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A Clinical Study of Shi Ho Cheong Gan-San on Blood Heat Pattern Atopic Dermatitis: a randomized, double-blind clinical trial

In-Hwa Choi[1] · Se-Hyun Kim[2] · Young-Chul Kim[3] · Young-Hee Yun[1]
[1] Department of Oriental Dermatology, Kyung Hee University, Kyung Hee Hospital at Gangdong, Seoul, Korea
[2] Graduate School of East-West Medical, Kyung Hee University, Seoul, Korea
[3] Department of Internal Medicine, College of Oriental Medicine, Kyung Hee University, Seoul, Korea

혈열형 아토피피부염에 대한 시호청간산의 유효성과 안전성 연구

최인화[1] · 김세현[2] · 김영철[3] · 윤영희[1]

목적 : 본 임상시험을 통하여 혈열(血熱)형으로 변증된 아토피피부염의 한약 치료 후 임상 효능과 안전성을 관찰함으로써 아토피피부염에 대한 한약치료의 유용성을 평가하고자 한다.

방법 : 본 임상시험은 무작위배정, 이중맹검, 양성대조군, 평행 설계로 진행되었다. 자의에 의해 임상시험 동의서에 서명한 대상자 중 선정기준 및 제외기준에 부합된 36명의 대상자들에게 시험약과 양성대조약 과립제를 1일 3회(5.0g * 3회/ 1일) 4주간 복용하도록 하였다. 36명 중 31명의 환자가 4주간의 치료를 종료하였다(시호청간산 복용군: n = 16, 소풍산 복용군: n =15). 아토피피부염 증상을 평가하기 위해 Scoring atopic dermatitis (SCORAD) index와 Eczemaarea and severity index (EASI) 를 사용하여 시험 시작 전과 4주 후 시험 종료일에 환자들의 피부소견을 평가하였다. 아토피 피부염에 대한 한약치료의 안정성을 평가하기 위하여 치료 전후 혈중 AST, ALT, BUN, creatinine 변화를 검토하여 한약치료의 간/신독성 여부에 대해 조사하였다.

결과 및 결론: 두 군 모두에서 유의하게 SCORAD 점수와 EASI 점수가 감소하였으나 두 군 간의 차이는 유의하지 않았다. 부종/구진, 찰상 항목의 점수에는 두 군 간에 유의한 차이가 관찰되었다. 31명의 환자에게서 한약 치료 후 간장과 신장에 미치는 독성이 발견되지 않았으며 한약투여와 관련된 이상반응은 보고되지 않았다. 위의 결과로부터 시호청간산과 소풍산이 혈열형 아토피피부염에 대한 효과적이고 안전한 치료 방법이 될 수 있을 것으로 생각된다.

Key words : atopic dermatitis, *Shi Ho Cheong Gan*-San, *So Pung*-San, SCORAD, EASI, blood-heat pattern

Ⅰ. Introduction

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease with an increasing prevalence that affects 10-20% of children and 1-3% of adults[1,2]. Various studies have suggested that prevalence of AD has increased during the past several decades in Europe[3,4] and Asia, like Japan[5-7], Hong Kong and Korea[8,9].

A consensus regarding the treatment of AD has been published as a series of guidelines for clinical practice in some countries[10,11]. However, there remains some AD patients are not satisfactorily improved by the therapeutic management recommended by the guidelines because of the latent adverse effects of the treatment, especially when it is applied over a long period, namely socio-economic problems, and the severity and activity of AD itself[12]. It is thus anticipated that new and more efficacious treatments for AD will become available. Traditional Chinese medicine (TCM) is an alternative therapy that can be used in the treatment of dermatologic disorders, including AD[13,14].

In general, TCM stresses the importance of catering the therapy to the needs of individual, as opposed to Western therapeutic approaches that are standardized and stress average efficacy in large, double-blind, placebo-controlled studies[13,15].

교신저자 : Younghee Yun, #149 Sangil-dong, Gangdong-gu, Seoul 134-090, Korea
(Tel: +82-2-440-6268, mobile: +82-10-2656-8443, Fax: +82-2-440-7143, e-mail: allergycosmetic@khnmc.or.kr)
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However, for methodological reasons, in all these studies one standard concoction was given to all patients in the treatment group, which contradicted the idea of the approach to treatment more common in TCM[16]. There has rarely been any serious study of herbal medicine treatment of AD based on any pattern identification diagnosis.

