Int J Clin Exp Med 2018;11(9):10002-10008
www.ijcem.com /ISSN:1940-5901/IJCEM0077702

Original Article

Clinical analysis of Yinzhi decoction combined with compound gargle solution chlorhexidine giuconatie in the treatment of recurrent aphthous ulcer and its effect on immune function and inflammatory factors in patients

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Received April 10, 2018; Accepted May 20, 2018; Epub September 15, 2018; Published September 30, 2018

Abstract: Objective: To study the therapeutic efficacy of Yinzhi decoction combined with compound gargle solution chlorhexidine giuconatie on recurrent aphthous ulcer and its effect on immune function and inflammatory factors of patients. Methods: A total of 126 patients with recurrent aphthous ulcer were divided into a study group (63 patients) and a control group (63 patients) by a random number table approach. The control group was treated by gargling with a compound gargle solution of chlorhexidine giuconatie. The study group was treated by gargling combined with oral Yinzhi decoction. The clinical efficacy, and pre-treatment and post-treatment changes of pain score, oral colony number, immune function indexes (levels of $CD3^+$, $CD4^+$, and $CD8^+$ T cells, and $CD4^+/CD8^+$ T cells ratio) and serum inflammatory factors (interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) were measured before and after treatment. Results: The overall response rate of the study group was significantly higher than that of the control group ($P<0.05$). The pain score and oral colony number of the study group after treatment were significantly lower than those before treatment and those of the control group (all $P<0.05$). The $CD3^+$ and $CD4^+$ T cell counts and $CD4^+/CD8^+$ T cells ratio of the study group after treatment were obviously higher than those before treatment and those of the control group, and the $CD8^+$ T cell counts was significantly lower than that before treatment and that of the control group (all $P<0.05$). The IL-1, IL-6, and TNF-α levels of the study group after treatment were significantly lower than that before treatment and that of the control group (all $P<0.05$). Conclusion: The treatment of recurrent aphthous ulcer with compound gargle solution chlorhexidine giuconatie in combination with oral Yinzhi decoction can effectively increase the response rate, reduce the pain score and oral colony number of patients, improve the immune function of patients, and lower inflammatory factor levels.

Keywords: Yinzhi decoction, recurrent aphthous ulcer, immune function, inflammatory factors

Introduction

Recurrent aphthous ulcer is one of the most common oral mucosal diseases, with an incidence as high as 20%. The main clinical manifestation is localized ulcer in the local part of oral mucosa [1]. It is a self-limited disease that can resolve after 7 to 10 days of self-healing, but it may reoccur after a period of remission [2]. At the onset, patients may feel a searing pain in the ulcer when drinking water, eating, or talking, which severely affects the living quality of patients.

The cause of this disease is unclear. It could be due to joint outcomes of multiple factors such as immunity, heredity, infection, and environment. Currently, oral gargle is often used in clinical practice to reduce the bacterial density in oral cavity and mitigate clinical symptoms of patients [3, 4]. Although it has some therapeutic efficacy, the long-term effect is not good [5]. From a perspective of traditional Chinese medicine, this disease can be classified into the category of aphtha, of which the heat accumulation of heart and spleen is the most common syndrome [6]. In this study, patients with this

disease were treated by Yinzhi decoction combined with compound gargle solution chlorhexidine giuconatie, aiming to observe the efficacy and its effect on immune function and inflammatory factors in patients.

Materials and methods

General data

A total of 126 patients with recurrent aphthous ulcer admitted to Dongfang Hospital Beijing University of Chinese Medicine from February 2015 to February 2017 were recruited, including 70 males and 56 females. The patients were aged 27-62 years old, with an average age of 47.63±9.87 years old, and the course of disease ranged from 2-11 days, with an average of 5.72±2.10 days. Patients were randomly divided into a study group (63 patients) and a control group (63 patients) by a random number table approach.

Inclusion criteria: 1) Patients diagnosed as recurrent aphthous ulcer (minor) according to the criteria in the 3rd edition of the *Diseases of Oral Mucosa* [7]; the disease occurred more than twice; the disease history was longer than one year, and the interval was less than one month from the last recurrence. 2) The heat accumulation of heart and spleen of aphtha was tallied with the *Guidelines of Clinical Trials on New Drugs of Traditional Chinese Medicine* [8]. 3) Patients came to hospital within 48 h after the onset of this disease. 4) Ulcer diameter ≤5 mm.

