Each patient signed a consent form according to the Declaration of Helsinki. With respect to each examination, any adverse effect or discomfort related to the therapy was documented. In these 78 patients, 30 patients (group A, 10 males and 20 females) were treated with 20 mg prednisolone/day (5 mg q.i.d.) plus herbal medicine (4 g gan-lu-yin q.i.d., 4 g zhi-bai-di-huang-wan q.i.d., and 4 g jia-wei-xiao-yao-san q.i.d.; the powder was dissolved in water and administered orally) for 4 weeks. Twenty-six patients (group B, 8 males and 18 females) were treated with the same regimen for 4 weeks without the medicinal herbs. These patients did not simultaneously accept herbal medicinal treatment because of individual factors such as time, economic factors, or a rejection of the taste of the herbal medicine. Twenty-two patients (group C, 6 males and 16 females) were treated with medicinal herbs only. These patients were accustomed to traditional medicine for treating oral ulcers, or had doubts about the side-effects of Western medicine, and were therefore only willing to accept the traditional medicinal treatment.

**Outcome measures**

The gender, age, medical history, symptoms, type, severity, sites of the lesions, and disease duration were recorded. A symptomatology score of pain was obtained using a visual analogue scale (VAS: 0–10). OLP lesions were scored according to the criterion scale described and modified by Thongprasom et al.14:

- Score 5: white striae with an erosive area of >1 cm²;
- Score 4: white striae with an erosive area of <1 cm²;
- Score 3: white striae with an erythematous area of >1 cm²;
- Score 2: white striae with an erythematous area of <1 cm²;
- Score 1: mild white striae only; and
- Score 0: no lesions, normal mucosa.

If the OLP lesions occurred on multiple sites of the oral mucosa, the most highly affected area was recorded. After treatment, patients were examined at weeks 2, 4, 6, and 8, and then every month for 12 months. At each visit, the pain score and disease score were recorded. Complete resolution of clinical signs was defined as the disappearance of all atrophic/erosive lesions and the total lack of white striae (OLP score 0). If a patient suffered from multiple lesions in the mouth, all lesions had to have been completely healed. Complete resolution of all symptoms was defined as a normal mucosa and the absence of any discomfort, corresponding to a VAS score of 0. For monitoring any adverse effects of prednisolone and in order to allow professional decisions as to the patients’ cortisol level control or management, we usually consulted and followed instructions given by the patient’s medical physician. Blood cortisol levels of patients were monitored prior to medical treatment and then during each visit. A morning visit was required by each patient, and patients were requested to check the cortisol level (08:00) prior to the consultation. In case the patient’s cortisol level exceeded the normal range (6–23 μg/dL) during treatment, the treatment was stopped, and the physician was consulted. If the patient was unavailable to cooperate, it was still important for the physician to closely monitor, based on the clinical signs and symptoms, any adverse reactions of prednisolone, such as edema, hypertension, suppression of the hypothalamic-pituitary-adrenal axis, Cushing syndrome, etc.

**Statistical analyses**

Analysis of variance (ANOVA) and Scheffe’s multiple comparisons were used to determine whether there was a significant difference in the age and recurrence time of OLP among the groups. The Wilcoxon signed-rank test was used to determine whether there was a significant difference in indices and pain scores before and after therapy in the 3 groups. The Kruskal–Wallis H test and Mann–Whitney U-test were used to analyze if there were significant differences in the recurrence severity among the groups.

