ORIGINAL RESEARCH

Improvement of Salivary EGF Levels and Serum Inflammatory Factors in Patients with Recurrent Oral Ulcers Treated with Shuanghuanglian Oral Solution

Xuejing Pang, MM; HangXue Li, MM; Lu Wang, MM; Yuping Zhang, BM

ABSTRACT

Objective • Recurrent oral ulcer (ROU) is a common oral mucosal disease with recurrent ulcerative lesions. Shuanghuanglian Oral liquid is a traditional Chinese medicine preparation widely used to treat oral ulcers. This study aimed to explore the effect of Shuanghuanglian oral liquid on the epidermal growth factor (EGF) level in saliva and serum inflammatory factors in patients with recurrent oral ulcers to provide a certain reference for clinical treatment.

Methods • A retrospective analysis of 90 ROU patients from 2018 to 2021 was divided into an observation group (n=45) and a control group (n=45). All patients were recruited from Kunming Stomatological Hospital North Downtown Campus. The control group used a mouthwash containing chlorhexidine, while the observation group used the same mouthwash with an additional topical application of Shuanghuanglian. The EGF level in saliva, serum inflammatory factor, clinical efficacy, pain and quality of life scores, recurrence rate, and incidence of adverse reactions were observed in the two groups.

Results • After treatment, EGF (RR 0.41, 95%CI 0.15-0.73, $P < .001$), tumor necrosis factor-α (TNF-α) (RR 0.68, 95%CI 0.53-0.77, $P = .003$), interleukin-10 (IL-10) (RR 0.64, 95%CI 0.48-0.75, $P < .001$), and C-reactive protein (CRP) (RR 0.52, 95%CI 0.35-0.65, $P < .001$) in observation group were significantly lower than those in the control group; The total effective rate of the observation group was significantly higher than that of the control group (RR 0.85, 95%CI 0.44-0.95, $P = .02$); Visual analogue scale (VAS) (RR 0.48, 95%CI 0.35-0.68, $P < .001$) and Oral Health Rating Scale (OHIP-4) scores (RR 0.61, 95%CI 0.47-0.84, $P < .001$) of observation group were significantly lower than those of control group after treatment; The incidence of total adverse reactions (RR 0.73, 95%CI 0.61-0.86, $P = .011$) and the recurrence rate at 6 months after treatment in the observation group were significantly lower than those in the control group (RR 0.78, 95%CI 0.69-0.91, $P = .015$).

Conclusion • Shuanghuanglian oral liquid has a remarkable effect on patients with ROU by reducing the levels of EGF and inflammatory factors in patients, reducing the pain degree of patients, improving the oral health of patients, improving the quality of life of patients, and reducing the incidence of adverse reactions and the recurrence rate of patients to a certain extent. (*Altern Ther Health Med.* 2024;30(12):188-193).

Xuejing Pang, MM; **HangXue Li**, MM; **Lu Wang**, MM; **Yuping Zhang**, BM, Department of Dentistry; Kun Ming Children's Hospital; Kun Ming; Yunnan Province; China.

Corresponding author: Yuping Zhang, BM
E-mail: zsgg2007pp@126.com

INTRODUCTION

Recurrent oral ulcer (ROU) is an ulcer that is confined to the mucous membrane of the mouth with periodic and recurrent clinical symptoms.[1] ROU is often found on the tongue, inside cheeks, and other mucous membranes and is characterized by a single ulcer or multiple ulcers joined by a creamy yellow or white film with clear borders and a red and swollen surrounding mucous membrane.[2,3] ROU is often accompanied by redness, swelling, heat, pain, and other symptoms, of which the pain of ROU is more prominent. The actions of ROU patients, such as eating and drinking water, are involved in the ulcer, which will cause severe pain and significantly affect patients' diet and quality of life.[4] Although ROU has limitations and can heal itself, it occurs repeatedly and greatly impacts patients' sleep, work, diet, etc. The pathogenesis of ROU may be related to the high susceptibility of the oral cavity to pathogens, immune dysfunction, and cellular secretion disorders. Still, there is no apparent cause for the disease.[5,6] Therefore, there is no specific drug for ROU, and clinical treatment is mainly symptomatic.[7] To date, the clinical management of ROU can be divided into systemic immunotherapy and local symptomatic treatment. Local treatment is mainly anti-inflammatory, analgesic, and wound healing, while systemic treatment is mainly immunotherapy.[8,9]

