

Therapeutic Evaluation of Recurrent Aphthous Ulcer with Integrated Traditional Chinese Medicine and Western Medicine

Xue Chen¹, Hailong Zhang¹, Xingmiao Quan², Feng Huo^{1*}

¹Stomatological Department, Affiliated Hospital of Chengde Medical University, Chengde, China

²Traditional Chinese Medicine Department, Affiliated Hospital of Chengde Medical University, Chengde, China

Email: *cyfycx@126.com

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Abstract

Objective: To observe the curative effects of Yiqing granule and Zhibai Dihuang pill combined with Oralpolin gel on recurrent aphthous ulcer. **Methods:** 150 patients with mild recurrent aphthous ulcer were classified as excessive internal heat type and deficiency internal heat type by traditional Chinese medicine theory. Then, they were randomly divided into the positive control group (thalidomide group), the trial group (Yiqing granule group/Zhibai Dihuang pill group), and the negative control group (topical medication group). All the patients in every group used Oralpolin gel. Additionally, the patients in the positive control group took thalidomide tablets orally and those in the trial group orally took proprietary Chinese medicine (Yiqing granule/Zhibai Dihuang pill). The treatment lasted for 4 weeks. The curative effects were all evaluated according to the “RAU Efficacy Evaluation Trial Standard” which was formulated by the Professional Committee of Mucosal Diseases of Chinese Stomatological Association. **Results:** Of all the 150 patients involved in this medical experiment, 146 cases finished it, including 66 ones in the trial group, 36 ones in the positive control group, and 44 ones in the negative control group. The total drop-out rate was 2.7%. For the excessive internal heat type, the effective rates in the thalidomide group, the Yiqing granule group and the local medication group were 91.7%, 52.6% and 52.9% respectively in order. For the deficiency internal heat type, the effective rates in the thalidomide group, the Zhibai Dihuang pill group and the local medication group were 87.5%, 71.4% and 40% respectively in order. The clinical efficacy of the Zhibai Dihuang pill group was better than that of the local medication group and similar to that of the thalidomide group ($P < 0.05$). **Conclusion:** Zhibai Dihuang pill is significantly effective in the treatment for mild recurrent aphthous ulcer of deficiency internal heat type without severe adverse reactions.

Keywords

Recurrent Aphthous Ulcer, Zhibai Dihuang Pill, Yiqing Granule

1. Introduction

Recurrent aphthous ulcer (RAU), also known as recurrent oral ulcer (ROU) or recurrent aphthous stomatitis (RAS), generally shows a round or oval shape, a sunken center, a surface covered with yellow-white pseudomembrane, and a flushed edge, and causes clearly-felt pains [1]. It is the most common oral mucosal ulcer disease, and its incidence among the population can reach 10% - 25%. The cause of the disease stays unclear, so there is still no specific therapy for it up to now. The commonly used systemic drugs for the disease [2] include glucocorticoids and immunosuppressants, among which thalidomide, as an immunosuppressant, has a good effect on inhibiting ulcers, but its long-term use will cause many adverse reactions. Zhibai Dihuang pill and Yiqing granule are proprietary Chinese medicine preparations. This study observed the efficacy of Zhibai Dihuang pill and Yiqing granule combined with Oralpolin gel in the treatment for recurrent aphthous ulcer of different TCM types, in order to provide a basis for the treatment for recurrent aphthous ulcer with the combination of traditional Chinese medicine and western medicine.

2. Materials and Methods

2.1. Clinical Data

1) Diagnostic criteria [3]: patients diagnosed with mild recurrent aphthous ulcer in terms of their past or current medical history and clinical manifestations according to Oral Mucosal Diseases (Fifth Edition, People's Health Publishing House). TCM syndrome: according to the 2002 edition of Guidelines for Clinical Research of New Drugs of Traditional Chinese Medicine (Trial), aphtha is divided into the following two types: solid fire type: acute onset, short course of disease, severe local pain, a large area and a large number of ulcers, red, swollen and protuberant surrounding mucous membrane, even fused into patches, likely accompanied by fever, thirst, irritability, constipation, halitosis, red corpora lingua, yellow tongue coating, rapid pulse and so on; deficiency fire type: slow onset, long course of disease, mild local pain, small area, small number and dispersion, light and non-red surrounding mucous membrane, often with a history of repeated attacks, long-term healing, likely accompanied by soreness and weakness of waist and knees, fatigue, red zygomatic region, dry mouth but no thirst, hot palms and soles, red tongue, little or dry tongue coating, thready rapid pulse and so on.