Exclusion criteria: 1) Patients with oral ulcer caused by Behcet's disease, malignant neoplasm and other oral mucosal diseases or periodontal disease. 2) Patients with severe systematic infection or immunodeficiency disease, who had to be hospitalized. 3) Patients treated with non-steroidal anti-inflammatory drugs 24 hours before hospitalization. 4) Patients treated with corticosteroids and immunosuppressant within 1 month. 5) Pregnant and lactating women allergic to investigational drugs. 6) Patients whose clinical data were incomplete. 7) Patients with poor compliance.

This study was approved by the Ethics Committee of Dongfang Hospital Beijing University of Chinese Medicine. Informed consent was signed and obtained from all patients.

Method

The control group was treated by gargling 10 mL of compound gargle solution chlorhexidine giuconatie (Shenzhen South China Pharmaceutical Co., Ltd.) for 5 minutes each time, 4 times a day, within half an hour after meal and before sleep [9].

The study group was treated by gargling with compound gargle solution chlorhexidine combined with oral Yinzhi decoction. The usage and dosage of gargle was the same as that of the control group. Yinzhi decoction prescription: honeysuckle (12 g), fructus Gardeniae (12 g), forsythia suspense (12 g), mint (8 g), almond (9 g), burdockseed (10 g), radix peucedani (8 g), platycodon grandifloras (9 g), liquorice (6 g), belamcanda chinensis (10 g), radix sophorae tonkinensis (12 g). One dose of those medicinal materials was prepared with 500 mL distilled water to make 250 mL traditional Chinese medicine liquid. Patients took 125 mL Yinzhi decoction each time, once dose per day, and two times in the morning and evening respectively. Both groups were treated for 1 week. During treatment, not eating spicy and greasy food, and abstaining from alcohol and tobacco were required. It was advised to drink more water to facilitate toxin excretion. If local irritation or worse condition appeared during mediation period, this medicine should was stopped. If the condition improved after 7 days, the treatment was continued until patients were cured. The therapeutic effect was evaluated 7 days after treatment.

Immune function: A total of 4 mL of fasting peripheral vein blood was collected from each patient in the morning, and lymphocytes were separated after EDTA anticoagulation. Subsequently, $CD3^+$, $CD4^+$, and $CD8^+$ T cell counts and $CD4^+/CD8^+$ T cells ratio of two groups before treatment and 7 days after treatment were detected by flow cytometry [10].

Inflammatory factors: A total of 4mL of fasting peripheral vein blood was collected from each patient in the morning. After centrifugal separation of serum, the IL-1, IL-6, and TNF-α levels of the two groups before treatment and 7 days after treatment were detected by ELISA [11].

Oral colony number: Oral microorganisms of two groups were detected before treatment and 7 days after treatment. After patients were

Table 1. Comparison of general data

	Gender (male/female)	Age (year)	Course (day)	Number of ulcers
Study group (n=63)	37/26	46.32±10.79	1.57±0.23	1.83±0.54
Control group (n=63)	33/30	48.22±9.52	1.63±0.34	1.72±0.56
t/χ^2	0.514	1.048	1.160	1.122
P	0.473	0.297	0.248	0.264

Table 2. Comparison of clinical efficacy (n, %)

	Cure	Improvement	Failure	ORR
Study group (n=63)	33 (52.38)	28 (44.44)	2 (3.17)	61 (96.83)
Control group (n=63)	20 (31.75)	26 (41.27)	17 (26.98)	46 (73.02)
χ^2				13.945
P				<0.001

Note: ORR, overall response rate.

administered with 10 mL of sterile saline solution every day before and after gargling, the foci of ulcers were embrocated repeatedly with throat swabs to measure the oral colony number and calculate the average [12].