In TCM, heat and dryness based on blood deficiency are considered to be two of the main pathogenic factors in AD. *So pung*-San (SP) is a genuine Korean prescription drug, which has been used for the treatment of allergic diseases, including AD in Korea[17,18]. SHCG could work to the patient of blood deficiency and heat syndrome[19]. We anticipated SHCG has the effect to eliminate of heat based on blood deficiency and recover dryness of skin with AD.

So we tried to observe the efficacy and safety of SHCG compared to SP on blood-heat pattern AD based on pattern identification diagnosis.

Abbreviations used:
AD: atopic dermatitis
SCORAD: the scoring atopic dermatitis index
EASI: eczema area and severity index
TCM: Traditional Chinese Medicine
KTM: Korean Traditional Medicine
SHCG: Shi Ho Cheong Gan-San
SP: So Pung -San

Ⅱ. Materials and Method

A. Patients

Using a recruit announcement, we screened

60 participants, and the 36patients recruited were those diagnosed according to Hanifin & Rajka's criteria[20]. The ages ranged from 5 - 35 years old. This study was approved by the Institutional Review Board, KyungHee University, Kyung Hee hospital at Gangdong. Informed consent was obtained from the patients who were 18 years old or older after a thorough explanation of the procedure. For patients under 18 years old, informed consent was obtained from parents or guardians.

1. Inclusion criteria

All patients in the study had been diagnosed with blood-heat pattern AD by Oriental Medicine Dermatology specialists.

We applied our own blood-heat pattern criteria to this study, and defined patients showing more than four of the following nine symptoms and signs as those suffering from blood-heat pattern AD: ① fever or fever sensation aggravated at night ② terrible itching ③ extreme nervousness, irritability ④ sudden reddening of skin ⑤ eye congestion ⑥ poor bowel movement ⑦ yellow - reddish urine; incomplete empting of bladder ⑧ red-colored tongue coated with dark-yellow fur ⑨ a pulse that was weak and fast or which produced a plucking sensation

2. Exclusion criteria

We excluded any patients who

- had taken any antihistamines and/or steroids in the 4 weeks prior to the study
- were epileptic
- pregnant or lactating
- needed prompt treatment for any serious infection in other organs - except dermatoses
- those who were initially cleared by the inclusion criteria, but later showed abnormal results in ALT, AST, BUN, Creatinine levels in the blood test at the baseline visit

B. Study design

We carried out a parallel group, randomized, active placebo controlled, double-blind trial to assess the efficacy and safety of SHCG compared to SP for the blood-heat pattern atopic dermatitis.

C. Procedure

1. Record of medical history: sex, age, onset of AD, state of lesions, family and past history related to allergic disease
2. Management: instructing patients on diet, environmental factors, and an explanation of beneficial moisturizing methods to all participants and their parents. In general, most patients with atopic dermatitis in Korea and their families tend to think their symptoms and signs are related to their diet and environmental factors, including specific allergens. This means they might be concerned about their diet and other environmental factors before participating in our study. Most of them in fact ask us how to better manage their life style, including diet and environmental factors, to help alleviate symptoms. So, in order to provide the same conditions to all our

patients, we recommended and suggested proper management methods to them, especially regarding diet, environmental management, and moisturizing based on consensus guidelines[11,21].

3. Randomization: Randomization was performed using computer-generated random number tables. In order to maintain the randomization, the random number tables and the intervention allocations were exposed after analyzing this study.
4. Blinding: One of the specialist related to this study performed the screening of recruited patients and after the patients to be enrolled this study were determined, another specialist allocated them randomly and gave them either the SHCG, or SP only through a pharmacist. The first specialist evaluated them whenever they visited and did not know which patient was taking which herb-medicine until the end of this study. We prepared SHCG and SP using packages of the same color and size. All participants were given the same identical-looking dose of either 5.0g SHCG, or a dose of 5.0g SP that looked the same and was dispensed in an identical package. The patients did not know which kind of herb-medicine -SHCG, or SP- they had taken.