In clinical practice, it is found that local treatment is more effective than systemic treatment, and systemic treatment has specific side effects, so local allopathic treatment is usually chosen when formulating ROU treatment plans. In clinical practice, western medicine has limitations in its effectiveness in treating ROU and cannot give a radical cure to the patient's recurrent episodes. For this reason, we consider the choice of Chinese medicine to treat ROU.[10]

In Chinese medicine, ROU is known as "mouth sores." In the Su Wen - The Great Treatise on the Crossing of Qi, it is stated that "when the gold of the year is not enough, the fire goes up ..... and the people become ill with mouth sores, and even then their hearts hurt." This was the first time that the occurrence of mouth sores was related to fire and heat in the body. Since then, many TCM practitioners have conducted more in-depth studies on mouth sores on this basis, and the pathogenesis of mouth sores has been refined, for example, about the weakness of the spleen and stomach and deficiency of cold in the middle jiao.[11] In Chinese medicine, it is believed that "the mouth is the organ of the spleen, the tongue is the seedling of the heart, the kidney veins are connected to the pharynx and the tongue, and the cheeks belong to the stomach and intestines". In accordance with the principles of traditional Chinese medicine as mentioned above, although oral ulcers occur within the oral cavity, this symptom is considered to be a manifestation reflecting the condition of organs such as the heart, kidneys, and gastrointestinal tract. The active ingredients of Shuang Huang Lian Oral Liquid are Jin Yin Hua, Scutellaria baicalensis, and Lian Qiao, which are effective in clearing heat and detoxifying toxins and promoting recovery of wounds, which is in line with the basic principles of treating recurrent oral ulcers in Chinese medicine. Still, few clinical studies on Shuang Huang Lian Oral Liquid on recurrent oral ulcers exist.[12]

Therefore, this study aimed to evaluate the effect of Shuanghuanglian oral liquid on improving EGF levels in saliva and inflammatory factors in serum in patients with recurrent oral ulcers. The results of this study are expected to provide new evidence and methods for treating oral ulcers, provide a basis for selecting appropriate clinical treatment plans, and provide a new idea for the treatment strategy of oral ulcers.

MATERIALS AND METHODS

General information

A total of 90 ROU patients treated in Kun Ming Children's Hospital from 2018 to 2021 were selected according to the inclusion and exclusion criteria. According to the lottery method, the odd number was the observation group, and the even number was the control group, with 45 cases in each group. There was no significant difference in the general data between the two groups, as shown in Table 1. The Ethics Committee approved this study.

Inclusion criteria: (i) the diagnosis in the "Guidelines for the Treatment of Recurrent Aphthous Ulcer (Trial)" [13] was met by clinical examination; (ii) the ulcer was persistent or showed recurrent episodes before admission; (iii) no other medication was used before treatment; (iv) the patient and family agreed to conduct a cooperative study.

Exclusion criteria: (i) patients with cancer; (ii) patients with other types of disease; (iii) unclear cognition or psychiatric problems; (iv) people with immune deficiency and related diseases; (v) Drug allergy; (vi) those who cannot cooperate with the treatment as scheduled; (vii) those with incomplete follow-up data at a later stage.

Methods

Control group The conventional topical symptomatic treatment regimen was used, and compound chlorhexidine-containing rinse (Haimen City, Jiangsu Province, China, Chen Brand Bond Pharmaceutical Co., LTD., Sinopod: H20058018, Specifications: Chlorhexidine gluconate 1.2mg and metronidazole 0.2mg per ml) was selected for mouth rinsing, once in the morning and once in the evening, 10-20ml each time, and the treatment duration was 2 weeks.

