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The Therapeutic Effect of Herbal Composition of *Scutellaria baicalensis* and *Eleutherococcus senticosus* in Patients with Recurrent Aphthous Stomatitis: A Randomized Controlled Trial

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ABSTRACT

Objective: *This study aimed at assessing the therapeutic effect of herbal composition of Scutellaria baicalensis and Eleutherococcus senticosus (SB-ES drug) on recurrent aphthous stomatitis (RAS).* ***Methods and materials:*** *The study was a placebo-controlled, double blind, randomized trial with one year follow-up after the treatment. 68 subjects (36 in study group, 32 in placebo group) attended the final follow-up. The active and placebo drugs were administered for 20 consecutive days to study group and placebo group, respectively. After a year, the responses of the patients to treatment efficacy (subjective changes at the end of study, adverse effect), the reductions in ulcer symptoms (frequency, pain score, size, duration of ulcers) were assessed.* ***Results:*** *Many patients (78%) from study group reported that their RAS was better than before the treatment. The adverse effects (diarrhea, constipation) were also reported in most of the patients in study group, and these were improved by combined use of antacids or laxatives during the period of treatment or cessation of taking drugs. And after a year, there were marked reductions (more than 50%) in frequency, pain score, size and duration of ulcers in study group and the differences between groups or between before and after study were statistically significant ($p<0.001$).* ***Conclusion:*** *According to 1-year study we conducted, the use of SB-ES drug can markedly improve the main symptoms of RAS (frequency and pain of ulcers) when used at a dose of 5 tablets, trice daily for 20 consecutive days in RAS patients.*

Keywords: Scutellaria Baicalensis, Eleutherococcus Senticosus, Herbal Drug, RAS, Pain Relief, Frequency Of Episode

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INTRODUCTION

Recurrent aphthous stomatitis(RAS) is one of the most common diseases characterized by painful, recurrent ulcerations of oral mucosa, which can be seen in both sexes of all ages and races.[1,2] The disease affects approximately 5 to 25% of the population in their lives.[3] The ulceration usually lasts 7 to 14 days and heals spontaneously without scar.[4] Ulcer-free period lasting a few weeks or months may exist between episodes and this period may be only a few days in severe cases.[5] Although many possible causative factors of RAS have been proposed including genetic factors, hypersensitivity, socio-economic status, stress,

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endocrine disorders and infectious agents, the etiology still remains unclear.[6,7]

There have been a lot of efforts to apply different systemic drugs such as levamisole, colchicine, thalidomide, dapsone, azathioprine, prednisolone and pentoxifylline for the treatment of RAS.[8-13]

Although many researchers have reported therapeutic effects of those drugs on RAS, the effects of these drugs are mainly limited to the palliation of symptoms and only a few data is available relating to the inhibitory effect on recurrence. Furthermore, several researchers have suggested that some drugs such as levamisole, colchicine, thalidomide, dapsone and pentoxifylline are less effective in short-term uses, while long-term uses cause severe side effects, leading to the challenge to the drug selection.[14-17]

Most of these drugs are thought to be immunomodulatory or immunosuppressive drugs. A Cochrane review showed that there are currently no recommendations for use of any particular systemic agent in the treatment of RAS.[18] The role of autoimmune response in the development of RAS was first suggested in the 1960s[19] and the accepted current hypothesis is that triggers release from normal suppression of an autoimmunity against oral mucosa in susceptible patients exposed to an unidentified infective or other agents. In most RAS patients, antibodies against epithelium, which are cytotoxic to oral epithelium, can be found[20].

The impairment of immune system is thought to be one of the etiologic factors associated with the development of RAS. The function of immune system is altered in response to unknown trigger such as bacterial, viral antigens and stress in patient with RAS. Many authors believe that the type1 helper T cell response plays the most important role in the development of RAS.[21,22]

Scutellaria baicalensis (SB) extract also contains 63 kinds of flavonoids and amino acids, soluble polysaccharides, minerals etc.[23] Others reported that S. baicalensis had significant anti-inflammatory effect because it inhibits NF-κB pathway.[24,25]

It was also found that SB had potent anti-inflammatory activity through the MAP kinase pathway.[26]

Some researchers[27,28] reported that SB modulated immune responses by influencing IL-5, IL-10 level, inhibited PG E_2 generation and suppressed the expression of COX-2, IL-1β in the skin-inflammation model. SB was the most frequently used herbal agent combined with other herbal compounds for the treatment of mouth sores in ancient Chinese medicine.[29,30] Meanwhile, *Eleutherococcus senticosus* (ES) can inhibit mast cell-mediated anaphylaxis in animal model and block transcription pathways in macrophages.[31,32] ES can also markedly inhibit the phosphorylation of early signaling pathway such as NF-κB and MAPKs activity.[33]