2) Inclusion criteria: patients are willing to participate in this study and sign the informed consent form (if a patient is under the legal age, the form must be signed by his legal guardian); ulcers occur at least once a month with a medical history of more than 1 year; birth control is performed during medication.

3) Exclusion criteria: severe, herpetic recurrent aphthous ulcer, Behcet's disease; systemic diseases: anemia, peptic ulcer, infectious diseases, autoimmune diseases; use of analgesics within 24 hours, use of antibiotics within 1 month, systemic use of corticosteroids and immunosuppressants within 3 months; smokers, alcoholics; pregnant and lactating women and those who recently have fertility requirements; drivers, machine operators, and others who engage in dangerous work.

4) Elimination criteria: a) cases of use of drugs not according to the established plan; b) cases of being unable to continue using drugs due to adverse reactions and events in the course of drug use; c) cases of using drugs outside the established plan; d) cases with no post-medication evaluation.

2.2. General Information

From January 2019 to June 2020, 150 patients with mild recurrent aphthous ulcer were treated in the Department of Stomatology, the Affiliated Hospital of Chengde Medical University. In order to realize the blind method and take into account the principle of syndrome differentiation and treatment of traditional Chinese medicine, the TCM doctors participating in the study first carried out the classification of traditional Chinese medicine on each selected patient (solid fire type/deficiency fire type) and then divided the two type patients randomly by the random number table method into three groups: positive control (thalidomide) group ($n = 37$), trial (proprietary Chinese medicine) group (Yiqing granule group, $n = 38$, Zhibai Dihuang pill group, $n = 28$) and negative control (local medication) group ($n = 46$). There was no significant statistical difference in sex, age, the number of ulcers and the interval of ulcers among the three groups ($P > 0.05$), which are comparable, as is shown in **Table 1** and **Table 2**. This study has been reviewed and approved by the Hospital Medical Ethics Committee and has received the informed consent of the patients.

2.3. Treatment Scheme

Positive control group: Thalidomide tablets, 50 mg each time, taken orally once before bedtime; Oralpolin gel, smeared in a proper amount on the ulcer surface 3 times a day.

Table 1. Demographic characteristics of excessive internal heat type group.

Group	n	Gender (n)		Age ($\bar{x} \pm s$, Years)	Number of Ulcers ($\bar{x} \pm s$, Persons)	Interval of Ulcers ($\bar{x} \pm s$, Days)
		Male	Female			
Positive Control Group (Thalidomide)	12	6	6	49.50 \pm 22.70	26.50 \pm 11.19	85.5 \pm 15.59
Trial Group (Yiqing Capsules)	38	20	18	46.16 \pm 16.21	20.58 \pm 12.20	82.89 \pm 40.55
Negative Control Group (Local Medication)	24	16	8	46.00 \pm 19.22	17.83 \pm 10.02	85 \pm 44.31
χ^2/F	-	1.447		0.174	2.321	0.032
P	-	0.538		0.841	0.106	0.969

Table 2. Demographic characteristics of deficiency internal heat type group.

Group	<i>n</i>	Gender (<i>n</i>)		Age ($\bar{x} \pm s$, Years)	Number of Ulcers ($\bar{x} \pm s$, Persons)	Interval of Ulcers ($\bar{x} \pm s$, Days)
		Male	Female			
Positive Control Group(Thalidomide)	24	12	12	40.75 ± 10.96	16.50 ± 5.08	82.50 ± 50.23
Trial Group (Zhibai Dihuang Pills)	28	10	18	38.86 ± 16.22	15.00 ± 6.43	88.29 ± 40.95
Negative Control Group (Local Medication)	20	8	12	40.64 ± 14.91	17.60 ± 10.58	77.00 ± 46.01
χ^2/F	-	1.117		2.169	0.735	0.392
<i>P</i>	-	0.599		0.122	0.483	0.677

Test group:

Excessive internal heat type: Yiqing granules, 7.5 g each time, taken orally three times a day; Oralpolin gel, smeared in a proper amount on the ulcer surface 3 times a day.