The observation group was treated with topical treatment based on the control group. Use cotton swabs to dip Shuanghuanglian oral liquid Harbin (Pharmaceutical Group Sanjing Pharmaceutical Co., LTD., Harbin City, Heilongjiang Province, China, Sinop OD code: Z10920053, specification: 10ml), and apply it on the ulcer and its surrounding area 2 times a day for 2 weeks.

Observation indicators

EGF index in saliva: 2ml of oral saliva was collected from patients before and after treatment, centrifuged at 3000 rpm, EGF levels were measured using Human Epidermal growth factor, EGF ELISA Kit, and the kit was selected from Mershack Biologicals Ltd (kt90077, Wuhan, China).

Inflammatory factors: Before and after treatment, 5ml of venous blood was collected from the patients at 2500 rpm, centrifuged for 10 min, and stored at -80°C. The levels of tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10), and C-reactive protein (CRP) were detected by Mindray Min-DRAYMR-96A enzyme-linked immunosorbent assay. Among them, the TNF-α detection kit was purchased from Wuhan Fenn Biotechnology Co., LTD.; the IL-10 test kit was purchased from Shanghai Yaji Biotechnology Co., LTD. CRP test kit was purchased from Beijing Biao Leibo Technology Co., LTD.

Efficacy: The change in ulcer diameter was measured before and after treatment. A reduction in diameter of 0.5 mm was considered effective, and a decrease in diameter of less than 0.5 mm was considered ineffective.

Table 1. Comparison of general data between the two groups

General information		Control group (n=45)	Observation group (n=45)	χ^2/t	RR (95%CI)	*P* value
Gender (n, %)	male	24(53.33)	20(44.44)	0.712	0.89(0.62, 1.12)	.399
	female	21(46.67)	25(55.56)			
Age (years,±s)		34.21±7.01	34.36±6.78	0.103	1.12(0.89, 1.21)	.918
Course of disease (years, ±s)		7.56±1.89	7.43±1.24	0.386	0.98(0.80, 1.19)	.701
Time from ulcer onset to hospitalization (d,±s)		2.18±0.67	2.49±0.81	1.978	0.79(0.31, 1.22)	.051
Ulcer site (n, %)	cheek	20(44.44)	16(35.56)	4.238	0.86(0.50, 1.33)	.120
	Tip of the tongue	10(22.22)	19(42.22)			
	lip	15(33.33)	10(22.22)			
Ulcer diameter (cm, ±s)		1.52±0.61	1.68±0.37	1.504	1.19(0.23, 3.40)	.136

Quality of life score: pain score: The Visual Analogue Scale (VAS) [14] is employed to assess changes in the level of pain experienced by patients. It features a movable scale between 0 and 10 on both the front and back sides. As patients adjust the scale, doctors can immediately observe the specific numerical value on the back, providing precision down to millimeters. A longer length on the scale indicates heightened pain, while a lower score signifies a lower level of pain. Prior to usage, it is crucial to provide patients with a detailed explanation, ensuring their comprehension of the method's concept and the relationship between pain measurement and actual pain. Subsequently, patients are encouraged to mark the corresponding position of their pain on the linear scale. The patient's quality of life was scored using the oral health impact profile (OHIP-14).[15] This scale comprises 14 items categorized into 7 sections, namely oral functional limitation, physical pain, psychological discomfort, physical disorder, psychological disorder, social disorder, and disability. Each item in the scale is subdivided into 5 levels, with corresponding scores (0 representing never, 1 for rarely, 2 for sometimes, 3 for often, and 4 for very often). The cumulative score ranges from 0 to 56, wherein lower scores denote better oral health. Incidence of adverse reactions: The incidence of adverse reactions, such as nausea, dry mouth and bitterness, was collected from patients during the treatment period and the incidence of adverse reactions was calculated.