Outcome measures

Primary outcomes: (1) Clinical efficacy: The therapeutic efficacy was evaluated according to the *Guidelines of Clinical Trials on New Drugs of Traditional Chinese Medicine* [13]. Cure: The mucosal hyperemia of the ulcer peripheral subsided. Both pain and ulcer disappeared. Oral feeding was possible. Improvement: The mucosal hyperemia of the ulcer peripheral subsided. The ulcer size decreased by more than half. Oral feeding was possible with existing slight pain. Failure: The mucosal hyperemia of the ulcer peripheral didn't subside significantly. The ulcer size decreased by less than half. Oral feeding was impossible. Total response rate (ORR) = (Cure + improvement)/total number of patients * 100%. (2) Duration of ulcer. (3) Pain score: The visual analogue scale (VAS) was used to evaluate the pain intensity. The VAS score ranged from 0 to 10. The higher the score was, the higher the pain intensity [14].

Secondary Outcomes: Oral colony number, adverse reaction rate and recurrence rate after 6-month follow up. Recurrence rate = number of recurrences/total number of patients * 100%.

Statistical analysis

SPSS 20.0 software was used for data processing. The measurement data including pain score, oral colony number, $CD3^+$, $CD8^+$ T cell counts, $CD4^+/CD8^+$ T cells ratio, and IL-1, IL-6, and TNF-α levels, is expressed as mean ± sd, and two groups were compared by t test, expresses by t. The count data, such as clinical efficacy, were expressed as percentage. χ^2 test and Fisher's exact probability test were adopted to the comparison of two groups, expressed by χ^2. P<0.05 means the difference has statistical significance.

Result

Comparison of baseline characteristics

The study group and the control group were compared from gender, age, course of disease and number of ulcers. The result showed no statistically significant difference between the two groups (all P>0.05) as shown in **Table 1**.

Comparison of clinical efficacy between two groups

The ORR of the study group was significantly higher than that of the control group (P<0.05) as shown in **Table 2**.

Comparison of pain score and oral colony number

The difference of two groups in pain score and oral colony number before treatment were not statistically significant (both P>0.05). The pain score and oral colony number of two groups after treatment were significantly lower than those before treatment respectively (all P< 0.05). The pain score and oral colony number of the study group were lower than those of the control group after treatment (P<0.05) as shown in **Table 3**.

Comparison of immune function between two groups

The difference of two groups in $CD3^+$, $CD4^+$, and $CD8^+$ T cell counts and $CD4^+/CD8^+$ T cells ratio

Table 3. Comparison of pain score and oral colony number before and after treatment ($\bar{x}$ ± sd)

	Pain score (score)				Oral colony number (CFU/cm^2)			
	Before treatment	After treatment	t	P	Before treatment	After treatment	t	P
Study group (n=63)	6.12±1.25	1.72±0.63	24.950	<0.001	86.72±12.05	2.84±0.36	55.227	<0.001
Control group (n=63)	6.07±1.12	2.87±0.70	19.231	<0.001	85.26±11.82	12.42±2.03	48.207	<0.001
t	0.236	9.692			0.687	36.882		
P	0.813	<0.001			0.494	<0.001		

Note: CFU, Colony-Forming Units.

Table 4. Comparison of immune function indexes before and after treatment ($\bar{x}$ ± sd)

	$CD3^+$ T cell (%)				$CD4^+$ T cell (%)			
	Before treatment	After treatment	t	P	Before treatment	After treatment	t	P
Study group (n=63)	50.82±6.24	63.47±7.39	10.381	0.000	0.40±0.11	0.48±0.10	4.271	<0.001
Control group (n=63)	51.22±5.85	57.23±6.38	5.511	0.000	0.39±0.10	0.44±0.12	2.541	0.012
t	0.371	5.073			0.534	2.033		
P	0.711	<0.001			0.594	0.044		

Table 5. Comparison of immune function indexes before and after treatment ($\bar{x}$ ± sd) (continued)

	$CD8^+$ T cell (%)				$CD4^+/CD8^+$ T cells ratio			
	Before treatment	After treatment	t	P	Before treatment	After treatment	t	P
Study group (n=63)	0.36±0.07	0.26±0.06	8.609	0.000	1.22±0.13	1.39±0.17	6.305	<0.001
Control group (n=63)	0.35±0.08	0.30±0.05	4.207	0.000	1.18±0.12	1.28±0.16	3.969	<0.001
t	0.747	4.065			1.795	3.740		
P	0.457	<0.001			0.075	<0.001		

Table 6. Comparison of serum inflammatory factors before and after treatment ($\bar{x}$ ± sd, ng/mL)

