

Therapeutic effect of traditional Chinese medicine bath combined with tacrolimus on atopic dermatitis and serum inflammatory mediators

Objective: To investigate the effect of traditional Chinese medicated bath combined with tacrolimus on atopic dermatitis (AD) and its effect on serum inflammatory factors of IgE, IL-4 and IL-5.

Methods: A total of 112 patients with AD were selected as the objects and randomly divided into control group and research group, 56 cases in each group. The control group was given tacrolimus ointment as exterior coating, and the study group was given traditional Chinese medicated on the basis of the control group. Eczema area severity index (EASI) score, serum levels of IgE, IL-4, IL-5, dermatological quality of life index (DLQI) scores of these two groups were compared between prior treatment and after 3 weeks treatment. The evaluation of clinical curative effect was given at the end of treatment assessment, drug adverse reactions were compared during the treatment period, understood the recurrence after 3 months follow-up.

Results: The effective rate of treatment in the research group was 89.3%, which was significantly higher than that in the control group of 69.6% ($P < 0.05$). There was no statistical significance of difference in EASI and DLQI scores, serum levels of IgE, IL-4 and IL-5 between the two groups before treatment ($P > 0.05$). After 3 weeks treatment, all of them in research group were significantly lower than those in the control group ($P < 0.05$). The adverse effect rate of cases in research group was 3.6% which was significantly lower than that in the control group of 10.7% ($P < 0.05$). Both groups were given 3 months follow up, during that time, 4 cases of recurrence in control group, the recurrence rate was 7.1%, while 5.4% in the research group with 3 cases of recurrence. There was no statistical significance of difference in the recurrence rate between the two groups ($P > 0.05$).

Conclusion: Chinese medicine bath combined with tacrolimus treatment has a good effect of AD, which effectively eliminating the skin lesions, reducing serum levels of IgE, IL-4, IL-5, improving patient-related quality of life, and with a lower adverse effects rate and recurrence rate, it is superior to effect of exterior coating tacrolimus ointment alone.

Keywords: Atopic dermatitis • Inflammatory mediator • Tacrolimus • Chinese medicated bath • IgE • IL-4 • IL-5

Introduction

Atopic dermatitis (AD), also known as atopic dermatitis and genetic allergic dermatitis, is a kind of inflammatory skin disease related to genetic and allergic diathesis, with high IgE tendency of chronic, refractory and pruritus [1]. Once suffered from AD, the quality of life of patients will be seriously affected. Because of the complex etiology and pathogenesis of AD, there was no specific effects of

treatment. At present, methods of treating AD include topical or systemic application of glucocorticoids, immunosuppressor and immunomodulators, antihistamines and etc. are systemic use of fluoride, however, it may be limited due to more serious adverse reactions or expensive treatment costs, or due to drug tolerance and high recurrence rate, the effect is not satisfactory [2,3]. Therefore, it is an important issue for clinical study to find an effective treatment with

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small side effects. In recent years, Chinese medicine bath has been gained more and more attention. Traditional Chinese medicated bath is a form of external therapy of the Chinese medicine which combines the double advantages of hyperthermia and medication, and the heat energy can promote the expansion of capillaries of human skin and subcutaneous tissue, as well as to improve the blood circulation speed, promote drug transdermal absorption, and seep into the depth of the lesion to achieve pharmacological action comprehensively [4]. Syngene tacrolimus is a new type of calcineurin inhibitors in macrolides, relevant data [5] shows that tacrolimus can inhibit T lymphocyte activation and inhibit release of synthesized media of skin mast cells and basophilic granulocyte, it has a certain effect in the treatment of atopic dermatitis disease. At present, the study on the curative effect of traditional Chinese medicine bath combined with tacrolimus in the treatment of AD reported are less. In view of these, the study mainly to investigate the effect of traditional Chinese medicine bath combined with tacrolimus on atopic dermatitis (AD) and its effect on serum inflammatory factors of IgE, IL-4 and IL-5.