Recurrence: follow-up after the end of treatment using telephone and WeChat for one year. Recurrence of ulcers was collected from patients. Calculate the patient's recurrence rate.

Statistical processing

Statistical analysis of the data was performed using SPSS version 22.0. This study uses relative risk (Risk ratio, RR) as an analysis statistic and calculates its 95% confidence interval (CI). Measurement data were tested for normality, all data conforming to the normal distribution were expressed by $\bar{x} \pm s$, and an independent sample t test was used to compare groups. Data that did not conform to the normal distribution were expressed by the median (quartile) and compared between groups using the Mann-Whitney U test. For classified count data, χ^2 or Fisher exact test was used for intergroup comparison of declassified data and the Mann-WhitneyU test. $P < .05$ was considered to be statistically significant.

RESULTS

Serum and saliva test results for both groups

After treatment, the indexes improved in both groups; further comparison between groups, EGF (RR 0.41, 95% CI 0.15-0.73, $P < .001$), TNF-α (RR0.68 , 95% CI 0.53-0.77, $P = .003$), IL-10 (RR 0.64 , 95% CI 0.48-0.75, $P < .001$) and CRP (RR 0.52, 95% CI 0.35-0.65, $P < .001$) in the observation group after treatment were significantly lower than the control group, see Table 1.

Comparison of patient outcomes between the two groups

In the observation group, 17 cases were significantly effective, 20 cases were effective, the total number of effective cases was 37, and the total effective rate was 82.22%, which were significantly higher than the control group (RR 0.85, 95% CI 0.44-0.95, $P = .02$), see Table 2 and Figure 1.

Table 2. Serum and saliva test results

Group	Time	EGF (ng/mL)	TNF-α (mg/L)	IL-10 (ng/mL)	CRP (mg/L)
Observation group	Before treatment	5.45±0.87	36.24±4.76	18.76±3.75	10.67±2.91
	After treatment	2.46±0.47	16.42±2.72	11.52±2.75	4.52±1.67
Control group	Before treatment	5.38±0.78	36.43±4.51	18.45±3.62	10.81±2.76
	After treatment	3.17±0.61	18.45±3.47	15.34±2.67	6.21±1.37
T Comparison between groups before treatment		0.402	0.194	0.399	0.234
RR Between-group comparison before treatment		0.36 (0.04-3.29)	1.28 (0.39-4.24)	3.19 (0.13-6.42)	0.30 (0.11-2.62)
P Between-group comparison before treatment		0.689	0.846	0.691	0.815
T Observation group same group comparison		20.284	24.252	0.444	12.296
RR Observation group same group comparison		0.48 (0.31-0.78)	0.30 (0.14-0.61)	0.32 (0.11-0.56)	0.31 (0.09-0.60)
P Observation group same group comparison		0	0	0	0
T Control group same group comparison		14.982	21.196	4.638	10.616
RR Control group same group comparison		0.55 (0.41, 0.75)	0.29 (0.20, 0.56)	0.22 (0.11, 0.45)	0.34 (0.20, 0.59)
P Control group same group comparison		0	0	0	0
T Comparison between the groups after the treatment		6.185	3.089	6.686	5.248
RR Comparison between the groups after the treatment		0.41 (0.15, 0.73)	0.68 (0.53 to 0.77)	0.64 (0.48, 0.75)	0.52 (0.35, 0.65)
P Comparison between the groups after the treatment		0	0.003	0	0

Figure 1. Comparison of clinical efficacy between the two groups (A.The proportion of treatment effect in control group; B. The proportion of treatment effect in observation group. N=45)

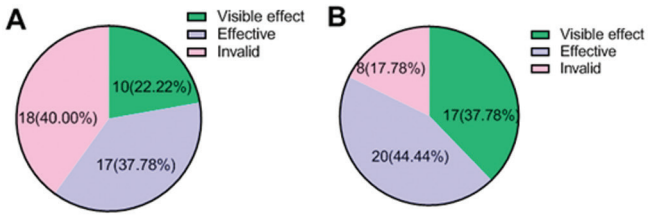


Table 3. Comparison of patient outcomes (cases)

