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Clinical Assessment of Efficacy, Safety and Usefulness of Traditional Herbal Medicine (THM) on Atopic Dermatitis

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아토피 피부염에 대한 한약치료의 효과, 안전성 및 유용성에 대한 임상 평가

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목적 : 본 연구를 통하여 아토피 피부염 환아의 한약치료 후 임상 효능, 안전성 을 평가하고, 나아가 효능과 안전성을 종합적으로 평가함으로써 아토피 피부염에 대한 한약치료의 유용성을 평가하고자 한다.

방법 : 경희대학교 한의과대학 부속한방병원 한방소아과에 내원한 아토피 피부염 환아 39명의 한약치료 전후의 의무기록을 검토하였다. 아토피피부염 치료에 대한 한약의 효능을 평가하기 위하여 치료 후 아토피 피부염의 개선 정도에 대한 부모의 평가를 VAS를 사용하여 분석하였다. 아토피 피부염에 대한 한약치료 후 안정성의 평가를 위하여 치료 전후 혈중 AST, ALT, BUN, creatinine 변화를 검토하여 한약치료의 간신독성 여부에 대해 조사하였고, 보호자에 대한 설문조사를 통하여 한약치료 후 발생한 부작용 및 불편한 증상의 종류 및 정도를 평가하였다. 나아가 한약의 효능 및 안정성을 종합적으로 평가하여 아토피 피부염에 대한 한약 치료의 유용성을 분석하였다.

결과 및 결론 : 환아 39명 중 27명 (69%) 의 부모가 한약치료가 아토피 피부염의 개선에 효과가 있다고 보고하였다. 안정성의 평가에 있어서, 39명의 환자에게서 한약 치료 후 간장과 신장에 미치는 독성이 발견되지 않았다. 2명의 환아가 일시적이고 경미한 복부 불쾌감을 호소하였으나, 한약투여와의 관련성은 관찰되지 않았다. 1명의 환아에서 경미한 복통이 발견되었으나, 의학적 치료 없이 증상은 소실되었으며, 치료 과정의 중단 없이 계획되었던 모든 치료 과정을 종료하였다. 치료 후 상기 환아는 아토피 피부염의 증상 개선 뿐 아니라 변비증상의 완화, 만성적 어지러움의 개선 등 제반 신체 조건의 호전을 보고 하였다. 임상적 효능과 안전성을 종합적으로 고려할 때, 환아 39명 중 27명 (69%) 의 사례에서 한약치료가 아토피 피부염의 유용한 치료수단으로 평가되었다. 이를 근거로 한약치료가 아토피 피부염에 대하여 안전성을 가진 유용한 치료방법이라 사료되며, 향후 임상적 효능과 안전성을 객관적으로 평가할 수 있는 대규모의 임상연구가 필요하리라 사료된다.

키워드 : Atopic dermatitis, Traditional Herbal Medicine, Efficacy, Safety, Usefulness

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Ⅰ. Introduction

Complementary or alternative medicine (CAM) approaches including traditional herbal medicine (THM) have been attracting public attention in Western countries. THM originated more than 2000 years ago and has been used in asian countries for centuries in the treatment of several diseases, including atopic dermatitis (AD)[1]. In Western countries, there are scientific evidences that support the efficacy and reveal the mode of action of THM in AD[2,3], which suggest THM as a potential therapeutic modality for AD. In Korea, several clinical studies have been reported on THM uses in AD. However, most of them were focusing on the effects of THM on AD, without safety assays. Therefore, we aim to evaluate the efficacy and the safety of THM uses on AD by examining the cases we experienced in our hospital. Further, in an attempt to weigh the merit and the demerit of THM uses on AD, we assessed clinical usefulness of THM on AD by taking both the efficacy and the safety measurement into consideration.

Ⅱ. Methods

1. Patients

Medical records of children with AD treated in the Department of Pediatrics, Hospital of Oriental Medicine, Kyung-Hee University from July 2005 to September 2005 were reviewed. AD was diagnosed according to Hanifin criteria[4]. Medical records were discarded (1) if medical records were not sufficient for confirming the efficacy or the safety of THM (2) if children had abnormal renal or liver function before THM administration (3) if children failed to take the decoction on more than 10 days in 45-day treatment period. Parents of children gave written informed consent. During the study, parents were asked to keep a diary to record any clinical discomfort for safety assessment. At initial and final visits, parents were required to answer the questionnaire for the estimation of THM efficacy and the identification of clinical discomfort.