It has been demonstrated that the combined use of ES and other herbal agents could reduce the severity and duration of infection.[34] These data suggest that SB and ES have significant immunomodulatory effects. As the corticosteroid hormones are the first choice drugs in the treatment of RAS and the drugs used in the treatment of RAS such as levamisole, colchicine, thalidomide, dapsone, azathioprine, and pentoxifylline, also have immunomodulatory or immunosuppressant effects, we assumed that combined use of SB and ES might be effective in the treatment of RAS because of its strong immunosuppressive property.

Based on these data, we developed new medicine, SB-ES drug containing herbal extracts of SB and ES, available to the treatment of recurrent aphthous ulcer. To our knowledge, no randomized controlled trial has been reported for the use of SB, ES alone, or combined use of them in the treatment of RAS. The aim of this study was, therefore, to clarify the efficacy of this drug in the treatment of the

patients with RAS in a randomized controlled trial. The null hypothesis to be tested was that there was no difference between the study (SB-ES drug) group and the control (placebo) group in the treatment efficacy of RAS.

METHOD AND MATERIALS

Study design and ethical approval

The study was a placebo-controlled, double-blind, randomized trial to assess the efficacy of SB-ES drug in patients with severe recurrent aphthous ulcers. It was reviewed and approved in March 2018 by the Ethics Board of the Health Office in Pyongyang People's committee(No:17/2018).

Sample size calculation

The key parameter for the assessment was reduction rate of frequency of episodes in a year. Considering the difference of more than 0.2 in reduction rate of the frequency of episodes in a year between groups to be clinically significant, 26 subjects were needed in each group at 5% statistical significant level and 80% power of the study. Expecting the attrition rate to be 20% in a year, the number was inflated to 32 per each.

Participants/inclusion criteria and recruitment

This study was conducted with reference to the methods described by some authors.[13]

Pretrial phase

The patients with RAS who read the advertisement of SB-ES drug on Health Website of National Network and agreed to participate in the study were scheduled for an appointment at the dental department of affiliated hospital, Pyongyang University of Medical Sciences. And those who visited the department for the treatment of their RAS and willed to participate were also included in the study. For these patients, eligibility assessments were performed. The criteria for assessing eligibility included following: (1) the patient who underwent at least more than 2 episodes of ulcer every month over 6 months, (2) the patient who was willing to stop current treatment for ulcer, (3) the subjects aged 16 to 75, (4) the subjects with no digestive diseases (gastro-intestinal cancer, acute gastritis, pancreatitis, gastric ulcer) and Behcet's syndrome, pellagra, (5) the subjects who hadn't taken any systemic drugs such as steroid hormones, (6) the subject with no pregnancy or lactation, (7) the subjects who wasn't allergic to study drug. The pretrial phase of study aimed at 1) assessing the eligibility of participants, 2) collecting the baseline data on ulceration.

On the first visit, the study was explained to every patient who signed consent form in more detail. Oral examination and investigation of family history of RAS for every patient were performed. Every patient was taught for self-examination and given a standardized record that needed to self-record the characteristics of new ulcer lesion throughout the study.

The characteristics of ulcers included the following: (1) Frequency of ulcers (number of new episodes per month), (2) Pain score (the number recorded at the peak of each ulcer episode on a scale of 0-10 using a visual analogue scale where 0 indicates no pain and 10 indicates the worst pain ever experienced with oral ulcers), (3) Size of ulcer (assessed at the peak of each ulcer episode by comparing ulcer size to a chart showing 6 circles of increasing diameter between 1 and 10mm and numbered 1 to 6, respectively.), (4) Duration of ulcer (determined from the day of onset of first prodromal sign of each ulcer).

After the 30 days' of pretrial period, patients were asked to visit the department again. On the 2nd visit (30th day), the patients were reexamined. Those who did not provide the satisfactory record, whose ulceration pattern didn't meet the eligible criteria, were excluded from the study.

Trial phase

The patients who reached the eligible criteria participated in the trial phase. Study planning and benefit from study, possible side

effect, possibility that might be allocated to placebo group were explained to all participants. Then written consents were obtained. Participants were asked to continue to record information throughout trial phase of the study (consisted of 20-day treatment and 12-month observation period). And they were also asked to record the side effect during trial phase.