D. Materials

1. SHCG (Han kook Shin Yak Co., Ltd, Korea) (Table 1)

2. SP (Han kook Shin Yak Co., Ltd, Korea) (Table 2)

Table 1. Components of *Shi Ho Cheong Gan - San*

Herbal medicine	Scientific name	Dose(grams)
Bupleuri Radix	*Bupleurum falcatum Linne*	0.52
Angelicae Gigantis Radix	*Angelica gigas Nakai*	0.32
Paeoniae Radix	*Paeonia lactiflora Pallas*	0.32
Cnidii Rhizoma	*Cnidium officinaleMakino*	0.32
Rehmanniae Radix Preparat	*Rehmannia glutinosa Libosch.*	0.32
Coptidis Rhizoma	*Coptis japonica Makino*	0.32
Scutellariae Radix	*Scutellaria baicalensis Georgi*	0.32
Phellodendri Cortex	*Phellodendron amurense Rupr.*	0.32
Gardeniae Fructus	*Gardenia jasminoides var. grandiflora Nakai*	0.32
Forsythiae Fructus	*Forsythia viridissima Lindl.*	0.32
Platycodi Radix	*Platycodon grandiflorum A. DC.*	0.32
Arctii Fructus	*Arctium lappa L.*	0.32
Trichosanthis Radix	*Trichosanthes kirilowii var. japonica Kitamura*	0.32
Menthae Herba	*Mentha arvensis var. piperascensMakinv.*	0.32
Glycyrrhizae Radix	*Glycyrrhiza uralensis Fisch.*	0.32
Total		5.00

SHCG: 5.0 g / 3times / day. In total 15.0 grams for one day.

Table 2. Components of *So Pung-San*

Herbal medicine	Scientific name	Dose(grams)
Ginseng Radix	*Panax ginseng*	0.38
Poria	Poria cocos Wolf.	0.38
Bombycis Corpus cum Batryticatus	*Bombyx mori L.*	0.38
Ligustici Rhizoma	*Ligusticum chuanxiong Hort*	0.38
Saposhnikovia Radix	*Ledebouriella divaricata Hiroe*	0.38
Agastachis Herba	*Agastache rugosa O. Kuntze*	0.38
Cicadae Periostracum	*Cryptotympana pustulata Fabricius*	0.38
Osterici Radix	*Angelica koreanum Kitagawa*	0.38
Aurantii Nobilis Pericarpium	*C. sinensis Osbeck*	0.19
Magnoliae Cortex	*Magnolia officinalis Rehder et Wilson*	0.19
Schizonepetae Spica	*Schizonepeta tenuifolia Briq.*	0.79
Glycyrrhizae Radix	*Glycyrrhiza glabra L.*	0.79
Total		5.00

SP: 5.0 g / 3times / day. In total 15.0 grams for one day.

3. *Schedule for taking medicine*: Over 4 weeks; taken 90 minutes after meals / 3 times/ day (Table 3)

Table 3. Dose Depending on Patients' Weight

Patients' Weight (kg)	Total Dose (grams)
Over 50	5.0
20-50	3.4
Less than 20	1.7

E. Parameters of Study

1. This study examined different combinations of medicine to treat AD but excluded all anti-histamine, steroid, and immune suppressant treatment. After counseling we allowed patients to use emollients, lotions and ointment that did not contain steroids.
2. Contradiction: antihistamines, steroids and immune suppressants.

F. Assessment schedule and evaluation

1. Outcome: The patients were clinically examined at the beginning of the study, then regularly after 1 week, 2 weeks, and 4 weeks, which marked the end of the study. The evaluation of the efficacy was carried out using three methods. They were evaluated by comparing them with the baseline and again after 4 weeks.
   a. The SCORAD was adopted in order to evaluate the severity of atopic dermatitis as objectively as possible.
   b. Eczema area and severity index (EASI)
   c. To observe the primary objective clinical manifestation of severity: those suffering from erythema, edema/papule, oozing/ crust, excoriation, lichenification, and dryness were grouped into the following four categories: 3: severe, 2: moderate, 1: mild, 0: absent. The efficacy was

evaluated by observing the decrease in each symptom.