		Study group (n=63)	Control group (n=63)	t	P
IL-1	Before treatment	1.45±0.32	1.43±0.27	0.379	0.705
	After treatment	0.52±0.15	0.86±0.18	11.518	<0.001
	t	20.887	13.942		
	P	0.000	0.000		
IL-6	Before treatment	177.34±18.03	172.50±17.62	1.524	0.130
	After treatment	73.29±7.82	94.46±10.65	12.718	<0.001
	t	42.023	30.086		
	P	0.000	0.000		
TNF-α	Before treatment	273.32±34.80	275.20±33.45	0.309	0.758
	After treatment	130.48±19.50	175.60±23.48	11.734	<0.001
	t	28.421	19.344		
	P	<0.001	<0.001		

Note: IL-1, interleukin-1; IL-6, interleukin-1; TNF-α, tumor necrosis factor-α.

before treatment had no statistical significance (all P>0.05). The $CD3^+$ and $CD4^+$ T cell counts and $CD4^+/CD8^+$ T cells ratio of two groups after treatment were apparently higher than that before treatment; the $CD8^+$ T cell counts was apparently lower than that before treatment (all P<0.05). The $CD3^+$ and $CD4^+$ T cell counts and $CD4^+/CD8^+$ T cells ratio of the study group were apparently higher than that of the control group; the $CD8^+$ T cell counts of the study group was significantly lower than that of the control group all (P< 0.05) as shown in **Tables 4**, **5**.

Comparison of serum inflammatory factor levels

The difference of two groups in IL-1, IL-6, and TNF-α levels before treatment had no statistical significance (all P>0.05). The IL-1, IL-6, and TNF-α levels of two groups after treatment were significantly lower than those before treatment (all P<0.05). The IL-1, IL-6, and TNF-α levels of the study group were significantly lower than those of the control group after treatment (P<0.05) as shown in **Table 6**.

Table 7. Comparison of duration of ulcer and recurrence rate between two groups

	Duration of ulcer (day)	Recurrence rate within 6 months (n, %)
Study group (n=63)	3.26±0.41	5 (7.94)
Control group (n=63)	5.01±1.26	20 (31.75)
t/χ^2	10.483	11.228
P	<0.001	0.001

Rate of adverse reaction, duration of ulcer, and recurrence rate

No patient in any group had serious adverse reaction during treatment. The duration of ulcer and recurrence rate of the study group were significantly lower than those of the control group (both P<0.05) as shown in **Table 7**.

Discussion

From a view of traditional Chinese medicine, the pathogenesis of recurrent aphthous ulcer is overeating sweet & greasy and pungent & spicy food, which results in heat accumulation of heart and spleen, organ dysfunction, and attack by six exogenous pathogenic factors that invade the body. This causes the heat toxin to stagnate *in vivo* and invade upward along meridians, leading to oral mucosa damage. Consequently, ulcers occur due to local hemodynamic disorder and massive bacterial growth. For this reason, "fire" and "stasis" are the key of the pathogenesis [15, 16]. The heat-toxin invading the body causes spleen and stomach impairment resulting in Qi damage and Yin impairment. The consequence is body fluid deficiency leading to weakened immunity and imbalance between Yin and Yang, which in turn aggravates the heat toxin. The therapy principle is clearing heat and detoxicating, and nourishing Yin to lessen fire. Yinzhi decoction is prescribed in the light of the pathogenesis of heat accumulation of heart and spleen and based on years of clinical experiences. In this prescription, the honeysuckle, forsythia suspense, mint, radix peucedani, belamcanda chinensis, liquorice, burdockseed and radix sophorae tonkinensis can achieve the effect of clearing heat and detoxicating, and relieving swelling and pain. The platycodon grandiflorus can achieve the effect of eliminating swelling and relieving sore throat. The Fructus Gardeniae and mint can achieve the effect of clearing heat, cooling blood and purging fire. The interaction of all constituents' effects clearing heat and detoxicating, stopping bleeding and cooling blood, and relieving swelling and pain. Modern pharmacology has demonstrated that honeysuckle has the antiviral, anti-inflammatory and antipyretic effect [17] and that fructus Gardeniae has the antipyretic and anti-microorganism effect [18]. This study found that the ORR of the study group was significantly higher than that of the control group, and that the pain score and duration of ulcer of the study group after treatment were significantly lower than those of the control group. As reported by Hong et al. in their study, the therapy of treating recurrent aphthous ulcer by Xipayi Collutory and Kouyanqing Granules has a good efficacy and it can hasten the healing of ulcer and reduce the recurrence, without increasing the rate of adverse reaction; in their study, the mean ulcer healing time was (4.36±1.22) days, lower than that of the study group (3.26±0.41) days; and the ORR was 90.00%, lower than that of the study group (96.83%) [19]. This might be related to the selection of patients treated with Yinzhi decoction had the symptom of heat accumulation of heart and spleen classified as aphtha, better fitting the characteristic of traditional Chinese medicine differentiation and treatment. Therefore, the therapy of treating recurrent aphthous ulcer (heat accumulation of heart and spleen) by oral administration of Yinzhi decoction has an exact effect, because it can greatly shorten the duration of ulcer and ease the pain in oral mucosa.