The participants who completed the trial phase were then asked to visit the hospital once more for the follow-up investigation. On the 3rd visit, consultation with participants was performed to assess the responses of the patients to the results of the treatment. Feelings on the efficacy of treatment and the possible adverse effects during the trial phase were discussed. And the changes of ulcer symptoms after the study were analyzed using the data collected from their records.

Medication and randomization of participants

SB-ES drugs (Hwanggum aphtha capsule, Pyongyang) were prepared at Koryo medicine pharmacy of the hospital. Placebo drug, containing starch, was also prepared as identical capsules. The patients were instructed to take 5 capsules three times daily after meal for 20 consecutive days and not to take any other drugs.

The participants were allocated trial number serially as they participated in the study. The dispensing of active drug or placebo was randomized at pharmacy using computer generated random number. The identical bottles labeled with trial number in which contained 300 capsules of active drug or placebo were given to participants. The pharmacy didn't release the computer-generated key showing what had been dispensed to each patient until the study had been completed. Therefore, the study was double-blinded.

Statistical analysis

The data was analyzed using the software SPSS for windows version 16.0. The differences in demographic characteristics between study group and placebo group were tested by Student-t test for age, Pearson chi-square test for sex and family history.

Pearson chi-square test was then used for analyzing the responses of the patients to the treatment efficacy. The changes of ulcer symptoms after 1 year were assessed based on the variations noted in the frequency, pain, size, duration of ulcers in comparison with the baseline data. Quantitative variables are expressed as mean±SD. And the improvement rate of symptom (*% change*) was calculated by the following formula.

% change = (value before treatment－value at the end of study)/value before treatment

For all the above mentioned parameters, the intra-, inter-group comparisons were performed using Mann-Whitney U-test.

RESULTS

Participants of the study

The flowchart of participants in the study is shown in the Fig. 1., 117 patients who responded to advertisement of the study drug on "Health" website of national network or visited dental department of affiliated hospital of Pyongyang University of Medical Sciences for the treatment of RAS during the period from May 2018 to April 2022 were assessed for the eligibility. On the 1st visit, of these 117 people, 31 patients were excluded from the study.

The reasons for exclusion were as follows: fewer than 2 ulcers per month within 6 months in his/her complaint (n=14), gastro-intestinal disorders (n=5), pellagra (n=1), Behcet's syndrome (n=3), pregnancy (n=1), the refusal to participate in the study (n=7). Therefore, 86 patients were enrolled in the pretrial phase of study. On the 2nd visit, 8 people were excluded from the study. Of 8 people excluded, 5 didn't successfully complete the record and 3 failed to attend the 2nd appointment. Thus, 78 patients participated in the trial phase of study.

At this phase of study, 10 participants were unable to follow-up investigation after randomization; 3 in study group, 7 in placebo group. The reasons for loss to follow-up were as follows: giving up filling in the record (2 in study group, 3 in placebo group), failing to attend (1 in study group, 4 in placebo group). Among 78 patients randomized, 68 people (87.18% of all the patients randomized) attended the final follow-up investigation and were included in both groups to be analyzed. The loss rate to follow-up was 12.82%.