Group	n	Visible effect (n,%)	Effective (n,%)	Invalid (n,%)	Total effective number of people(n,%)	Total effective rate (%)
Observation group	45	17(37.78)	20(44.44)	8(17.78)	37(82.22)	82.22
Control group	45	10(22.22)	17(37.78)	18(40.00)	27(60.00)	60
χ^2		5.409				-
RR (95%CI)		0.85(0.44, 0.95)				
P value		.020				-

Both group's Patients Quality of life scores

After treatment in both groups, the scores of OHIP-4 were better than before,; further comparison between groups, the scores of OHIP-4 (16.23±2.81) in the observation group after treatment were significantly lower than those in the control group (RR 0.61, 95% CI 0.47- 0.84, $P < .001$), see Table 3.

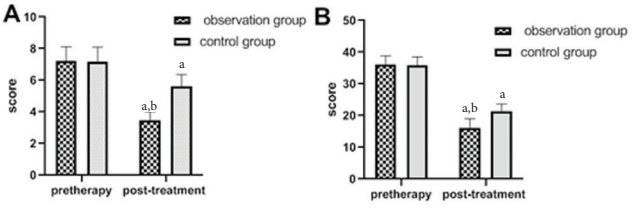
VAS scores of patients in both groups

In both groups, VAS was better after treatment; further comparison between groups, VAS score was (3.45±0.57) in the observation group after treatment, both significantly lower than the control group (RR 0.48, 95% CI 0.35-0.68, $P < .001$), see Table 4 and Figure 2.

Table 4. Patient quality of life scores

Group	Time	OHIP-14
Observation group	Before treatment	36.24±2.56
	After treatment	16.23±2.81
Control group	Before treatment	35.83±2.67
	After treatment	21.34±2.31
T Comparison between groups before treatment		.744
RR Comparison between groups before treatment		0.52(0.16, 1.42)
P Between-group comparison before treatment		.459
T Comparison of observation groups with the same group		35.312
RR Comparison of observation groups with the same group		0.38(0.20, 0.55)
P Observation group same group comparison		.000
T control group same group comparison		27.531
RR control group same group comparison		0.49(0.17, 0.66)
P Control group was compared with the same group		.000
T Comparison between the groups after the treatment		9.424
RR Comparison between the groups after the treatment		0.61(0.47, 0.84)
P Comparison between the groups after the treatment		.000

Figure 2. Comparison of quality of life between the two groups A. Comparison of VAS scores between the two groups; B. Comparison of OHIP-14 scores between the two groups. N=45



[a]Compared with before treatment, *P <.001;
[b]Compared with the control group, #P < .001.

Table 5. Patients' VAS scores

Group	Time	VAS
Observation group	Before treatment	7.24±0.87
	After treatment	3.45±0.57
Control group	Before treatment	7.18±0.91
	After treatment	5.64±0.72
T Comparison between groups before treatment		0.32
RR Comparison between groups before treatment		1.28(0.39, 4.23)
P Comparison between groups before treatment		.75
T Comparison of observation groups with the same group		24.444
RR Comparison of observation groups with the same group		0.28(0.13, 0.57)
P Observation group same group comparison		.00
T control group same group comparison		8.903
RR control group same group comparison		0.51(0.34, 0.74)
P control group same group comparison		.00
T Comparison between groups after t-treatment		15.998
RR Comparison between groups after t-treatment		0.48(0.35, 0.68)
P Comparison between groups after treatment		.00

Incidence of adverse reactions in both groups

In the observation group, there were 2 cases of dry mouth and 3 cases of loss of appetite; the total number of adverse reactions occurred in 5 cases, and the total incidence of adverse reactions was 11.11%, all significantly lower than the control group (RR 0.73, 95% CI 0.61- 0.86, P = .011), see Table 5.