2. Patients had blood tests [AST, ALT, BUN, and Creatinine] taken at the beginning of the study and then after 4 weeks. Also their serum total IgE and CBC, D/C were evaluated at the baseline.
3. Safety evaluation

   The safety of this study was assessed using adverse event reporting throughout this study and with laboratory tests (e.g. AST, ALT. BUN, and Creatinine) at the first and final visits. Also, physical examinations were taken at the beginning of the study, after 1 week, 2 weeks, and 4 weeks.

G. Countermeasures to Adverse effects

All patients experiencing adverse events, for example: nausea, vomiting, stomach discomfort, fever, and/or diarrhea, were monitored by clinical examination. Any adverse events were considered as possibly or probably related to the sensitization and the severity of the symptoms.

H. Statistics:

The comparison the between two groups, and any changes comparison between the baseline and after 4 weeks were performed using the student *t*-Test except for the SCORAD score. For the SCORAD index, we used an Analysis of Covariance (ANCOVA) after adjusting for the baseline because the SCORAD index of the two groups at the baseline was significantly different based on our analysis using the student *t* test. For a categorical variation, we used Fisher's exact test (version 9.1; SAS Institute, NC, USA). A P-value of ⟨0.05 was considered as indicating a statistical significance.

Ⅲ. Results

A. Patients

In total, 15 (83.3%) patients in the SHCG group completed the 4-week study, compared with 16 (89.9%) in the SP group. Two (11.1%) patients in the SHCG group were released from the study one patient was pregnant after starting this study and the other was released because we could not contact them. Three (16.7%) patients in the SP group were removed from the study because one did not want to continue, due to unsatisfactory therapeutic effects; two of them were lost to follow up(Fig. 1).

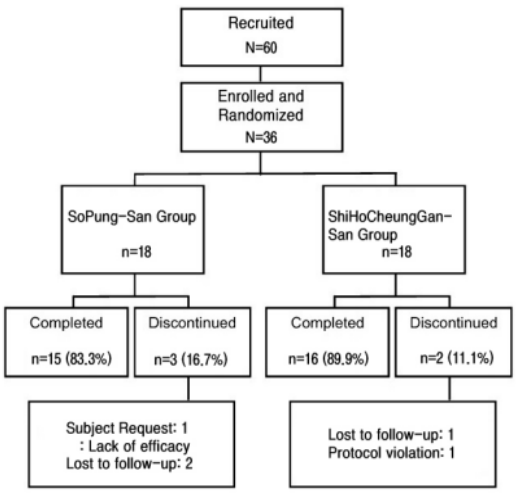

Fig. 1. Patients' flow chart

A total of 36 patients were randomly assigned to receive either SHCG (n = 18), or SP (n = 18). There were no clinically or statistically significant demographic differences between the two groups except the SCORAD. So after adjusting, we compared the SCORAD of two groups(Table 4).

B. Efficacy

1. The SCORAD index

The primary efficacy measure was the severity of AD assessed by the SCORAD index of the SHCG compared to the SP group. The mean modified SCORAD (±SD) after 4 weeks decreased in both groups compared to baseline: -20.0±15.0 in SHCG group, and -13.8±8.2 in SP group. The reduction found in the SHCG group was greater than in the SP group however there was no significant difference statistically(Table 5).

2. EASI score

For the EASI score, the decrease in the mean modified EASI score (± SD) compared the SHCG with the SP group. The mean modified EASI score (± SD) after 4 weeks decreased in both groups compared to baseline:

Table 4. Baseline Demography and Clinical Characteristics

Characteristics	No.(%) or mean±SD		p-value
	SP	SHCG	
Age	17.1±8.3	16.7±9.0	0.89†
Sex			0.51‡
Male	11	8	
Female	7	10	
Duration of Atopic Dermatitis (Years)	11.6±6.7	11.6±8.1	0.97†
Western treatment experience (yes)	14	14	1‡
Oriental treatment experience (yes)	8	8	1‡
Past history	10	12	0.73‡
Allergic rhinitis	8	11	0.51‡
Allergic asthma	1	2	1‡
Allergic conjunctivitis	3	2	1‡
Food allergy	2	4	0.66‡
Family history	8	13	0.17‡
EASI score	5.9±6.2	9.8±6.9	0.08†
SCORAD	32.1±10.0	41.1±10.5	0.01†
Serum total IgE			0.69‡
Normal	3	5	
Abnormal	15	13	
Eosinophil count			1‡
Normal	9	8	
Abnormal	9	10	