The study found that the serum IL-1, IL-6, and TNF-α levels of patients with oral ulcer were apparently higher than that of the healthy population, suggesting the occurrence and development of oral ulcer is closely related to the inflammatory response [20, 21]. Inflammatory factors (IL-1, IL-6, and TNF-α) are critical mediators in the pathological process of oral ulcer [20]. IL-1 and IL-6 are early inflammatory mediators that can actively activate inflammatory and immune cells, and the elevated expression level of IL-1 and IL-6 is likely to cause the inflammatory response. TNF-α is a multifunctional factor which plays an important role in the pathogenetic process such as inflammatory lesion, shock, and immune defense, and the excessive expression level of TNF-α is very likely to cause the inflammatory response [22]. This study revealed that the IL-1, IL-6, and

TNF-α levels of the study group after treatment were apparently lower than those before treatment and that of the control group, suggesting the oral administration of Yinzhi decoction can remarkably inhibit the inflammatory response of patients with recurrent aphthous ulcer and thus contribute to the healing of ulcer. The oral colony number of the study group was significantly lower than that of the control group, which is in line with the findings reported by Xie et al. [23]. They reported Kangfuxin Liquid can reduce the inflammatory factor levels of patients with recurrent aphthous ulcer and alleviate their clinical symptoms. Taken together, these results suggested oral administration of Yinzhi decoction could remarkably inhibit the inflammatory response of patients with recurrent aphthous ulcer and reduce the number of bacteria in oral mucosa, which contributes to the healing of ulcer.

$CD3^+$, $CD4^+$, and $CD8^+$ T cell markers are key indicators of immune function that can effectively reflect the level of immune function of patients [24, 25]. The study by Cai et al. reveals that the use of Utilin's, a multi-functional immunopotentiator, can effectively improve the imbalance of peripheral T-lymphocyte subsets, enhance the immune function, promote the healing of recurrent aphthous ulcer and increase the cure rate [26]. In this study, the $CD3^+$ and $CD4^+$ T cell counts and $CD4^+/CD8^+$ T cells ratio of the study group after treatment were apparently higher than that before treatment and that of the control group, and the $CD8^+$ T cell counts was lower than that before treatment and that of the control group. The recurrence rate of the study group was significantly lower than that of the control group, suggesting the oral administration of Yinzhi decoction can enhance the immune function of patients with recurrent aphthous ulcer and prevent the recurrence of ulcer, which agrees with the report mentioned above and indicates Yinzhi decoction is effective to improve the immunological imbalance of patients [26].

No patient in any group had serious adverse reaction during treatment, suggesting the therapy of treating the patients with recurrent aphthous ulcer with compound gargle solution chlorhexidine giuconatie in combination with oral Yinzhi decoction is good in safety and tolerance and is worth popularizing. However, this study is only a preliminary study for the small sample size, and it is necessary to probe deeply into the difference in long-term efficacy by further expanding the sample size and extending the observation time.

In conclusion, treating patients with recurrent aphthous ulcer by compound gargle solution chlorhexidine giuconatie combined with oral Yinzhi decoction can effectively increase the response rate and reduce the pain score and oral colony number of patients. The mechanism of action may be associated with improving the immune function of patients while lowering the inflammatory factor levels.

Disclosure of conflict of interest

None.

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