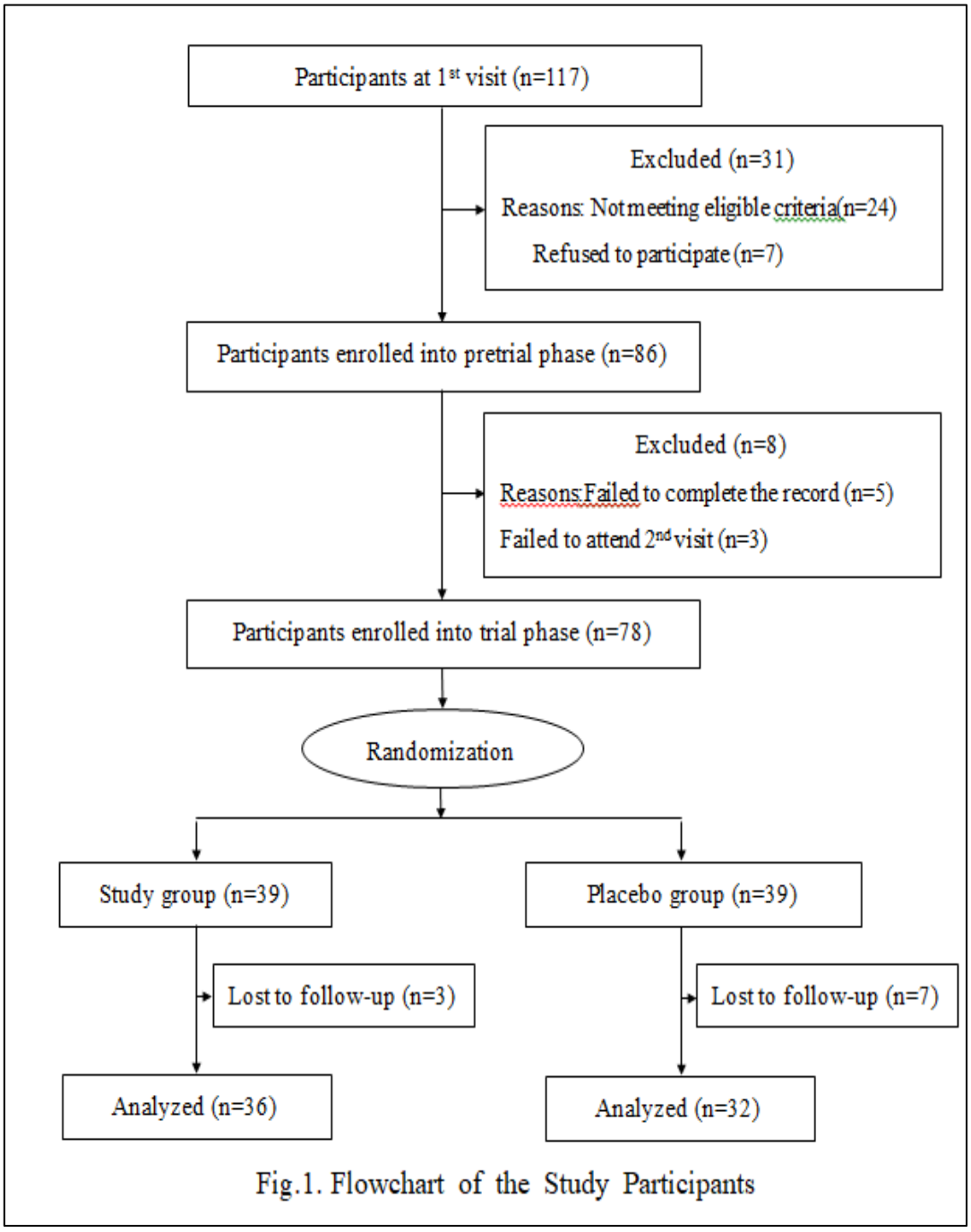

Fig.1. Flowchart of the Study Participants

Table 1. Demographic data of participants at the end of trial phase of the study

Group	Age	Sex		Family History	
	Mean±SD(range), year	Male	Female	Yes	No
Study(n=36)	43.19±15.53(16-74)	11 (30.6%)	25 (69.4%)	27 (75.0%)	9 (25.0%)
Placebo(n=32)	41.34±13.55(18-65)	8 (25.0%)	24 (75.0%)	25 (78.1%)	7 (21.9%)
P value	.602	.610		.761	
Total(n=68)	42.32±14.54(16-74)	19	49	52	16

Table 1 presents the demographic characteristics of both groups analyzed at the end of the study. Among the total of 68 patients analyzed at the end of trial phase, 49(72.1%) were female patients and only 19 (27.9%) were males. Mean age of the patients was 42 years, and 52 patients (77%) reported family history of RAS. No statistically significant differences ($p>0.01$) were found regarding age, sex, family history between study and placebo group.

Response of the participants to treatment efficacy

The patients' responses to the treatment efficacy were evaluated based on consultation data with them at the end of the trial phase.[13] The results are shown in Table 2.

Table 2. The response of the participants to treatment efficacy

parameter	Study group (n=36)	Placebo group (n=32)	P value
Subjective changes at the end of study(ie, feeling on the efficacy of treatment)			
Cure	9(25.0%)	0	<.001
A lot better	17(47.2%)	0	
A little better	2(5.6%)	5(15.6%)	
No difference	8(22.2%)	23(71.9%)	
A little worse	0	4(12.5%)	
A lot worse	0	0	
Adverse effect			
Yes	32(88.9%)	3(9.4%)	<.001
No	4(11.1%)	29(90.6%)	

Much more participants taking study drug believed their RAS was better during the trial phase compared with those taking placebo. 9 out of 36 patients reported that no ulcer lesion developed during the trial phase. For about 78% (28 out of 36) of patients taking study drugs, the improvement of symptom was considered to be substantial. Meanwhile, most of the patients included in placebo group reported no improvement (23 out of 32) or

worsening (4 out of 32) in their symptoms. Most of patients (32 out of 36) in study group complained of adverse effects during the period of taking active drugs. (Table 2) The most common adverse effect was mild diarrhea accompanied by discomfort of abdomen (n=27). Constipation (n=5) was also reported to be another adverse effect.

