Clinical Observation on the Treatment of Oral Lichen Planus with Total Glucosides of Paeony Capsule Combined with Corticosteroids

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Abstract

Introduction: Oral lichen planus (OLP) is a relatively common, chronic immune-mediated disease.

The main treatment for OLP has been the administration of topical or systemic corticosteroids, but side effects have limited their use. We aimed to assess the effect and adverse reaction of total glucosides of paeony capsule (TGPC) in combination with corticosteroids for the treatment of OLP.

Methods: Eighty one patients with a confirmed clinical and histopathologic diagnosis of OLP (44 reticular OLP [ROLP] patients, 37 erythematous/erosive OLP [EOLP] patients) were enrolled. Patients were treated with topical or systemic corticosteroids, with or without 1200 mg TGPC in the ROLP and EOLP groups, respectively. Patients were followed for 6 months. The pain and severity of the lesions were recorded at the initial visit and monthly thereafter during the follow-up period.

Results: Seventy three of 81 patients completed the scheduled treatment period. In the ROLP patient group, combined treatment significantly reduced the visual analogue scale (VAS) at months 3, 5, and 6. The clinical signs (CS) of ROLP patients worsened during the follow-up period in control group. However, CS in the combined treatment group remained largely unchanged at months 4–6. In the EOLP patient group, the VAS decreased almost equally in patients with and without combined treatment at months 1–2, but continued to significantly decrease in the combined treatment group in months 4–6. The CS of the combined treatment group decreased gradually over time in the study period, with significantly lower scores in the treatment versus control group (which decreased slightly in the first three months, then remained almost unchanged during the following

visits). The effective rates of combined treatment were statistically higher versus control groups both in ROLP and EOLP patients.

Conclusions: TGPC is a safe and effective drug for OLP with rare side effects. Combined treatment of TGPC with corticosteroids shows a definite therapeutic effect. More than four months of medical treatment of TGPC is recommended to achieve the full effect.

Keywords: oral lichen planus, total glucosides of paeony capsule, corticosteroids, combined therapy, clinical observation.

Introduction

Oral lichen planus (OLP) is considered to be a chronic immune-mediated oral mucosal disease that affects 0.3%–2.3% of the general adult population [1, 2]. It occurs more frequently among women after the fourth decade of life, and may present in two main types: reticular and erythematous/erosive ones [3]. Symptoms can range from none to extremely painful lesions ones that may significantly affect quality of life; and there is a premalignant potential for OLP [4, 5]. Although there is no established cure for OLP, topical or systemic corticosteroids is currently the most effective approach to improve the appearance of the lesions and reduce pain [6-8]. However, some patients are refractory to this treatment, and side effects and rebound of symptoms after stopping medication have limited the use of corticosteroids [1]. Therefore, an effective and less morbid treatment is needed.

Total glucosides of paeony (TGP) are powdered substances extracted from the roots of

Paeonialactiflora pall, a traditional Chinese herbal medication [9]. TGP contains paeoniflorin, hydroxy-paeoniflorin, paeonin, albiflorin, and benzoypaeoniflorin; its main effective component is paeoniflorin, which is present in over 90% of all substances [10]. TGP has been reported to have anti-inflammatory, immunoregulatory, anti-oxidative, and hepatoprotective activities, and is effective for treating rheumatoid arthritis, Sjogren's syndrome, chronic urticarial, and SLE [11-15]. However, the investigation of TGP in the treatment of OLP is rare. We aimed to evaluate the effectiveness and safety of combined administration of total glucosides of paeony capsule (TGPC) with corticosteroids in the treatment of OLP.

Methods

Participants

This prospective, randomized controlled clinical trial was performed in the Department of Oral Mucosal Diseases, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine between April 2014 and May 2015. Eighty-one patients with OLP were enrolled, including 44 reticular OLP patients (ROLP) and 37 erythematous/erosive OLP patients (EOLP). The diagnosis in all patients was clinically and histopathologically confirmed.