Deficiency internal heat type: Zhibai Dihuang pills, 9 g each time, taken orally twice a day; Oralpolin gel, smeared in a proper amount on the ulcer surface 3 times a day.

Negative control group: Oralpolin gel, smeared in a proper amount on the ulcer surface 3 times a day.

Treat all the three groups with 2 weeks as a course of treatment and a total of 2 courses of treatment.

Perform blood cell analysis before and after medication.

2.4. Curative Effect Evaluation

2.4.1. Indexes of Curative Effect Observation

Patients were instructed to pay subsequent visits or accept telephone follow-ups by telephone within 1 - 4 weeks, 5 - 8 weeks, 9 - 12 weeks, 13 - 16 weeks, 17 - 20 weeks and 21 - 24 weeks after medication. The number of ulcer occurrence and the interval time of ulcer attacks in each observation period were recorded.

2.4.2. Indexes of Curative Effect Evaluation

Total interval time (interval, I): the sum of ulcer-free time in the evaluation periods. Total number of ulcers (number, N): the sum of recurrent ulcers in the evaluation periods.

2.4.3. Gradation of Indexes of Curative Effect Evaluation

I¹: the total interval time is prolonged; I⁰: the total interval time does not change.

N¹: the total number of ulcers decreases; N⁰: the total number of ulcers does not change.

2.4.4. Criteria of Curative Effect Evaluation

Refer to the RAU evaluation criteria adopted by the Professional Committee of Oral Mucosal Diseases of Chinese Stomatological Association in December 2002.

Significantly effective: I_1N_1 , that is, the total interval time is prolonged and the total number of ulcers is reduced.

Effective: I_1N_0 or I_0N_1 , that is, the total interval time is prolonged and the total number of ulcers does not change, or the total interval time does not change and the total number of ulcers decreases.

Ineffective: I_0N_0 , that is, neither the total interval time nor the total number of ulcers changes.

2.5 Statistical Method

SPSS 18.0 professional statistical software is used to process the data, and the measurement data are expressed as $(\bar{x} \pm s)$. Paired sample t-test is used to compare the data before and after treatment, and χ^2 -test is used to compare the counting data. The difference of $P < 0.05$ is statistically significant.

3. Results

3.1. Shedding of Cases

A total of 150 subjects were included in this study, and 146 cases completed the experiment. 1 case shed among the 37 cases in the positive control group and the shedding rate was 2.7%; 1 case shed among the 67 cases in the experimental group and the shedding rate was 1.5%; 2 cases shed among the 46 cases in the negative control group and the shedding rate was 4.3%; the total shedding rate was 2.7% (<20%).

3.2. Analysis of the Curative Effect of Excessive Internal Heat Type

The total effective rate of the three groups was more than 50%. By pairwise comparison, there was statistically significant difference in the total effective rate between Yiqing granule group and thalidomide group $\chi^2 = 5.898$, $P = 0.018$ ($P < 0.05$). There was no statistically significant difference in the total effective rate between Yiqing granule group and local medication group $\chi^2 = 2.212$, $P = 0.191$ ($P > 0.05$). However, by comparing marked effectiveness with effectiveness, after χ^2 -tests of Yiqing granule group and local medication group $\chi^2 = 30.780$, $P = 0.000$ ($P < 0.05$), we found that the markedly effective rate of Yiqing granule group was higher than that of local medication group (Table 3).

3.3. Analysis of the Curative Effect of Deficiency Internal Heat Type

By pairwise comparison, there was no statistically significant difference in the

Table 3. The efficacy rates of the trial group, positive control group and negative control group of excessive internal heat type [n (%)].