Recurrence in both groups

The number of relapses in the observation group after one year of follow-up was 10, and the number of non-relapses was 35. The relapse rate was 22.22 %, significantly lower than that of the control group (RR 0.78, 95% CI 0.69-0.91, P = .015), see Table 6.

Table 6. Patient adverse reactions (cases)

Group	n	Nauseating (n, %)	Vomiting (n, %)	Dry mouth (n, %)	Loss of appetite (n, %)	Total number of adverse reactions (n,%)	Incidence of adverse reactions (%)
Observation group	45	0(0.00)	0(0.00)	2(4.44)	3(6.67)	5(11.11)	11.11
Control group	45	3(6.67)	3(6.67)	5(11.11)	4(8.89)	15(33.33)	33.33
χ^2		6.429					-
RR (95%CI)		0.73(0.61, 0.86)					
P		.011					-

Table 7. Patient relapses (cases)

Group	n	Number of relapses (n, %)	Number of people who did not relapse (n, %)	Recurrence rate (%)
Observation group	45	10(22.22)	35(77.78)	22.22
Control group	45	21(46.67)	24(53.33)	46.67
χ^2		5.954		-
RR (95%CI)		0.78(0.69, 0.91)		
P value		.015		-

DISCUSSION

Oral ulcer is a common disease in daily life, and its cause is very complicated. Some scholars believe that oral ulcers may be more closely related to the environment, including more significant mental pressure, disturbed work and rest, poor sleep quality, etc., thus causing abnormal body immune response and presenting ulcerative lesions of the oral mucosa.[16] At present, symptomatic treatment is mainly carried out in patients with this disease, and the healing of ulcer wounds is promoted by local oral medication. Recurrent chlorhexidine gargle contains chlorhexidine gluconate, which can expose the intracellular substances of bacteria and destroy bacteria to achieve the antibacterial effect. Using gargling liquid can make the drug entirely in contact with the wound to kill the pathogenic bacteria effectively. Mouthwash facilitates optimal contact of medications with wounds, effectively eradicating pathogenic bacteria and creating a conducive environment for wound recovery. However, it is not intended for targeted treatment of the underlying causes. Mouthwash has demonstrated certain efficacy in the treatment of recurrent oral ulcers; nevertheless, its impact on disease recurrence remains uncertain.[17]

Traditional Chinese medicine believes that oral ulcers are mainly caused by the deficiency of fire and Yin deficiency of the lungs and kidneys, so they should be treated with a fire source, nourishing Yin and clearing heat. Shuanghuanglian oral liquid is mainly made of scutellaria baicalensis, honeysuckle, forsythia, and other Chinese patent medicines, and the whole formula can play the effect of clearing heat and detoxifying, dissipating wind and resolving surface. Based on this, Shuanghuanglian oral liquid was applied to ROU in this study and showed an excellent therapeutic effect.

The results of this study showed that the effective rate of treatment in the observation group was significantly higher than that in the control group, indicating that Shuanghuanglian oral liquid has a better therapeutic effect in ROU patients. The main reason is that honeysuckle in Shuanghuanglian oral liquid has the effects of clearing heat, detoxifying, dispelling evil, cooling blood, and stopping interest.[18] Modern pharmacological studies show that honeysuckles can resist inflammation, resist pathogens, reduce blood lipids, kill

bacteria, and inhibit bacteria.[19] Forsythia has the effects of detoxification, clearing heat, and reducing swelling.[20] Scutellaria scutellaria has anti-inflammatory and anti-glory, improving the immune function of patients, effectively preventing mucosal infection, and accelerating the healing speed of ulcer surface[21] (The main bioactive compounds of Scutellaria baicalensis Georgi. for alleviation of inflammatory cytokines: A comprehensive review). Therefore, the treatment effect of patients in the observation group was more prominent.