Inclusion criteria were as follows: biopsy-confirmed OLP in combination with a compatible clinical appearance. Patients over 18 years of age who did not undergo treatment with immunomodulatory agents in the previous 3 months, and without heart, brain, liver, and renal disease were eligible for enrollment. Patients were excluded if they had cancer, diabetes mellitus, or other systemic diseases, or if they were pregnant or lactating.

The 81 patients were randomly divided into intervention or control groups based on a random numbering table (ROLP: groups A, B; EOLP: groups C, D). This study was approved by the Institutional Review Boards at the Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. Written informed consent was obtained from each patient prior to study enrollment.

Treatment

ROLP patients (groups A, B) were treated with compound powder of adrenocorticoids (dexamethasone acetate 0.1%, made by Shanghai Ninth People Hospital, China) twice daily until symptom resolution. Group B patients also received TGPC (Ningbo Lihua Pharmaceutical Co. Ltd., China, batch number 071007, 200 mg capsules, 400 mg thrice daily), which contained no less than 104 mg of total glucosides of paeony. Erythematous/erosive OLP patients received oral prednisolone (Xinhua Pharmaceutical Co. Ltd., Shandong, China, 15 mg daily for two weeks/month). If the erosive lesions healed, the dose was tapered to 10 mg in the following month, and 5 mg in the subsequent month until discontinuation in the third month. Group D patients received TGPC in addition to prednisolone.

All patients rinsed their mouth with 1% sodium bicarbonate (10 ml for 5 minutes, thrice daily) prophylactically for oral candidiasis [16]. Patients were followed up monthly for 6 months. Seventy-three of 81 patients completed the treatment and follow-up period.

Clinical assessment

Clinical assessment was performed by a single experienced investigator who was blinded to group allocation. All patients were evaluated at baseline (Day 0: D0), once a month during treatment (Month

1-6: M1-6). Evaluations involved the recording of gender, age, duration of the illness (initial visit), symptoms, symptom scores, and clinical signs (CS). The symptom scores were measured using a visual analogue scale (VAS)(0 = no pain, 10 = unbearable pain). The size of all oral lesions was recorded with a periodontal probe, including the mucosa of the cheek, tongue, gingiva, and palate at each visit. CS were scored as 0 = no lesions, 1 = mild white striae only, 2 = white striae with atrophic area $\leq 1 \text{ cm}^2$; 3 = white striae with atrophic area $> 1 \text{ cm}^2$, 4 = white striae with erosive area $\leq 1 \text{ cm}^2$, 5 = white striae with erosive area $> 1 \text{ cm}^2$.

Complete improvement was defined as a total absence of signs and symptoms of the lesions (For ROLP, VAS=0, CS=0/1; for EOLP, VAS=0/1, CS=0/1). Marked improvement was defined as a reduction of the lesions or relief of symptoms. Aggravation was defined as an increase of the lesions or deterioration of symptoms. Refractory was defined as no change of signs and symptoms. The effective rate (%) was defined as (cases of complete improvement + cases of markedly improved) / total cases observed $\times 100\%$.

Laboratory tests, including hepatic and renal function, fasting plasma glucose, and routine blood examination were performed at baseline and at the first, fourth, and final visit. Side effects and compliance were observed simultaneously during the therapeutic session.

Statistical analysis

Data are expressed as means $\pm$ standard error of mean (SEM). Statistical significance was analyzed using the Student's *t*-test, chi-squared test, and two-way ANOVA test. All statistical analyses were performed using Graph Prism 6 (GraphPad Software, CA, USA). A p-value of less than 0.05 was considered statistically significant.

Results

Three patients dropped out of the trial due to intolerable diarrhea (two from group B, one from group D), and five patients were absconded (two from group A, three from group C). This study was finally completed in 73 patients. Table 1 summarizes the baseline comparison of patients. There were no significant differences between ROLP and EOLP groups with regards to gender, age, duration of illness, and VAS.