Changes of ulcer symptoms in both groups before and after study

The changes of ulcer symptoms (frequency, pain score, duration, size of ulcers) at baseline and at the end of study are shown in table 3.

Table 3. Changes of ulcer symptoms in both groups before and after study

parameter	Study group (n=36)	Placebo group (n=32)	P_2 value
Frequency of ulcer(mean ±SD)			
Baseline	2.67±0.48	2.53±0.51	.258
1 year later	1.17±1.07	2.28±0.63	<.001
% change	56.2%	9.9%	
P_1 value	<.001	.120	
Pain score of ulcer(mean ±SD)			
Baseline	8.64±0.90	8.56±1.04	.901
1 year later	3.58±3.07	8.19±1.80	<.001
% change	58.6%	4.3%	
P_1 value	<.001	.707	
Duration of ulcers(mean ±SD, days)			
Baseline	13.14±5.65	13.22±5.17	.919
1 year later	6.39±5.53	12.44±5.09	<.001
% change	51.4%	5.9%	
P_1 value	<.001	.673	
Size of ulcers(mean ±SD, mm)			
Baseline	5.14±2.91	5.47±2.59	.523
1 year later	1.79±1.55	5.03±2.32	<.001
% change	65.2%	8.0%	
P_1 value	<.001	.515	

P_1 value: p value of intragroup comparison, P_2 value: p value of intergroup comparison

The results revealed that there were marked reductions (more than 50%) in frequency, pain score, duration, size of ulcers at the end of study compared with those at baseline in study group ($p<0.001$), while the placebo group showed insignificant reductions. On comparisons between study and placebo group, there were no significant differences in ulcer symptoms at baseline, however, significant differences were found at the end of study ($p<0.001$).

DISCUSSION

Recurrent aphthous ulcer is known to be one of the most prevalent oral mucosal diseases, and the exact etiology of RAS remains unclear.[1,2] Current therapies for RAS do not yield the satisfactory results. The effects of drugs used in the treatments of RAS are mainly limited to the improvement of symptoms, and most of these drugs are associated with severe long-term adverse effect.

Some authors suggested that some treatments using traditional herbal extracts may be effective in the treatment of RAS, although high quality studies would be necessary to confirm those findings.[35] And according to a systematic review with meta-analyses of natural products in the treatment of RAS, the treatment by some natural products seemed to reduce pain and size of ulcers with low to moderate quality of evidence.[36]

Scutellaria baicalensis, a traditional medicinal plant of China, has been used against microbial infections of respiratory organ and gastrointestinal tract, cancer and brain disorder over the last 2000 years.[29,37] Meanwhile, *Eleutherococcus senticosus*, another one of the traditional medicines of China, also known as "Siberian ginseng" in Russia, are native to Eastern Asia, the Himalayas, and Northeastern Russia.[34] It has been reported ES elicit effects on inflammation.

No clinical study on combined use of SB and ES in the treatment of RAS has been found in the literature. Therefore, this double-blind, randomized placebo-controlled trial was conducted to evaluate the efficacy of SB-ES drug in the treatment of patients with RAS.

Little information on the exclusion criteria used for patient selection was given. Hence, we selected exclusion criteria through our preliminary study. According to our preliminary study, many patients taking study drugs complained of indigestion. Therefore, RAS patients with severe gastro-intestinal disorders were excluded from the study. And those taking systemic drugs such as glucocorticoids were also excluded because they might influence the outcome of study. The patients with Pellagra, Behcet's syndrome were also excluded from the study because of lack of therapeutic efficacy.

Our preliminary study also showed that the use of a high dose of study drugs for 20 consecutive days was most effective in the treatment of RAS. Therefore, we set the treatment period to 20 days and the daily dose of 5 capsules 3 times daily.

Demographic analysis for the study population showed that there were no differences between study and placebo group in terms of age, sex, and family history (table 1). A study[13] reported that 62% of patients with RAS participated in the study had at least 1 other family member with a history of RAS. According to our result, the proportion of patients with family history of RAS was 77.9%, which was higher than that of above study.