† t-Test
‡ Fisher's Exact Test

Table 5. Change of SCORAD Score

Group	0 week		4 week		Difference between 0 and 4 weeks
	Mean±SD	(n)	Mean±SD	(n)	
SP	32.1±10.0	(18)	16.7±8.7	(15)	-13.8±8.2
SHCG	41.1±10.5	(18)	20.2±8.6	(16)	-20.0±15.0
p-value	0.01†		0.27†		0.5695‡

† t-Test

‡ ANCOVA after adjusted by baseline SCORAD score

Table 6. Change of EASI Score

Group	0 week		4 week		Difference between 0 and 4 weeks
	Mean±SD	(n)	Mean±SD	(n)	
SP	5.9±6.2	(18)	1.6±2.9	(15)	-4.5±4.4
SHCG	9.8±6.9	(18)	2.9±2.3	(16)	-7.0±6.9
p-value	0.08†		0.21†		0.25†

† t-Test

Table 7. Basic Characteristics of the SCORAD Intensity

Intensity score	0	1	2	3
Erythema	1	6	25	4
Edema/Papule	12	14	10	
Oozing/Crust	14	11	11	
Excoriation	14	10	8	4
Lichenification		10	17	9
Dryness		4	9	23

Table 8. Change of SCORAD Intensity Score

Intensity	SP Group	SHCG Group	p-value*
	Mean±SD	Mean±SD	
Erythema	-1.0±0.7	-0.6±1.1	0.27
Edema/Papule	-0.1±0.5	-0.8±0.9	0.02
Oozing/Crust	-0.7±0.8	-0.9±1.0	0.54
Excoriation	-0.5±0.6	-1.3±1.1	0.01
Lichenification	-0.7±0.6	-0.9±1.0	0.62
Dryness	-0.5±0.6	-0.3±1.2	0.66

* t-Test

-7.0±6.9 in the SHCG group, and -4.5±4.4 in the SP group. The reduction found in the SHCG group was greater than in the SP group however there was no significant difference statistically(Table 6).

C. The Primary objective clinical manifestation severity

The primary objective clinical manifestation severity of 36 patients suffering from blood-heat pattern atopic dermatitis in this study - based on pattern identification - is as follows as: scale of erythma 0 = one patient; erythma 1 = six patients; erythma 2 = 25 patients; erythma 3 = four patients; edema/papule 0 = 12 patients, edema/papule 1 = 14 patients; edema/papule 2 = 10 patients; oozing/crust 0 = 14 patients oozing/crust 1 = 11 patients; oozing/crust 2 = 11 patients; excoriation 0 = 14 patients; excoriation 1 = 10 patients; excoriation 2= 8patients; excoriation 3= five patients; lichenification 1= 10 patients lichenification 2 = 17 patients; lichenification 3 = 9 patients; dryness 1 = four patients; dryness 2 = nine patients; dryness 3 = 23 patients (Table 7).

We observed the changes in primary objective clinical manifestation severity between both groups. There were significant differences in severity reduction in edema/papule and excoriation severity between the two groups statistically(Table 8).

D. Safety

There was no report of either any adverse event during this study, or any abnormality of AST, ALT, BUN and creatinine level after 4 weeks of testing in both groups.

Ⅳ. Discussion

AD is one of the most common skin diseases and is characterized by a chronic and relapsing inflammatory dermatitis with immunologic disturbance, and pruritic and ezematous skin lesions[22]. Furthermore, the incidence of AD has continued to increase over several decades in industrialized countries widely[23]. In Korea, according to the study of prevalence of AD in Korean elementary students, the incidences are 15,3%, 17.9%, and 21.8%; 1995, 2000, and 2006, respectively[9].