**Results**

At the baseline, differences in the age and OLP index among the 3 groups of patients were statistically insignificant (Tables 2–4). Therefore, we were able to conduct further comparisons and analyses among the 3 groups after treatment. Significant differences in the before and after therapy OLP indices, and the before and after pain scores of the 3 groups were found, as assessed by the Wilcoxon signed-rank test (P < 0.001) (Table 5). The nonparametric Kruskal–Wallis test and Mann–Whitney U-test, which were used to analyze the OLP index when recurrent in groups A versus B and A versus C, significantly differed (P = 0.000, 0.003) (Table 4). The 24 patients (87.7%) in group A experienced no symptom recurrence of OLP within 6 months of follow-up, and neither did 10 patients (38.5%) in group B nor 8 patients (36.4%) in group C. Likewise, 17 patients (56.7%) in group A had no recurrence of OLP within 1 year, and neither did 7 patients (27.8%) in group B nor 6 patients (27.3%) in group C. The average time to flare-up in group A (within 1 year) was 30.90 ± 7.4 weeks, while that for group B was 19.5 ± 5.7 weeks and 20.8 ± 5.0 weeks for group C. Times to flare-ups for groups A versus B and A versus C significantly differed (ANOVA and Scheffe’s post-hoc test, P = 0.000) (Table 3). Plasma cortisol levels and systemic conditions were monitored in patients using prednisolone. None of the patients exhibited abnormal cortisol levels or any systemic side-effects. With the exception of 2 patients with mild oral candidiasis in each group (6.7% of group A and 7.7% of group B), no other obvious side-effects or complaints were reported. Patients with oral candidiasis were also given antifungal therapy.
A large body of evidence supports a role for immune dysregulation in the pathogenesis of OLP, specifically involving the cellular arm of the T cell-mediated immune system. In this research, we used 3 kinds of traditional medicine, gan-lu-yin, zhi-bai-di-huang-wan, and jia-wei-xiao-yao-san, which are often administered together to treat chronic mucositis and oral ulcers in Taiwan, and are generally considered to improve immunity and reduce the inflammatory response. Gan-lu-yin can enhance hypoxic tolerance and sedation, produce antibacterial effects, increase the duration of antibodies in vivo, and prevent inflammation. The actions of this formula are to expel heat, remove dampness, resolve inflammation, and clean the blood. Recent studies showed that gan-lu-yin can relieve certain side-effects of radiation therapy in the treatment of nasopharyngeal cancer including soreness of the larynx, weight loss, and decreased secretion of saliva. It is particularly effective in reducing damage to oral membranes. In addition, it is also beneficial in improving physiological and psychological health such as stabilizing the mood and alleviating anxiety, improving the oral intake of solid food, reducing dryness of the mouth, and relieving dyspnea. Studies investigated several constituent herbs of gan-lu-yin, such as Radix et Rhizoma Rehmanniae Preparata, Fructus Citri immaturus, Radix Glycyrrhizae Preparata, Herba Artemisiae Scopariae, Folium Eriobotryae, Radix Scutellariae, and Radix et Rhizoma Rehmanniae, and found that they are involved in anti-inflammation, anti-histamine release, decreased expression of cyclooxygenase (COX)-2, and immunomodulation.

Zhi-bai-di-huang-wan is a kind of di-huang-wan. This remedy has been used for centuries in China and was approved by the Department of Health in Taiwan. Zhi-bai-di-huang-wan has an antipyretic effect, and increases stamina. Most of the herbs in zhi-bai-di-huang-wan, such as Radix et Rhizoma Rehmanniae Preparata, Corni Fructus, Poria, Dioscorea Opposita, Cortex Moutan, and Cortex Phellodendri, are described as being anti-inflammatory and an immunosuppressant against cellular immune responses, and able to modulate cytokine expressions. The data also suggest that zhi-bai-di-huang-wan functions directly on cytokine gene expressions of activated peripheral blood mononuclear cells. Jia-wei-xiao-yao-san can enhance the anti-inflammatory effect of blood platelet inflammatory mediators such as 5-HT and others.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Statistical descriptions of age, oral lichen planus (OLP) index, pain score, and differences in the recurrent index and recurrence time of the prednisolone group, herbal medicine group, and prednisolone plus herbal medicine group.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>Prednisolone</td>
</tr>
<tr>
<td></td>
<td>Herbal medicine</td>
</tr>
<tr>
<td></td>
<td>Prednisolone plus herbal medicine</td>
</tr>
<tr>
<td>n</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>26 54.1 (10.80)</td>
</tr>
<tr>
<td>Recurrence time (wk)</td>
<td>19 19.5 (5.67)</td>
</tr>
<tr>
<td>OLP index before therapy</td>
<td>26 4</td>
</tr>
<tr>
<td>OLP index after 4 wk of therapy</td>
<td>26 1</td>
</tr>
<tr>
<td>Recurrence OLP index</td>
<td>19 3</td>
</tr>
<tr>
<td>Difference in the index of recurrent OLP</td>
<td>19 -1</td>
</tr>
<tr>
<td>Pain score before therapy</td>
<td>26 7.25</td>
</tr>
<tr>
<td>Pain score after 4 wk of therapy</td>
<td>26 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>ANOVA of age and recurrence time among the prednisolone plus herbal medicine group (group A), prednisolone group (group B), and herbal medicine group (group C). According to the test results, the patients’ ages across groups did not differ. However, the recurrence time of the 3 groups significantly differed. Therefore, Scheffe’s post-hoc test was used to determine which particular group means differed. The resulting multiple-comparison output is displayed in the last column. It was found that the recurrence time of patients with combined therapy was significantly longer than those of patients in the other 2 groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Group</td>
</tr>
<tr>
<td>Age</td>
<td>Combined (group A)</td>
</tr>
<tr>
<td></td>
<td>Prednisolone (group B)</td>
</tr>
<tr>
<td></td>
<td>Herbal medicine (group C)</td>
</tr>
<tr>
<td>Recurrence time</td>
<td>Combined (group A)</td>
</tr>
<tr>
<td></td>
<td>Prednisolone (group B)</td>
</tr>
<tr>
<td></td>
<td>Herbal medicine (group C)</td>
</tr>
</tbody>
</table>