Materials and methods

Materials

In this study, 112 cases of AD patients who treated in dermatology and inpatient departments of our hospital from July 2015 to January 2017, which were all in line with diagnostic criteria of Hanifin, Rajka atopic dermatitis. Inclusion criteria: AD patients who conformed to the above diagnostic criteria: aged from 12 to 50 years old; inactive with other anti-allergy treatment and stopped more than half a month; without chronic diseases of blood system, liver, kidney and etc.; without corticosteroids hormone treatment or withdrawal of more than 1 month; got the informed consent of patients and cooperated with the whole. Exclusion criteria: under 12 years old or above 50 years old; photosensitive diseases,

pregnant women and breast-giver; suffered with chronic diseases of blood system, liver, kidney and others; stopped within 1 month by corticosteroid therapy or other treatment less than half months; combined with other skin diseases or infectious diseases. There were 70 males and 42 females in 112 cases, ranged in age from 12 to 47 years old, with an average of (23.5 ± 2.1) years old, with a disease course of 1 to 10 years, averaged of (6.2 ± 1.5) years. They were divided into control group and research group randomly, 56 cases in each group, two groups of patients were comparable in gender, age, disease course and other distribution, the difference had no statistical significance. As shown in **TABLE 1**.

Therapeutic methods

Patients of the control group was given tacrolimus ointment external application: treated with 0.03% tacrolimus ointment (trade name: Protopic, Astellas Pharmaceutical Co., Ltd.) smeared the affected area 2 times a day, required 10 -14 hours of interval between 2 times.

The research group added traditional Chinese medicine bath treatment on the basis of the control group. The components of Chinese medicine bath: 10g dittany bark; 10g caltrop; 10g Kuh-seng; 6g golden cypress; 10g fructus kochiae; 5g rhubarb; 15g caulis spatholobi; 10g radix stemonae and 10g radix clematidis. First, soaked the above-mentioned drugs for 0.5h, and then wrapped with gauze boiled for 30min, taken 2.5 L fried juice into the bathtub, added water to 10 L, with 40 °C of temperature, soaked for 10-20 min, 1 time a day, one times for each two-days when patients improved. Coated with Cetaphil moisturizer (Gingderma of French) immediately after the bath and massage gently, smeared the affected area at 0.03% tacrolimus ointment after 2 hours, 2 times a day. During the treatment period, dietary appropriate was delicate and goluptious, avoided having spicy food of two groups. The course of treatment is 3 weeks.

Table 1. Comparison of the basic clinical data of two groups of patients

Group	n	Gender (Male/Femal)	Age (Year)	Course of disease (Year)
Control group	56	36/20	22.4 ± 2.1	5.7±1.4
Research group	56	34/22	24.8±3.2	6.4 ±1.9
F	-	0.856	1.127	1.095
p	-	> 0.05	> 0.05	> 0.05

Evaluation index

(1) EASI scores of prior treatment and after treatment for three weeks were compared. The score was calculated according to the eczema area and severity index (EASI).

(2) Clinical effects of two groups were compared. According to improvement rate of EASI score, which is equal to (EASI score of prior treatment-EASI score after 3 weeks of treatment) / pre-treatment EASI score × 100%, it was divided into healed basically, marked effect, improved, and inefficient.

- Clinical recovery: improvement rate of EASI score ≥ 90%;
- marked effect: improvement rate of EASI score 70% -90%;
- improved: improvement rate of EASI score 30% -70%;
- inefficient: improvement rate of EASI score was less than 30%. To collect the effective rate based on clinical cure and marked effect.

(3) The levels of serum inflammatory factors IgE, IL-4 and IL-5 were compared between the prior and after 3 weeks treatment. Fasting 3 ml blood of the elbow from the morning, sodium citrate anticoagulation, centrifugal separation of serum. Serum IL-4 and IL-5 levels were measured by enzyme-linked immunosorbent assay (ELISA). RAST FEIT was used in IgE experiments, reagents and apparatus were provided by the Swedish law Masia company, and the detection equipment was made by UniCAP 100 allergic detection equipment

(4) The quality of life was compared between the two groups of prior treatment and after treatment for 3 weeks. The quality of life of the patients was assessed by the Dermatological Quality of Life Index (DLQI).

(5) The adverse drug reactions of the two groups during the treatment were recorded and compared.

After the treatment, the patients were followed up for 3 months to observe the recurrence.