In conventional AD treatment, the first step involves using topical steroids, topical tacrolimus, emollients and oral antihistamines. However, some adverse effects, and sometimes an emotional fear based on long-term use of those treatments have caused steroid/tacrolimus phobia in substantial numbers of AD patients worldwide; they would like to avoid these topical agents if possible[24]. Finally, there are no consistent guidelines on treatment of AD based upon disease severity[21]. So the use of TCM for AD has been increasing, even in the Western world[25], where some herbs and oriental herbal formulations are commonly used to treat eczematous conditions. The patient and their families are looking for safer herb-medicine treatments that possess therapeutic effects, but without the recurrence of

symptoms and long-term harmful consequences that can result from other treatment[26]. Most AD patients and their families who visit Korean Traditional Medicine (KTM) clinics and hospitals in Korea are looking for similar things.

However, those studies that researched supported for these theories could be only identify a small number of studies. Due to the existing barrier posed by the Chinese language, especially in studies published mainly in North East Asia, the availability of information on TCM is additional hindered. Moreover, the general methodological quality of the studies on TCM appears low[25].

In 2005, the efficacy of this treatment was assessed by the Cochrane Collaboration in a large review[27], including four randomized controlled trials meeting the inclusion criteria, until 2004[28-31]. They concluded Chinese herbal mixtures may be effective in the treatment of AD. However, only four small, poorly reported RCTs of the same product, Zemaphyte, were found, and the results were inconclusive[31]. Also, the side effects of the use of Zemaphyte raised concerns about potential hepatic and renal toxicity in herbal medicine use[32].

Recently, some studies have been showed positive results of the PentaHerbs formula on AD, both experimental and clinical study[33-35].

Another multi center, double bind, randomized, placebo-controlled study reported the efficacy and safety of a traditional herbal medicine, *Hochu-ekki-to* on *Kikyo*, [or delicate constitution] patients with AD. It demonstrated that *Hochu-ekki-to* significantly reduced the required dosage of topical steroids and/or tacrolimus without aggravating the condition[36]. In addition, the lack of pharmacokinetic and pharmacodynamic data for TCM formulation has limited our understanding regarding the mechanism of action of the medicine.

For methodological reasons, all these studies have used the same herbal mix for all patients. It could be influenced to these efficacy results of herb medicine in these studies.

Due to the contradictory results of previous studies and the lack of trials assessing the effect of herbal medicine in AD, we conducted this study based on pattern diagnosis. We observed the efficacy and safety of SHCG compared to SP on blood-heat pattern AD.

In TCM, wind, dampness and heat are considered to be the main pathogenic factors. The itching sensation is one of the main symptoms of AD and it is caused heat pathogen. SP has been used for treating any itching sign regardless of the original disease.

The dryness symptom is another main aspect of AD and it is cause blood deficiency and heat. SHCG could work to better treat patients with this blood deficiency and heat syndrome. So we were looking forward to seeing whether or not SHCG could treat AD patients suffering from blood-heat symptoms based on blood deficiency.

SP, a traditional Korean medicine, has often been used as a therapeutics treatment for allergic diseases such as AD. It is claimed - via reports of folk medicine treatments - to have medicinal value in allergic disorders in

folk medicine, but its mechanism of action is poorly understood[17].

In an in vitro study, SP was administered orally to Nc/Nga mice, which led to the remarkable suppression of the development of dermatitis, as determined by a histological examination and analysis of the serum IgE levels. Moreover, SP inhibited the production of thymus- and activation-regulated chemokine (TARC) and its mRNA expression in a keratinocyte cell line, HaCaT, which had been stimulated with tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ)[18].

In another study, Na et al. investigated the effect of SP on mast cell-mediated anaphylactic reactions and cytokine production in in vivo and in vitro murine models. In this study, SP inhibited the degranulation and histamine release from the rat peritoneal mast cells. SP also showed an inhibitory effect on passive cutaneous anaphylaxis reaction[17].

In an in vitro study, Park et al. studied change of external dermal formation, change of leukocytes in vasculature, change of lipid formation in strarum corneum and distribution of ceramide through administering SHCG extract after forcing injury to mice's back skin. This study shows that SHCG has effect on suppressing the dermal injury through the recovery of lipid protection formation in stratum corneum[19].

A total of 36 patients were randomly assigned to receive either SHCG (n = 18), or SP (n = 18). We also surveyed factors such as the duration of AD, treatment experience with both conventional western medicine and Oriental treatment, any past history related to allergy, and the serum total IgE and eosinophil count in WBC D/C. There were no clinically or statistically significant demographic differences between the two groups except SCORAD(Table 4).