***Differences were significant at the P < 0.01 level of significance.
also strengthens the suppressive effect against microorganisms.\textsuperscript{34} It is an effective herbal medicinal prescription used to treat functional dyspepsia associated with the syndrome of liver stagnation, spleen deficiency, and symptoms of a poor appetite, dry mouth, and bitter taste in the mouth. It can also improve gastrointestinal movement and has an antidepressant-like effect.\textsuperscript{34–36} Significant treatment utility of inflammatory pain, anti-histamine release, regulation of immune complexes, antimicrobial effects, and immunomodulatory activities of several constituent herbs of jia-wei-xiao-yao-san were found, including Radix Angelicae sinensis, Rhizoma Atractylodis macrocephalae, Adix Paeoniae alba, Radix Blupleuri, Poria, Radix Glycyrrhizae preparata, and Cortex Moutan.\textsuperscript{37–40}

Various treatment regimens such as the administration of a systemic or topical corticosteroid, cyclosporin, retinoid, and/or tacrolimus were attempted to improve refractory OLP lesions. None of the above agents used for OLP resulted in long-term remission, and when they are withdrawn, the disease usually recurs. As no therapy is curative, the goal for symptomatic patients is to palliate symptoms. The abovementioned treatments are non-specific and directed at eliminating inflammation. They are therefore only partially successful, and their effects are temporary. Moreover, there are few data on long-term therapeutic outcomes for OLP patients.\textsuperscript{41} Therefore, there is no definitive treatment that results in long-term remission.\textsuperscript{4} Levamisole was found to have a therapeutic effect on OLP in recent years. It was originally developed as an antihelminthic drug, but it has attracted interest as an effective agent with immunomodulating properties that influence a host's cell-mediated immune mechanisms.\textsuperscript{42} Levamisole was found to restore the normal phagocytic activity of macrophages and neutrophils, to immunomodulate or immunopotentiate T cell-mediated immunity, and to potentiate the activity of human interferon and interleukin (IL)-2.\textsuperscript{43–45} However, some side-effects such as flu-like symptoms, granulocytopenia, and skin rashes may occur in some patients taking levamisole.\textsuperscript{42,43}

Prednisolone is a well-known, anti-inflammatory and immunosuppressive drug that acts on lymphocytes, and interferes with the inflammatory response. However, the toxicity of prednisolone requires that it be used only when necessary, at the lowest dose possible, and for the shortest duration of time.\textsuperscript{12} Carbone et al.\textsuperscript{7} prescribed a high dose (50 mg/d) of prednisolone for patients with OLP. They affirmed that after 6 months of prednisolone therapy, 68.2% of patients had experienced complete remission, and 22.7% showed partial remission. They also found that in 50% of patients, results were not maintained after an average period of 8.9 months. However, 32% of those patients experienced adverse effects from therapy. Lozada and Miranda administered quite a high dose of prednisolone (up to 80 mg/d), and side-effects occurred in up to 61% of cases.\textsuperscript{4} Thongprasom et al. reported that patients given 2 years of treatment for OLP resulted in complete remission rates of 77.3%, 21.4%, and 17.0% among patients respectively administered with fluocinolone acetonide in orabase (FAO), fluocinolone acetonide in solution (FAS), and FAS/FAO.\textsuperscript{46} The percentages of OLP patients with oral