Comparison of Symptom Scores

All patients included in this study had baseline symptoms. There was no significant difference in VAS between groups in ROLP/EOLP patients prior to treatment. Mean VAS significantly decreased at every follow-up visit in all four groups. The VAS of group B ROLP patients dropped more rapidly than in group A, with obviously lower scores at every visit, and statistically significant scores at months 3, 5, and 6 (Figure 1a). The VAS of group C EOLP patients decreased almost equally as group D in the beginning two months, but it turned to a fluctuating trend in the following treatment phase. However, the VAS of group D kept decreasing during the follow-up. Differences between these two groups were statistically significant at months 4–6 (Figure 1b).

Comparison of Clinical Scores

At baseline, group A and group B ROLP patients exhibited similar mean CS, similar to the two groups of EOLP patients. Some patients' CS increased in both groups during the first four visits (Table

3). However, the CS of group B patients remained largely unchanged during months 4–6, with some group A patients showing worsening CS. The chi-squared test showed statistically significant differences between groups at the 4 and 6 month visits ($p < 0.05$; Table 3).

The CS of group C EOLP patients decreased slightly in the first three months, but remained almost unchanged at subsequent visits. However, the CS of group D patients decreased gradually over time in the study period, with significantly lower scores compared with group C at months 5 and 6 ($p < 0.01$; Figure 2).

Comparison of Clinical Effectiveness

The effective rates were calculated at different follow-up periods. For ROLP patients, the effective rate of group B were significantly higher than that of group A at months 1, 3, and 6 (50% vs. 23.5%, 90.9% vs. 64.7%, and 100% vs. 64.7%, respectively). The former was significantly better than the latter (two-way ANOVA; Figure 3a). Similarly, for group D EOLP patients, the effective rates were significantly higher than in group C at months 1, 3, and 6 (82.4% vs. 64.7%, 88.2% vs. 64.7%, and 100% vs. 88.2%, respectively; Figure 3b).

Discussion

Although the etiology of OLP remains unclear, there is evidence that it is an immune-mediated disease. Pathologically, it is characterized by liquefaction degeneration of the basal layer, overlying keratinization, and a dense infiltration of T-lymphocytes in the subepithelial region [17]. Currently, there is no specific treatment for oral lichen planus other than symptomatic [18]. Among the

therapeutic options available for OLP, corticosteroids are the most widely used due to their rapid effect in controlling symptoms [19]. However, these treatments are limited, due to their significant side effects following long-term or short course glucocorticoid use; symptoms may quickly reproduce after drug withdrawal [20, 21]. It is important to find safe and effective immunoregulating medications for OLP, either as the sole treatment or in conjunction with corticosteroids.

Recently, studies on administering natural or herbal origin medications to treat OLP, such as cedar honey, anthocyanins, and quercetin, have emerged [20, 22, 23]. Total glucosides of paeony, a new type of immunoregulator, has been widely used in the clinical setting to treat immune-related disease, and has demonstrated biological safety after long-term use without serious side effects [11-15]. A recent study showed that TGP has anti-inflammatory, and immunoregulatory actions, especially with regards to Th cell function [14, 24, 25]. Xie et al. suggested that the proportion of peripheral Th1 and Th17 cells was significantly increased in patients with OLP, especially in atrophic-erosive OLP; and serum IL-17 levels in OLP patients were significantly higher than that of controls [26]. Piccinni et al. found that Th17, Th0, and Th2 cells may have a role in the pathogenesis of oral lichen planus [27]. It has been demonstrated that TGP can inhibit maturation and activation of dendritic cells (DC), leading to impaired Th1 and Th17 differentiation, which are now believed to play crucial roles in the pathogenesis of OLP [28]. DC maturation and function might be inhibited by TGP through selective blockade of TLR4/5 activation [29]. The study of Zhao et al. suggested that TGP could induce regulatory CD4(+)CD25(+) T cell differentiation by increasing Foxp3 demethylation in lupus CD4(+) T cells [15]. Considering the unique immunoregulating mechanisms of TGP, which mainly regulate earlier responses of pathologic process, TGP was used to treat patients with different immune-related diseases.

We aimed to evaluate the efficiency and safety of TGPC combined with corticosteroids in the treatment of OLP.