2. Assessment of efficacy

Efficacy of THM was assessed after treatment by parents using a visual analogue scale (VAS). Then the parental assessment of THM efficacy on AD was analyzed as described in the previous study by Jung et al[5]; THM efficacy on AD was estimated by five categories based on the improvement of VAS (1) supremely efficacious (more than 75% of improvement on VAS), (2) more than efficacious (from 50% to 75%), (3) efficacious (from 25% to 50%), (4) non-effective (under 25%), and (5) aggravating.

3. Assessment of safety

The safety of THM was estimated in combination of clinical discomfort and laboratory

safety assessment. When children showed clinical discomfort or adverse drug effect, we investigated the association between THM uses and clinical symptom(s). For the laboratory safety assays, AST, ALT, BUN, and creatinine were investigated from venous blood before intake of THM formulas and the end of the treatment period. The severity of clinical adverse effects was defined as follows (1) none: no negative consequences or existence of transient troublesome symptom(s) interpreted not associated with the administration of THMs. (2) mild adverse effect; transient clinical discomfort associated with THM use, but without any abnormal change in laboratory safety parameters, and (3) severe adverse effect; obvious clinical discomfort which caused medicine change, or and toxicity on liver and kidney function.

4. Assessment of usefulness

The usefulness of THM on AD was estimated as described in the previous study[5]. We evaluated the grade of usefulness with five categories taking the efficacy and the safety into consideration: (1) supremely useful (supremely efficacious and no adverse effects), (2) more than useful (supremely efficacious and mild adverse effects, more efficacious and no adverse effects, or efficacious and no adverse effects), (3) useful (more efficacious and mild adverse effects, or efficacious and mild adverse effects), (4) non-useful (more than efficacious and severe adverse effects, or non-effective and no adverse effects), and (5) detrimental (non-effective and any adverse effects, or aggravating regardless of adverse effects).

Ⅲ. Results

1. Patients

46 children were treated with THM formulas; several modified forms of *Naesohwajoongtang* decoction with the addition of extra herbs and granuled type of *Sunbangpaedoktang, Tonggyutang, Bangpoongtongsungsan, or Bangpoonghaedoktang* decoctions were used according to the concomitent diseases and patients' characteristics. Out of 46, data of 39 were included in the final analysis (Table 1, and 2); 4 children failed in taking blood sample for the laboratory safety assessment. the other 3 were also excluded, because they had insufficient medical records for evaluation of the efficacy and the safety.

2. Assessment of efficacy

27 of 39 parents (69%) stated AD improved after THM treatment (The sum of percentages of supremely efficacious, more than efficacious, and efficacious was 69%) (Fig. 1, and Table 1).

Table 1. Case Summary

NO	Sex	Age	Past History of Allergic disease	Family History of Allergic disease	Improvement on VAS (%)	Adverse Effect
1	M	14.11	+	+	70	none
2	M	14.1	+	+	30	none
3	F	13.8	+	+	40	none
4	F	12.6	+	+	30	none
5	F	12.11	+	+	80	none
6	F	12	+	+	20	AP**
7	F	11.1	-	-	0	none
8	F	10.7	+	+	50	none
9	M	10.6	+	+	40	none
10	M	10.1	+	+	0	none
11	F	9.4	+	+	-20	AD*
12	M	8.7	+	+	80	none
13	M	8.3	-	+	60	none
14	M	8.2	-	-	40	none
15	M	8.11	+	+	40	none
16	M	7.8	+	+	0	AD*
17	F	7.7	-	+	70	none
18	F	7.4	+	+	30	none
19	F	7.4	+	-	0	none
20	F	7.3	+	+	20	none
21	M	7.3	+	+	80	none
22	F	7.11	+	+	60	none
23	F	7.11	+	-	-10	none
24	M	7.11	+	-	50	none
25	F	7.1	-	+	0	none
26	M	6.7	+	+	30	none
27	F	6.11	-	+	10	none
28	M	5.9	+	-	20	none
29	M	5.8	+	+	50	none
30	F	5.3	+	+	50	none
31	F	5.2	+	+	30	none
32	F	5.11	+	+	50	none
33	F	4.11	-	+	10	none
34	M	4.11	-	+	40	none
35	M	3.3	+	+	50	none
36	M	3.11	-	-	30	none
37	F	3.1	+	+	60	none
38	M	2.7	+	+	30	none
39	F	2.11	-	+	90	none

* AD means mild transient abdominal discomfort. However, there was no association between abdominal discomfort and administration of THM in these 2 cases.