### Table 4
Comparison analysis of the oral lichen planus (OLP) index before and after 4 weeks of therapy, recurrent OLP index, and differences in the recurrence index of the prednisolone plus herbal medicine group (group A), prednisolone group (group B), and herbal medicine group (group C). The nonparametric Kruskal–Wallis test was applied to test for differences across groups A, B, and C. From the statistical results, we found only the variable of the index of recurrent OLP significantly differed across the 3 groups. In order to determine which 2 groups differed, we further used the Mann–Whitney U-test to make pair-wise comparisons. According to the results, compared to the other 2 groups, group A had the smallest difference in the index of recurrent OLP among the 3 groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Kruskal–Wallis test Chi-squared\textsuperscript{a}</th>
<th>P value</th>
<th>Multiple comparison (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLP index before therapy</td>
<td>0.843</td>
<td>0.656</td>
<td></td>
</tr>
<tr>
<td>OLP index after 4 wk of therapy</td>
<td>2.913</td>
<td>0.233</td>
<td></td>
</tr>
<tr>
<td>Recurrence OLP index</td>
<td>5.645</td>
<td>0.059</td>
<td></td>
</tr>
<tr>
<td>Difference in the index of recurrent OLP</td>
<td>16.195\textsuperscript{***}</td>
<td>0.000</td>
<td>A &lt; B (0.000)\textsuperscript{b****}</td>
</tr>
</tbody>
</table>

\textsuperscript{***} Differnces were significant at the P < 0.01 level of significance.
\textsuperscript{a} Three groups’ comparison was performed by the Kruskal–Wallis test.
\textsuperscript{b} Multiple comparisons were performed by the pair-wise Mann–Whitney U-test.

### Table 5
Statistical analysis of the oral lichen planus (OLP) indices before and after therapy, and pain scores before and after therapy of the prednisolone group, herbal medicine group, and prednisolone plus herbal medicine group.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>OLP index after 4 wk of therapy</th>
<th>P value</th>
<th>Pain score before therapy</th>
<th>Pain score after 4 wk of therapy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>26</td>
<td>4.5</td>
<td>&lt;0.001</td>
<td>7.25</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Herbal medicine</td>
<td>22</td>
<td>4</td>
<td>&lt;0.001</td>
<td>7.5</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prednisolone plus herbal medicine</td>
<td>30</td>
<td>4.5</td>
<td>&lt;0.001</td>
<td>7.25</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Wilcoxon signed-rank test.
candidiasis in the 3 groups after treatment were 38.3%, 14.3%, and 13.6%, respectively. Clobetasol propionate appears to be another effective topical steroid in an adhesive base. Carbome et al. also found that after 6 months of topically administered clobetasol therapy, 69.6% of patients had experienced complete remission of symptoms, and 54.5% of lesions were recurrent after an average period of 7 months. Compared to the aforementioned therapeutic studies of steroids, the complete OLP remission rates for patients who received prednisolone plus traditional medicinal herbs were 88.9% within 6 months and 55.6% within 1 year. With the exception of 2 patients (representing 6.7% of study group A) who experienced slight candidiasis infections, the [side-effect?] occurrence rate of the combined medicinal therapy was lower than that of patients who took other types of steroids. We demonstrate that this corticosteroid-sparing, combination drug approach for OLP patients seems to produce clinical control with a lessening of the side-effects of oral candidiasis related to long-term and high-dose administration of prednisolone. Sun et al. also indicated that combination therapy for OLP with prednisolone plus medicinal herbs was superior to single therapy (prednisolone). Compared to non-steroid medicines such as cyclosporin, retinoid, and tacrolimus, treatment with prednisolone plus medicinal herbs has the potential to improve OLP symptoms, prolong the time to flare-ups, and have fewer side-effects of oral candidiasis. Furthermore, the cost of daily administration of the 3 kinds of traditional herbs is about US$2 per day; it is more cost-effective than systemic therapy. However, the exact efficacy and clinical roles of prednisolone plus herbal medicines were not convincingly demonstrated in this study because of the lack of a blinded approach and some statistical concerns, and only the possibility of its efficacy was examined. Therefore, a double-blinded trial with greater patient numbers and a placebo control to evaluate the efficacy of combined medical therapy needs to be done in a further study. This study lacks the associating immunological markers (such as IL-6, IL-8, or squamous cell carcinoma-associated antigen) for evaluating the therapeutic effects. This is also an area that requires further study.

Conclusions

Treatment of OLP with prednisolone plus traditional medicinal herbs can improve symptoms, relieve pain, reduce recurrent severity, and prolong the disease-free period, is more cost-effective, and has fewer side-effects of oral candidiasis than treatment with other medications. The benefit of combined therapy for OLP should be investigated by conducting a prospective randomized clinical trial in the future.

References