Group	<i>n</i>	Marked Effectiveness	Effectiveness	Total Effectiveness	No Effectiveness
Positive Control Group (Thalidomide)	12	9 (75)	2 (16.7)	11 (91.7)	1 (8.3)
Trial Group (Yiqing Capsules)	38	18 (47.3)	2 (5.3)	20 (52.6)	18 (47.4)
Negative Control Group (Local Medication)	24	0 (0)	18 (52.9)	18 (52.9)	16 (47.1)

total effective rate between Zhibai Dihuang pill group and thalidomide group $\chi^2 = 3.408$, $P = 0.086$ ($P > 0.05$), but there was statistically significant difference between Zhibai Dihuang pill group and local medication group $\chi^2 = 4.741$, $P = 0.040$ ($P < 0.05$). The curative effect of Zhibai Dihuang pill group was better than that of local medication group but similar to that of thalidomide group (Table 4).

3.4. Adverse Reactions of Patients after Taking Drugs

Among the patients given thalidomide, the indexes of blood cell analysis of one case decreased significantly in part after taking thalidomide, and returned to normal one month after stopping taking thalidomide; the constipation of two cases was relieved after symptomatic treatment; the lethargy of 2 cases and the dizziness of 1 case were improved without special treatment after stopping taking thalidomide. There was no obvious abnormality in the test group and the negative control group.

4. Discussion

Recurrent oral ulcer is a kind of oral mucosal disease characterized by “red, yellow, concave and pain” [4]. Although it does not endanger the patients’ life, it seriously affects the patients’ quality of life [5] [6], and since its etiology and pathogenesis are not clearly known, there is still no specific treatment for the disease at present, and the general treatment for it is local and systemic medication. The main function of local medication is to relieve inflammation and pain and shorten the ulcer period. Systemic therapy can reduce the number of ulcers and prolong the interictal period, and it is often used when the ulcer attack is severe and there is no obvious effect of local treatment [7] [8]. The drugs routinely selected for systematic therapy are glucocorticoids, immune enhancers and immunosuppressants. Although these drugs have a positive curative effect, but their long-term application will cause many adverse reactions. Traditional Chinese medicine has been used in the treatment for recurrent aphthous ulcer for over a thousand years, showing outstanding characteristics and efficacy in long-term clinical practice [9]. Recurrent aphthous ulcer belongs to the category of “aphthous ulcer” and “mouth chancre” in traditional Chinese medicine. In ancient and modern times, aphthous ulcers are divided by “deficiency” and “excess” [10]. It is generally believed that the three factors of wind, heat and dryness out of the six climatic exogenous pathogens are more closely related to aphthous ulcer, among which heat has the closest relation with the disease. Both

Table 4. The efficacy rates of the trial group, positive control group and negative control group of deficiency internal heat type [n (%)].

Group	n	Marked Effectiveness	Effectiveness	Total Effectiveness	No Effectiveness
Positive Control Group (Thalidomide)	24	17 (70.8)	4 (16.7)	21 (87.5)	3 (12.5)
Trial Group (Zhibai Dihuang Pills)	28	12 (42.9)	8 (28.6)	20 (71.4)	8 (28.6)
Negative Control Group (Local Medication)	20	4 (20)	4 (20)	8 (40)	12 (60)

“deficiency internal heat” and “excessive internal heat” of aphthous ulcer have heat signs in clinical manifestations and are easy to be confused. Therefore, syndrome differentiation is particularly important, only with which can “treatment based on syndrome differentiation” be effective.