In total, 15(83.3%) patients in the SHCG group completed the 4-week study, compared with 16 (89.9%) in the SP group. Two (11.1%) patients in the SHCG group were released from the study one patient was pregnant after starting this study; the other was released, because we could not be contacted with the patient. Three (16.7%) patients in the SP group were removed from the study because one did not want to continue, because of unsatisfactory therapeutic effects; two of them lost to follow up(Figure 1).

The primary efficacy measure was the severity of AD assessed by the SCORAD index of SHCG compared to SP group. There was significant differences between the SCORAD of two groups statistically. So after adjusting, we compared the SCORAD of two groups. The mean modified SCORAD (±SD) after 4 weeks decreased in both groups compared to baseline. The reduction found in the SHCG group was greater than in the SP group however there was no significant difference statistically(Table 5).

For the EASI score, the decrease in the mean modified EASI score (± SD) compared the SHCG with the SP group. The mean modified EASI score (± SD) after 4 weeks decreased in both groups compared to baseline. The reduction found in the SHCG

group was greater than in the SP group however there was no significant difference statistically(Table 6).

We observed the changes in primary objective clinical manifestation severity between both groups. There were significant differences in severity reduction in edema/papule and excoriation severity between the two groups statistically(Table 8). In general, the heat pathogen induces papule, and, when AD patients have serious itching and flare signs, excoriation increases.

As for safety concerns, there was no report of adverse events, including nausea, vomiting, stomach discomfort, fever and diarrhea during this study and no reported abnormality of AST, ALT, BUN and creatinine levels after 4 weeks of testing in both groups.

In conclusion, although we were looking toward the SHCG group showing more effective results than the SP group in blood-heat pattern AD, there was no significant difference. However, both groups of patients showed some improvement in their symptoms and signs without any adverse events, or any hepatic and renal toxicity. We therefore concluded that we can apply both SHCG and SP to blood-heat pattern AD patients.

We noted the four participants of SHCG group improved remarkably compared to the other participants. The mean modified SCORAD (±SD) after 4 weeks decreased compared to baseline: - 41.1±3.8 in the four participants of SHCG, and -13.8±8.2 in the other 27 participants. The mean modified SCORAD (±SD) of the SHCG group excluding those four participants was similar to the SP group': -13.0±9.3 and -13.8±8.2, respectively. Thus the results of these four participants should be considered important because those results produced the differences between the two groups. We could not determine any special characteristics for them based on their medical history. However, we speculate the SHCG could be worked to ascertain a pattern for patients showing remarkable improvements in their AD signs. This will require further in - depth studies, including other genetic diagnosis.

Our study has several potential limitations, including the relatively-small number of patients and lack of a sustained follow-up period after cessation of these interventions. It is very important to assess any long - term effect when referring to AD treatment because AD is a chronic disease with relapse and remission cycles, that maybe influenced by other factors.

The SCORAD score in our study showed significant differences between the two groups at those baselines. The group allocation of patients was accomplished according to their starting order by random number tables. We expect the stratified randomized allocation would help in the homogeneity formation of two groups in a small sample size.

In order to deal with any methodological difficulties, we performed our study with an active placebo. It is very hard to make a placebo for herbal medicine, based on its unique taste, smell, and effect, without it producing any other effects (including toxicity). Furthermore, we have no standard treatment

for AD that utilizes evidence-based medicine. Therefore, it is very hard for us to rate our intervention when compared to any standard herb medicine.

We have no reliable criteria of pattern diagnosis yet, so we evaluate our patients using Oriental medicine doctors'decisions based on Oriental medicine philosophy. One of the most important things in individualizing treatment is the identification of any pattern. We applied our own blood-heat pattern criteria in this study, and chose patients exhibiting more than four of the following nine symptoms and signs as having blood-heat pattern AD.

One of the important limitations of clinical study in TCM is a lack of standardization of pattern identification, even though it should be essential to any treatment parameters. This leads us to conclude that we should standardize the pattern identification based on Oriental medicine philosophy.

Furthermore we need a continuous study of specific herbal medicines for long-term treatment of AD based on pattern identification; a study that has therapeutic benefits and is efficacious in treating AD without adverse events or consequences.

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