In the present study, the VAS and CS of ROLP patients were both lower than those of EOLP patients, perhaps due to the lower disease activity of ROLP. We found that the effectiveness of combined therapy (TGPC + topical corticosteroids) was higher in relieving VAS compared with topical corticosteroids alone at every visit, and significantly higher at months 3, 5, and 6 (Figure 1a). The CS of some patients in both groups was aggravated during the follow-up period. However, the CS of group B patients remained low at the last two visits, with 3 and 4 patients in group A, respectively, showing more serious CS (Table 3). The effective rates of group B were all significantly higher than group A at months 1, 3, and 6 (Figure 3a). These data indicate that the effectiveness of combined therapy for ROLP was better than that of topical corticosteroids alone, and that this advantage was more apparent in easing the pain of ROLP patients. Although TGPC did not completely resolve the disease, it could improve VAS in ROLP patients, and prevent aggravation of CS. In ROLP patients, lesion sizes remained small and stable; the effectiveness of combined therapy in reducing the lesions was not as obvious as in pain relief.

For EOLP patients with higher VAS and CS, the advantage of combined TGPC and corticosteroid treatment was more obvious. We found that TGPC not only eased symptoms, but also reduced EOLP lesions when used in combination with systemic corticosteroids. Systemic glucocorticoids alone slightly decreased the VAS of EOLP patients in the first three months, almost equal to that of combined treatment; however, it did not work in subsequent visits. The VAS of group C patients even increased during the last three visits. However, combined treatment with TGPC gradually decreased the VAS during the follow-up period, leading to a significantly lower VAS in group D patients during months

4–6 (Figure 1b). Similarly, combined treatment showed higher efficiency in controlling CS (Figure 2).

In 10 group D patients (58.8%), symptomatic erosive lesions converted into reticular lesions with barely any symptoms (VAS=0/1; CS=0/1) at the end of the 6-month follow-up period, whereas only one patient in group C (5.9%) was completely healed. At the 1, 3, and 6 month visits, group D patients showed higher effective rates than group C (Figure 3b).

We also found that corticosteroid administration can improve clinical signs and symptoms in OLP patients, though less efficient in comparison to combination therapy with TGPC, and more common rebound symptoms following drug withdrawal. These findings were consistent with previous studies, which reported CS improvement with corticosteroids ranging from 56% to 100% [30-32]. However, combined treatment is more reliable to maintain a curative effect. The advantage of combined treatment can be seen after a long period of administration, perhaps because TGPC addresses the OLP condition itself by regulating immune function, which is a lengthy process [14, 25]. In combined therapeutic strategy, corticosteroids can reduce symptoms quickly in the early stages of treatment; the combined therapy of TGPC with corticosteroids can prevent relapse, improve and consolidate the therapeutic effect.

However, it cannot be ignored that poor compliance may be caused due to relatively long-term treatment and thrice administration a day. Relatively, administration of steroids is a more simple (daily for two weeks/month) and inexpensive therapy. Regular follow ups can help enhance the medication compliance for the patients.

In the present study, TGPC was well tolerated without liver, kidney, or neurogenic toxicities. Three patients (3.7%) dropped out due to intolerable diarrhea; one of the most frequent adverse events of TGP [24, 33, 34]. Therefore, we confirmed that TGPC, when used in combination with corticosteroids in the

treatment of OLP patients, improves the illness, consolidates clinical therapeutic efficacy, and reduces symptom rebound.

Conclusion

In summary, the effectiveness of TGPC in the treatment of OLP is indisputable, although a lengthy period of administration is required. According to our study, more than four months of medication administration is recommended. To the best of our knowledge, this is the first report demonstrating TGPC to be a safe and effective drug for OLP.

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Figure legends

Figure 1. Mean visual analogue scale (VAS) (standard error of mean) during experimental period. (a) Both groups demonstrated significant improvements in ROLP patients, and the VAS of group B dropped more rapidly than that of group A at M3, M5, and M6 visits. (b) The VAS reduced almost equally in the two groups in the first two months but the VAS of group D continued to decrease, leading to lower CS at the M4-M6 visits. * $p < 0.05$, ** $p < 0.01$.