** AP means mild abdominal pain. One patient reported mild abdominal pain after THM intake. However, the symptom soon disappeared without medical care and the child completed treatment protocol as scheduled.

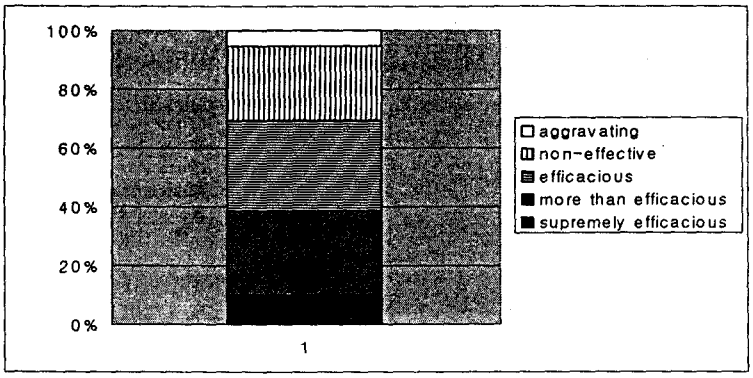

Fig. 1. Percentage of effectiveness of THM on AD in terms of assessment of efficacy by parents

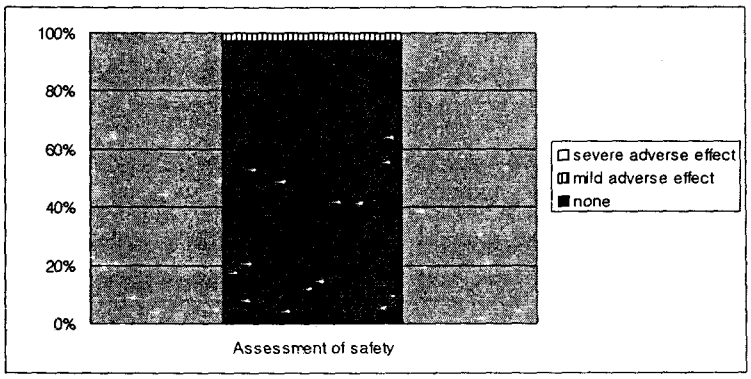

Fig. 2. Percentage of safety evaluation. Both clinical discomfort and laboratory safety assessment were taken into consideration for the evaluation of THM safety.

Table 2. Subject population

Gender (male/female)	18/21
Age (years)	7.69 ± 2.23
Past History of allergic disease, n (%)	29 (74%)
Family history of allergic disease, n (%)	32 (82%)

3. Assessment of safety

There was no evidence of toxicity on both liver and kidney function. Clinically, 2 children reported transient mild abdominal discomfort, however we couldn't find any association between THM administration and abdominal discomfort. One child reported mild abdominal pain after THM intake. This patient had constipation and occurrence of transient abdominal pain is considered as a consequence of THM effect on bowel move-

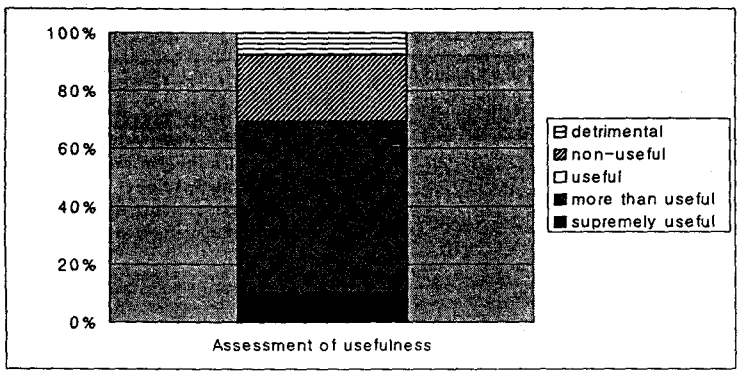

Fig. 3. Percentage of usefulness evaluation. Both the efficacy and the safety measurements were taken into consideration for the assessment of THM usefulness on AD.

ment. Abdominal pain soon disappeared without medical care and the patient completed treatments as scheduled (Fig. 2, and Table 2). Further, the patient experienced improvement of AD symptoms as well as general condition including constipation, halitosis, and chronic dizziness.

4. Assessment of usefulness

The sum of percentages of supremely useful, more than useful, and useful was 69%. This represents in 27 cases of 39 children (69%), THM was regarded as a useful treatment agent for AD (Fig. 3).