Response of the participants to treatment efficacy

In the present study, we evaluated the effects of this drug on improvement of RAS symptom through consultation with patients at the end of the study to examine the response of patients to treatment efficacy. Now, no consistent criteria for assessment of treatment efficacy have been established. Therefore, in this study, we considered the parameter "patient response" described by some authors[13] as one of important indices reflecting the efficacy of drug. We finally analyzed the association between patients' responses to treatment efficacy and the changes of ulcer symptoms. According to the analysis, the patients that reported "cure" were all ones with no ulcer during trial phase, and "a lot better" were strongly associated with a

marked decrease in the frequency of ulcers with reduction of ulcer pain score, size and duration. And "a little better" were associated with reduction of pain score, size and duration without any change of frequency of ulcers. Whether this will be a criterion for evaluating the effect of drug will be discussed further. According to the results of the study (table 2), 28 out of 36 participants (78%) in the study group reported that their symptoms were improved before the treatment. Among 9 patients in the study group that reported no onset of ulcer during the trial phase of study, one patient didn't have any ulcer lesion for 3 years and 8 months after administration of drug (administered in 2018) and other one (administered in 2019) for 2 years and 3 months, another one for 18 months. This proportion is also expected to increase as the observation period increases. It is considered a very positive result that not even one episode occurred for more than 1 year in many patients who had more than 2 episodes per month before the treatment. No patient in the study group complained that the symptoms were worse than before the treatment.

Most drugs used in the treatment of RAS are associated with serious short term, long-term adverse effects that limit their use.[8-13] The majority of patients (88.9%) included in the study group complained of adverse effects during the periods of drug use. (table2) The main adverse effect complained by patients was indigestion. But, the patients reported that these adverse effects were deemed well tolerable. In cases with severe side effect, the gastrointestinal symptoms could be alleviated by the combined use of antacids or laxatives during the period of taking drugs or by cessation of taking active drugs.

Changes of ulcer symptoms in both groups before and after study

One of the ulcer symptoms that showed the most significant improvements in our study was the frequency of ulcers. Several studies[8-13, 38] have reported decreases in frequencies of ulcers in their patients following the use of different drugs. However, the observation periods of most of these studies were less than 6 months. In the study, we evaluated the long-term effect of this therapy by setting the follow-up period to 1 year. Our results (table 2) showed a significant decrease in the frequency of ulcers at the end of the study compared to before the treatment in the study group ($p<0.001$). And no significant difference was found in the frequency of ulcers in both groups at baseline, but there was significant reduction in the frequency of ulcers in study group after 1 year compared to that of placebo group ($p<0.001$). The percentage reduction of study group was 56.2%.

Pain is the main reason why patients with RAS visit the hospital and reducing pain is an important goal of treatment. In our study, the treatment by active drug achieved the satisfactory goal by the significant reduction in pain score after treatment ($P<0.001$). However, the placebo group didn't show any statistically significant pain reduction. Several researchers reported reduction of pain score when used the some drugs such as pentoxifylline, levamisole etc.[13-16] And it has been reported that combination of levamisole and prednisolone (immunosuppression and anti-inflammatory) showed more reduction in pain score than levamisole used alone (38%, 33%, respectively).[38]

According to our results, the percentage reduction of pain score in the study group after study compared to before the study was 58.6%, showing more reduction than above-mentioned study. The average size of ulcers recorded at the peak of each ulcer episode was significantly decreased in the study group at the end of study (table2, $p<0.001$). And statistically significant difference ($p<0.001$) in ulcer size was also seen between both groups after the completion of study. And marked reduction in the duration of ulcers before

study and after the completion of study was also seen in study group (table 2).

Some researchers demonstrated in an ex vivo human nasal mucosal model that combination of SB, ES, Vitamin C could block allergic early and late phase mediators and significantly suppress the release of proinflammatory, Th1-, Th2, Th17- derived cytokines, which was at least comparable to a topical corticosteroid.[39] And it has been found that SB and ES herbal nasal spray could relieve nasal congestion in a mucosal model and in clinic. They suggested that this spray can be potentially used in acute and chronic sinusitis, allergic rhinitis, viral infections of upper respiratory tract.[40] With reference to these facts, the efficacy of SB-ES drugs on RAS seemed to be due to the combination of immunosuppressive effects and other pharmacological effects of both herbal compounds.

The limitations of the study were that application methods (dose and frequency of drug application, etc.) in relapsed patients who were not cured was not established, and the long term effects of the drug for more than 1 year were not elucidated.

CONCLUSION

According to this 1-year study, the use of SB-ES drugs can markedly improve the main symptoms of RAS (frequency and pain of ulcers) when used at a dose of 5 tablets, trice daily for 20 consecutive days in RAS patients with no digestive disease, or Behcet syndromes, or pellagra. Further studies are needed to evaluate the long-term effect of the drug, and to compare with other drugs for the treatment of recurrent aphthous stomatitis.