Figure 2. Mean clinical score (CS) (standard error of mean) during experimental period. The CS of group D decreased gradually over time in the study period, showing significantly lower scores at the M4-M6 visits in comparison to group C, which decreased slightly in the first three months, but remained unchanged during the following visits. ** $p < 0.01$, *** $p < 0.001$.

Figure 3. Comparison of Clinical Effectiveness. (a) For ROLP patients, the effective rates of group B were significantly higher at the M1, M3, and M6 visits (50% vs. 23.5%, 90.9% vs. 64.7%, and 100% vs. 64.7%, respectively; ** $p < 0.01$). (b) For EOLP patients, group D showed obviously higher effective rates than group C at M1, M3, and M6 (82.4% vs. 64.7%, 88.2% vs. 64.7%, and 100% vs. 88.2%, respectively; ** $p < 0.01$). Differences were analyzed by a two-way ANOVA test.

Table 1. General characteristics of the sample at baseline.

Baseline characteristic	ROLP (n=39)		p-value	EOLP (n=34)		p-value
	A	B		C	D	
Case	17	22		17	17	
Gender, n (%)						
Male	8 (47.1%)	8 (36.3%)	NS	8 (47.1%)	7 (41.2%)	NS
Female	9 (52.9%)	14 (63.6%)	NS	9 (52.9%)	10 (58.8%)	NS
Age, year, Mean $\pm$ SD	41.06($\pm$ 3.40)	42.05($\pm$ 2.27)	NS	46.31 ($\pm$ 3.47)	49.65 ($\pm$ 2.60)	NS
Duration, months, Mean $\pm$ SD	6.59 ($\pm$ 3.77)	5.81($\pm$ 0.51)	NS	5.94 ($\pm$ 2.17)	7.41 ($\pm$ 2.18)	NS
VAS, Mean $\pm$ SD	2.35 ($\pm$ 0.27)	2.52($\pm$ 0.32)	NS	4.18($\pm$ 0.31)	4.18($\pm$ 0.32)	NS
Sites of involvement						
Buccal mucosa	16 (94.1%)	21 (95.5%)		17 (100%)	17 (100%)	
Tongue	5 (29.4%)	4 (18.2%)		3 (17.6%)	5 (29.4%)	
Lips	1 (5.9%)	0		0	3 (17.6%)	
Gingiva	0	0		1 (5.9%)	1 (5.9%)	

*Significant difference between two groups; Numbers at the table represent the number of patients.

Table 2. Comparison of therapeutic effectiveness.

Group	Case	Treatment duration	Total therapeutic effectiveness (%)				Total effective rate (%)
			Complete improvement	Marked improvement	Refractory	Aggravation	
A	17	Month 1	1 (5.9)	3 (17.6)	8 (47.1)	5 (29.4)	23.5
		Month 3	2 (11.8)	7 (38.9)	4 (23.5)	4 (23.5)	64.7
		Month 6	4 (23.5)	7 (38.9)	2 (11.8)	4 (23.5)	64.7
B	22	Month 1	2 (9.1)	9 (40.9)	11 (50)	0	50
		Month 3	5 (22.7)	15 (68.2)	2 (9.1)	0	90.9
		Month 6	16 (72.7)	6 (27.3)	0	0	100
C	17	Month 1	0	11 (64.7)	5 (29.4)	1 (5.9)	64.7
		Month 3	5 (29.4)	6 (35.3)	4 (23.5)	2 (11.8)	64.7
		Month 6	1 (5.9)	14 (82.3)	1 (5.9)	1 (5.9)	88.2
D	17	Month 1	1 (5.9)	13 (76.5)	3 (17.6)	0	82.4
		Month 3	3 (17.6)	12 (70.6)	2 (11.8)	0	88.2
		Month 6	10 (58.8)	7 (38.9)	0	0	100

Numbers at the table represent the number of patients.

Table 3. Comparison of aggravation rates of ROLP patients.

Group	Total cases	Number of aggravation cases					
		M1	M2	M3	M4	M5	M6
A	17	2	1	3	5*	3	4*
B	25	0	1	3	1	0	0

*Significant difference between groups

(a)

(b)

(a)

(b)