Ⅳ. Discussion and Conclusion

The exact pathophysiology of atopic dermatitis (AD) is not clearly revealed. Currently, topical steroids remain as mainstay of treatment. However, when treated for a long time, topical steroids have been reported to have a risk such as systemic side effects and skin atrophy[6], which increases the need to use a complementary therapeutic agent. Traditional herbal medicine (THM) has been used for centuries in Asian countries to treat symptoms similar to those of AD and the prevalence is continuously increasing in Western countries[1]. Several studies done in western countries have suggested that THM may be beneficial in the treatment of AD[2,3]. In Korea, there were several studies aimed to estimate the efficacy of THM on AD, apart from clinical reports on a single case. Kim et al. evaluated the efficacy of modified formula of *Yang-we-tang* using SCORAD index. SCORAD score deceased significantly (before treatment; 46.8 ± 18.1, after treatment; 30.5 ± 20, and $p < 0.05$) in 35 children with AD[7]. 9 THM formulas derived from Sasang constitutional medicine were ad-

ministered to 43 patients with AD. 36 patients (84%) reported marked improvement[8], measured as described in previous study[9]. Lee et al. reviewed medical records of 27 children treated with *Bopejungchentang*. After treatment, the percentage of improvement, unresponsiveness, and depravation was 51.9%, 37%, and 11.1%, respectively[11]. Nam et al. modified Grading of the severity of AD by Rajka et al[9]. to measure the efficacy of 6 different formulas. In 19 patients, clinical severity (intensity of itching, extent of erythema, lichenification, scaling, dryness, erosion and oozing) decreased markedly (before treatment; 1.47 ± 0.77, after treatment; 0.58 ± 0.84, and $p < 0.01$)[11]. 42 children treated with modified formula of *Yeoldahansotang* showed significant improvement of AD severity (mild group; before treatment 1.8 ± 0.3, after treatment 1.4 ± 0.4, and $p < 0.05$, moderate group; before treatment 3.2 ± 0.3, after treatment 2.5 ± 0.5, and $p < 0.05$, severe group; before treatment 4.5 ± 0.5, after treatment 3.5 ± 0.7, and $p < 0.05$)[12]. Recently, we observed AD-mitigating effect of modified formula of *Naesohwajoongtang* ($p < 0.05$)[13] by SCORAD index which is validated and commonly used for standardized evaluation of AD severity[14].

However, to our knowledge, there is no report that weighs benefit and demerit of THM uses on AD even though concerns on safety of THM exist[15,16,17]. As a preliminary step to determine whether THM use in Korea could be a possible therapeutic agent of AD with safety, we aimed to evaluate the efficacy, the safety, and the usefulness of THM uses. In the current study, we observed beneficial effects of THM on AD as reflected by favorable assessment of efficacy and safety.

It must be addressed that several THM formulas were used in this study. Basically, THM is a 'tailored medicine' and places primary importance on characteristics of individuals[2]. Unfortunately this characteristic of THM causes difficulty in evaluation of efficacy. However, given that THM paradigm is based on its unique medical system different from the orthodox Western scientific medicine and therefore, standardization of herbal formula is contradictory to THM philosophy[18], it is inevitable in the clinical setting to use 'personalized' formulas which are designed for each individuals.

Anti-inflammatory and immunomodulatory effects of several herbs used in this study may explain the effects of THM formulas on AD; *Glycyrrhiza uralensis* has been used for skin eruptions, including dermatitis, and eczema[19]. Glycyrrhizin, one of major element of *Glycyrrhiza uralensis* is known to have anti-inflammatory effect[20,21]. *Fructus crataegi* shows anti-inflammatory effect as demonstrated by inhibiting tumor necrosis factor (TNF) - alpha[22]. Ginsenoside Rg1, one of the key components of *Panax ginseng* modulates immune functions by enhancing the immune activity of CD4 (+) T cells as well as repressing Th1 specific cytokine production[23]. *Ephedrae herba* significantly suppressed IgE-mediated histamine release in vivo[24]. *Zingiber officinale Roscoe* (ginger) not only significantly inhibited T lymphocyte proliferation in vi-

tro but suppressed the delayed type of hypersensitivity response in vivo[25].

In conclusion, we suggest that THM could be a useful therapeutic agent with safety for AD. However, this study has limitation in the sense that it is not a placebo-controlled trial, which lacks methodological rigor to draw a concrete conclusion. Randomized clinical trials with placebo group based on a large sample are needed to confirm the efficacy and the safety of THM in the future.

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