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REFERENCES

1. Porter SR, Scully C, Pedersen A. Recurrent aphthous stomatitis. Crit Rev Oral Biol Med. 1998;9:306-321.
2. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol. 1993;129:92-96.
3. Slebioda Z, Szponar E, Kowalska A. Recurrent aphthous stomatitis: genetic aspects of etiology. PostepyDermatol Alergol.2013;30:96-102.
4. Rogers RS III: Recurrent aphthous stomatitis: Clinical characteristics and associated systemic disorders. SeminCutan Med Surg 1997;16:278-283.
5. Akintoye SO and Greenberg MS: Recurrent aphthous stomatitis. Dent Clin North Am 2014;58:281-297.
6. Reich RF, Kerpel SM, Freedman PD. Differential diagnosis and treatment of ulcerative, erosive, and vesiculobullous lesions of the oral mucosa. Oral and Maxillofacial Surgery Clinics of North America 1998;10:95-101.
7. Chavan M, Jain H, Diwan N, Khedkar S, Shete A, Durkar S. Recurrent aphthous stomatitis: a review. J Oral Pathol Med 2012; 41: 577-583.
8. Gil H, Perrin S, Dupond J-L, Meaux-Ruault N, Hafsaoui C, Limat S, Magy-Bertrand N. Recurrent aphthosis: Safety of low dose thalidomide. La Revue de médecine interne 2010;31:403-405.
9. Lynde CB, Bruce AJ, Rogers RS 3rd. Successful Treatment of Complex Aphthosis With Colchicine and Dapsone. Arch Dermatol 2009;145:273-276.
10. Handfield-Jones S, Allen BR, Littlewood SM. Dapsone use in oral genital ulcers. Br J Dermatol 1985;113:501.
11. Sharda N, Shashikanth MC, Kant P, Jain M. Levamisole and low-dose prednisolone in

the treatment of recurrent aphthous stomatitis. J Oral Pathol Med 2014;43:309-316.
12. Brown RS, Bottomley WK. Combination an immunosuppressant and topical steroids therapy for treatment of recurrent major aphthae. Oral Surg Oral Med Oral Pathol 1990;69:42-44.
13. Thornhill MH, Baccaglini L, Theaker E, Pemberton MN. A randomized, double-blind, placebo-controlled trial of pentoxifylline for the treatment of recurrent aphthous stomatitis. Arch Dermatol 2007;143:463-470.
14. Belenguer-Guallar I, Jiménez-Soriano Y, Claramunt-Lozano A. Treatment of recurrent aphthous stomatitis. A literature review. J Clin Exp Dent 2014;6:E168-174.
15. Challacombe SJ, Alsahaf S, Tappuni A. Recurrent Aphthous Stomatitis: Towards Evidence -Based Treatment? Curr Oral Health Rep 2015;2:158-167.
16. Sánchez J, Conejero C, Conejero R. Recurrent Aphthous Stomatitis. Actas Dermosifiliogr 2020;111:471-480.
17. Scully C, Porter S. Oral mucosal disease: Recurrent aphthous stomatitis. British Journal of Oral and Maxillofacial Surgery 2008;46:198-206.
18. Brocklehurst P, Tickle M, Glenny AM. Systemic interventions for recurrent aphthous stomatitis (mouth ulcers). Cochrane Database Syst Rev 2012;9:CD005411.pub2.
19. Lehner T. Autoimmunity in oral diseases, with special reference to recurrent oral ulceration. Proc R Soc Med 1968;61:515-524.
20. Thomas DW, Bagg J, Walker DM. Characterization of the effectorcells responsible for the in vitro cytotoxicity of blood leukocytes from aphthous ulcer patients for oral epithelial cells. Gut 1990;31:294-299.
21.Buno IJ, Huff C, Weston WL, Cook DT, Brice SL. Elevated levels of interferon gamma, tumor necrosis factor a, interleukins 2, 4, and 5, but not interleukin 10, are present in recurrent aphthousstomatitis. Arch Dermatol 1998;134:827-831.
22.Albanidou-Farmaki E, Markopoulos AK, Kalogerakou F, Antoniades DZ. Detection, enumeration and characterization of T helper cells secreting type 1 and type 2 cytokines in patients with recurrent aphthous stomatitis. Tohoku J Exp Med 2007;212:101-105.
23.Zhao T, Tang H, Xie L, Zheng Y, Ma Z, Sun Q, Li X. Scutellaria baicalensis Georgi. (Lamiaceae): A Review of Its Traditional Uses, Botany, Phytochemistry, Pharmacology and Toxicology. J Pharm Pharmacol 2019;71:1353-1369.
24.Caiyun H, Yubo W, Ning J, Xin Z, Kai Q, Xiangshu P, Jingdong Y. The involvement of NF-K B/P38 pathways in Scutellaria baicalensis extracts attenuating of Escherichia coli K88-induced acute intestinal injury in weaned piglets. British J of Nutrition 2019;122:152-161.
25. Lixuan Z, Jingcheng D, Wenqin Y, Jianhua H, Baojun L, Xiaotao F. Baicalin attenuates inflammation by inhibiting NF-kappaB activation in cigarette smoke induced inflammatory models. Pulmonary Pharmacology and Therapeutics 2010;23: 411-419.
26. Kim EH, Shim B, Kang S. Anti-inflammatory effects of Scutellaria baicalensis extract via suppression of immune modulators and MAP kinase signaling molecules. J of Ethnopharmacol 2009;126:320-331.
27. Kim J, Lee IS, Park S, Choue R. Effects of Scutellariae radix and Aloe vera gel extracts on immunoglobulin E and cytokine levels in atopic dermatitis NC/Nga mice. J Ethnopharmacol 2010;132:529-532.
28. Lim H, Son KH, Chang HW, Kang SS, Kim HP. Inhibition of chronic skin inflammation by topical antiinflammatory flavonoid preparation, Ato Formula. Arch Pharm Res 2006;29:503-507.
29.Rui X, Hui D. Data Mining-Based Research on the Prescriptions of Ancient Chinese Medicine Prescription Book Type Documents