Research has found that,[22] the EGF levels in the ROU patients with recurrent mouth ulcers are significantly higher than normal. This is related to the immune response the body generates to mouth ulcers and reflects the body's self-protection mechanism. When the level of EGF in saliva was increased, it indicated that the oral mucosa was damaged, and the body often responded by promoting EGF secretion and accelerating mucosal repair; when the mucosal repair was completed, or the oral ulcer was gradually healed, EGF secretion was reduced, which showed that EGF expression in patients with recurrent oral ulcers was closely related to mucosal damage and repair.[23]

According to the results of this study, the indexes of the two groups improved after treatment; further comparison between the groups showed that the EGF level in the observation group was significantly lower than that in the control group after treatment. This indicates that Shuanghuanglian Oral Liquid was able to lower the EGF level. The reason for this may be that Scutellaria baicalensis in Shuanghuanglian Oral Liquid can enhance the function of T lymphocytes, resulting in a significant increase in $CD4^+$, $CD4^+/CD8^+$, which leads to a rise in the level of TNF-α in the body, thus achieving the effect of regulating human immune function and reducing the level of EGF in saliva to a certain extent.

In Sun Xiaohu's study, it was found [24] that baicalin polysaccharide in Scutellaria baicalensis is an important active ingredient that enhances the body's immunity and inhibits the inflammatory response and plays a specific protective role. At the same time, baicalin polysaccharide can increase the TNF-α level and strengthen the affected organism's inhibitory and killing effect on bacteria.[25,26]

TNF-α and CRP are important indicators of the inflammatory response. TNF-α is an active cytokine induced by the inflammatory response and can play an early warning role in early inflammation. Some studies have shown that the level of TNF-α in the blood of patients with recurrent oral ulcers is significantly higher than the normal range, which is related to the immune dysfunction of the body due to recurrent oral ulcers and also suggests that the TNF-α factor is involved in the occurrence and development of recurrent ulcers.[27] Reports suggest that,[28] increased levels of the inflammatory factors TNF-α and CRP are risk factors contributing to the condition in patients with mouth ulcers; IL-10 can bind to the corresponding receptors, thus promoting the expression of a range of inflammatory factors and stimulating the development of ROU.

The results of this study found that the indexes of TNF-α, CRP, and IL-10 decreased to different degrees in both groups after treatment, and the degree of decrease was more obvious in the observation group, indicating that the development of inflammation was better controlled after the combination of drugs. At the same time, the clinical efficacy of the observation group was significantly better than that of the control group. In addition, the VAS and OHIP-4 scores of both groups were better after treatment. Still, the VAS scores of the observation group were significantly lower than those of the control group after treatment. This shows that Shuanghuanglian Oral Liquid can effectively reduce patients' inflammatory response, lessen their pain, and thus improve their quality of life. The possible reason for this is that the gold yinhua and forsythia in Shuanghuanglian Oral Liquid, through anti-NO activity and inhibition of TNF-α production, resulted in a reduction of inflammatory factors in the body, further making the body less inflammatory. Liang Xuejun et al.[29] found that honeysuckle had significant anti-NO activity and down-regulation of IL-1β, IL-6 and COX-2 mRNA expression. Meanwhile, honeysuckle significantly inhibited TNF-α-mediated proliferation of MES13 and significantly down-regulated IL-6 and MCP-1 expression in a dose-dependent relationship;[30-31] forsythia contains active ingredients such as forsythol and volatile oil, which have inhibitory effects on various pathogens, thus achieving antipyretic and anti-inflammatory effects. Tests in rat croton oily sarcomeres showed that forsythia extract had a significant anti-permeability impact when used in an intraperitoneal injection and reduced the fragility of the vascular wall at the site of inflammation without affecting the formation of the inflammatory barrier.[32] Also, the number of infiltrated erythrocytes in croton oil-based granulocytes was significantly reduced in 32P isotope-labeled erythrocyte assays, suggesting a facilitative effect of forsythia on the inflammatory response. The combined action of these active ingredients resulted in relief of the oral cavity's inflammatory condition, allowing the ulcerated tissue's redness to improve and the ulcerated surface to gradually repair, which in turn relieved pain, such as in ulcerated patients, and improved sleep and diet.