Recurrent aphthous ulcer of excessive internal heat type can be divided into spleen and stomach latent fire, heart fire inflammation, liver stagnation and heat accumulation and other types. Yiqing granule is derived from Sanhuang Xiexin decoction recorded in Synopsis of Prescriptions of the Golden Chamber written by Zhang Zhongjing, a medical scientist in the Eastern Han Dynasty. It is a proprietary Chinese medicine composed of *Scutellaria baicalensis*, *Coptis chinensis* and rhubarb. Previous studies have shown [11] [12] that Yiqing granule has a good effect on aphthous ulcer of spleen and stomach heat accumulation type. A multicenter clinical study by Peng Lisu *et al.* showed that Yiqing capsule was similar to Niu Huang Jiedu capsule in the treatment for recurrent aphthous ulcer (with heat toxin syndrome) while this study showed that after the patients had been treated for six months, the curative effect of Yiqing granule group was similar to that of local medication group ($P > 0.05$). On one hand, it is considered that most of the patients in Yiqing granule group in this study belong to the types of heart fire inflammation, liver stagnation and heat accumulation of excessive internal heat type, so the application of Yiqing granule to these patients may not be completely symptomatic; on the other hand, Peng Lisu evaluated the efficacy of the drug 7 days after medication and attached greater importance to short-term effects such as changes in the pain degree of aphthous ulcers, while this study evaluated long-term effects such as the number of ulcers and interictal periods. In terms of the results of this study, the total effective rates of both Yiqing granule group and local medication group were more than 50%. Among the total effective cases, the markedly effective rate of Yiqing granule group was significantly higher than that of local medication group, which shows that the local application of Oralpolin gel is effective in promoting ulcer healing and shortening ulcer time, while Yiqing granule has a certain effect in both reducing the number of ulcers and prolonging interictal periods. In the case of expanding the sample size and performing more accurate TCM classification, there will be a greater improvement in the total effective rate of Yiqing granule group.

Hyperactivity of fire due to yin deficiency is the most common type of aphthous ulcers of deficiency internal heat type, which is manifested mostly as kidney yin deficiency, and partly as heart yin deficiency, and liver and kidney yin deficiency and other types. Although the deficiency syndrome is more found, it is mostly accompanied by hyperactivity of fire with the performance of deficiency fire. Zhibai Dihuang pill is composed of *Rhizoma Anemarrhena*, *Cortex Phellodendri*, *Radix Rehmanniae*, yam, *Poria cocos*, *Cornus officinalis*, *Cortex moutan*, *Rhizoma Alismatis* and so forth. It is a derivative prescription of Liuwei Dihuang pill, *Anemarrhena* has antipyretic, detoxifying and bacteriostatic effects. Phel-

lodendron phellodendron can clear heat and dry dampness, relieve fire and detoxify, retreat asthenia heat [13]. Cooked rehmannia sweet and warm, nourishing marrow and kidney; Chinese yam has the effect of nourishing spleen and kidney; Dogwood converges and nourishes the kidney; Moutan peel can cool blood and retreat deficiency fever [14]. The recipe has the effect of nourishing yin and reducing fire [15] [16]. In this study, 28 patients with recurrent aphthous ulcer caused by deficiency fire were treated with Zhibai Dihuang pill for four weeks on the basis of topical application of Oralpolin gel. Six months after treatment, the total effective rate of Zhibai Dihuang pill group was higher than that of local medication group ($P < 0.05$), and the curative effect was similar to that of thalidomide group ($P > 0.05$). But after comprehensive consideration of the facts [17] that thalidomide with severe teratogenicity should be used by people at gestational age only when they take contraception measures and that thalidomide may result in many adverse reactions, such as peripheral neuritis, leukopenia, lethargy, headache, dizziness, constipation, fatigue, dry mouth and so on, the author thinks that Zhibai Dihuang pill plus Oralpolin gel is more applicable, safer and easy to be accepted by patients.

Traditional Chinese medicine is the crystallization of the wisdom of ancestral doctors, and it has been proved to be good medication in thousands of years of medical practice and has achieved good results in the treatment for recurrent aphthous ulcer [18], but most of the treatment schemes are based on the clinical experience of doctors with lack of a more systematic theoretical basis, which indicates that the concept of traditional Chinese medicine needs to be changed from empirical medicine to evidence-based medicine. At present, the decrease of cellular immune function and the imbalance of T-lymphocyte subsets are considered to be one of the important pathogenic factors of recurrent aphthous ulcer [19] [20]. Previous studies have shown that *Cornus officinalis* and Cortex Phellodendri in Zhibai Dihuang pill can regulate immunity [13] [21]. This can be taken as a cut-in point to provide a new objective index for TCM “syndrome” and syndrome differentiation from the mechanism of Zhibai Dihuang pill in the treatment for recurrent aphthous ulcer.

5. Conclusion

Treatment of RAU based on syndrome differentiation, especially for patients with hypofire RAU, has a good effect in both reducing the number of ulcers and prolonging interictal periods.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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