for Mouth Sores. MEDS Chinese Med 2022;4:40-46.
30.Magdalena O , Paweł N , Xymena S , Anna S, Małgorzata M. Mixtures of Scutellaria baicalensis and Glycyrrhiza L. Extracts as Antibacterial and Antiviral Agents in Active Coatings Coatings 2021;11:1438-1459.
31. Yi JM, Hong SH, Kim JH, Kim HK, Song HJ, Kim HM. Effect of Acanthopanax senticosus stemonmast cell dependent anaphylaxis. J Ethnopharmacol 2002;79:347-352.
32. Jung CH, Jung H, Shin YC. Eleutherococcus senticosus extract attenuates LPS-induced iNOS expression through the inhibition of Akt and JNK pathways in murine macrophage. J Ethnopharmacol 2007;113:183-187. 33.Xiaobin Y, Zhem C, Rui M, Hua G, Qingpeng Z, Xiaodong W, Lingbo K,Dingjun H. Eleutherococcus senticosus Inhibits RANKL-induced osteoclast formation by attenuating the NF-KB and MAPKs signaling pathway. Int J Clin Exp Pathol 2017;10:4514-4521
33. Kulichenko LL, Kireyeva LV, Malyshkina EN, Wikman G. A randomized, controlled study of Kan Jang versus amantadine in the treatment of influenza in Volgograd. J Herbal Pharmacotherapy 2003;3:77-93.
34. Zhou P, Mao Q, Hua H, Liu X, Yan Z. Efficacy and safety of Chinese patent medicines in the treatment of recurrent aphthous stomatitis: a systematic review. J Am Dent Assoc 2017;148:17-25.
35. Katherine SP, Wallace CCM, Joeseph MP, Kamal AE, Reyes E. Systematic Review with Meta-Analyses of Natural Products in the Treatment of Recurrent Aphthous Stomatitis Int J Oral Dent Health 2019;103:1-17.
36. Zhao Q, Chen XY, Martin C. Scutellaria Baicalensis, the Golden Herb from the Garden of Chinese Medicinal Plants. Sci. Bull. 2016;61:1391-1398.
37. Neelkamal S, Shashikanth MC, Priyanka K, Manika J. Levamisole and low-dose prednisolone in the treatment of reccurent aphthous stomatitis. J Oral Pathol Med 2014;43: 309-316.
38. Nan Zh, Koen VC, Gabriele H, Claus B. A Herbal Composition of Scutellaria baicalensis and Eleutherococcus senticosus Shows Potent Anti-Inflammatory Effects in an Ex Vivo Human Mucosal Tissue Model. Evidence-Based Complementary and Alternative Medicine 2012;Article ID 673145:1-9.
39. Michael K, Van Crombruggen K, Holtappels G, Kuhn FA, Fichandler CE,Kuhn-Glendye CA, Anon JB, Melroy CT, Karanfilov B, Haegen TW, Kastanioudakis I, Bachert C, Zhang N.A herbal composition of Scutellaria baicalensis and Eleutherococcus senticosus shows vasocontrictive effects in an ex-vivo mucosal tissue model and in allergic rhinitis patients ,Clin Phytoscience 2017;3:1-6.