This study showed that the number of recurrences in the observation group was significantly lower than in the control group when the recurrences were counted after a one-year follow-up. At the same time, adverse reactions in the treatment were also significantly lower in the observation group than in the control group. It demonstrated that the topical treatment of recurrent oral ulcers with Shuang Huang Lian Oral Liquid could effectively reduce the recurrence rate and had higher safety and efficacy compared with the general conventional treatment. The reason for this analysis was that the combination of Scutellaria baicalensis-Lian Qiao could greatly improve the inhibitory effect on inflammatory factors, significantly reducing the recurrence rate of oral ulcers in patients. Dai and Sen et al.[33] showed that by analyzing the drug I component target network of Scutellaria baicalensis-Lian Qiao for treating severe pneumonia, quercetin and lignocaine were the components with higher activity. Quercetin significantly inhibited the hemolytic and cytotoxic effects caused by

Streptococcus pneumoniae hemolysin (PLY), greatly reduced PLY-induced cell damage, and inhibited the release of inflammatory factors such as IL-1β and TNF-α. It could also limit bacterial growth by promoting cellular oxidative stress and reducing local L-tryptophan availability through activation of the kynurenine pathway; lignocaine could inhibit LPS-induced expression of miR-132 in BEAS-2B cells, reducing LPS-induced apoptosis in BEAS-2B cells and decreasing the release of inflammatory factors, thereby alleviating the inflammatory response induced by LPS.

CONCLUSION

In conclusion, the active ingredients in Shuanghuanglian Oral Liquid, such as Scutellaria baicalensis, forsythia, and jinyinhua, can inhibit the release of inflammatory factors and other factors and improve the immune function of patients, thus achieving the effects of anti-inflammatory and pain relief and promoting the recovery of wounds. In contrast, the incidence of adverse effects is low, representing a better safety of this type of treatment. EGF level in saliva is an important regulatory factor in oral mucosa's repair and healing process. This study evaluated the influence of Shuanghuanglian oral liquid on the EGF level of the oral mucosa, which also provided a new perspective for treating oral ulcers to a certain extent. At the same time, inflammatory factors are closely related to the occurrence and development of oral ulcers. This study also provides new evidence for understanding the anti-inflammatory effects of Shuanghuanglian oral liquid in terms of the influence of inflammatory factors on serum. In addition, this study adopted the method of clinical experiment to evaluate the effect of Shuanghuanglian oral liquid in treating patients with recurrent oral ulcers. It provided a basis for the clinical selection of an appropriate treatment plan.

However, this study still has some shortcomings: (1) The sample size used in this study is small, which may affect the reliability and generalization of the results; (2) This study adopted a single-blind randomized controlled trial design, but not a double-blind randomized controlled trial design, which may introduce bias; (3) This study did not compare Shuanghuanglian oral liquid with other standard oral ulcer treatment methods, so it is impossible to evaluate its advantages and disadvantages in clinical practice. Therefore, in future studies, the following improvements can be considered to make the research results more comprehensive and reasonable: (1) To improve the reliability and popularization of the research results, the following experiments need to expand the sample size and increase the statistical efficacy of the research; (2) The study adopted a double-blind, randomized controlled trial design to reduce the influence of experimental errors and biases; (3) Through an in-depth understanding of the mechanism of Shuanghuanglian oral liquid, to explore more potential effects on the treatment of oral ulcer; (4) Compare and analyze Shuanghuanglian oral liquid with other common oral ulcer treatment methods to evaluate its advantages and disadvantages in clinical practice.

DISCLOSURE STATEMENT

The authors declare that they have no competing interests.

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DATA SHARING

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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