Statistical analysis

SPSS 21.0 software was used for data processing and analysis, the measurement data was described as ($\bar{x} \pm s$) with the t test; the enumeration data was tested by

χ^2 , $p < 0.05$ showed that the difference was statistical significance.

Results

The Comparison of clinical efficacy between the two groups

The effective rate of treatment was 89.3% in the research group, which was significantly higher than that in the control group of 69.6%, ($P < 0.05$) as shown in **TABLE 2**.

The Comparison of two groups of EASI and DLQI scores

There was no statistical significance of the difference in EASI and DLQI scores of the two groups ($P > 0.05$). After 3 weeks of treatment, EASI and DLQI scores of the research group were significantly lower than those of the control group ($P < 0.05$) as shown in **TABLE 3**.

The comparison of the levels of inflammatory cytokines in two groups

There was no statistical significance of the difference in IgE, IL-4 and IL-5 levels between the two groups ($P > 0.05$). After 3 weeks of treatment, the levels of IgE, IL-4 and IL-5 in the study group were significantly lower than those in the control group ($P < 0.05$), as shown in **TABLE 4**.

The comparison of adverse reactions between the two groups

The incidence of adverse reactions in the control group was 10.7% (6/56 cases), included 1 case of burning heat sensation, 2 cases of papules, 1 case of dry skin, 1 case of stabbing pain and 1 case of pruritus; the incidence of adverse reactions in the research group was 3.6% (2/56 cases), 1 case of papules, 1 case of dry skin. The incidence of adverse reactions in the research group was significantly lower than that in the control group ($P < 0.05$). adverse reactions of two groups were mild and resolved spontaneously in 24 hours without special handling.

The comparison of recurrence between the two groups

Three months of follow-up were given of two groups. The recurrence rate was 7.1% in the control group with 4 cases and 5.4% in the research group with 3 cases. There was no statistical significance of the difference in the recurrence rate between the two groups ($\chi^2 = 0.653, P > 0.05$).

Table 2. Comparison of clinical efficacy between the two groups(cases)

Group	n	Clinical recovery	Marked effect	Efficient	Inefficient	Effective Rate (%)
Control group	56	26	24	5	1	89.3
Research group	56	10	29	11	6	69.6
X ²	-	-	-	-	-	7.935
p	-	-	-	-	-	<0.05

Table 3. Comparison of two groups of EASI and DLQI scores

Group	n	EASI Score		DLQI Score	
		Prior treatment	After 3 weeks of treatment	Prior treatment	After 3 weeks of treatment
Control group	56	22.5±3.5	12.2±1.3	11.7±2.8	7.4±1.5
Research group	56	22.6±2.8	4.8±1.5	11.9±2.5	4.3±1.1
t	-	0.471	5.792	0.563	6.778
p	-	>0.05	<0.05	>0.05	<0.05

Table 4. Comparison of the levels of inflammatory cytokines in two groups

Group	n	IgE(IU/ml)		IL-4 (pg/ml)		IL-5 (pg/ml)	
		Prior treatment	After 3 weeks of treatment	Prior treatment	After 3 weeks of treatment	Prior treatment	After 3 weeks of treatment
Control group	56	1367.3±178.4	976.3±136.6	106.7±15.4	75.6±12.2	62.9±10.8	42.3±8.4
Research group	56	1368.5±182.3	748.2±103.2	107.1±13.8	60.9±7.7	63.1±9.5	35.7±4.6
t	-	0.375	7.816	0.413	7.659	0.562	8.004
p	-	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Discussion

Atopic dermatitis (AD), also known as atopic eczema, is a kind of inflammatory skin disease related to chronic, recidivistic and allergic diathesis, its major performance includes itching, eczema-like lesions and dry skin disease symptoms, and often develops in Infantile or adolescent period, sometimes may accompanies with elevated serum IgE levels and personal history or family history of allergic rhinitis or asthma [6]. Epidemiological survey showed [7] that in recent years the incidence of AD increased gradually, which affecting the quality of life of patients seriously, so the correct treatment of AD should be familiar contents to dermatologists [8]. The principles of AD treatment are to restore the normal humidity of the skin, find and remove the predisposing factors, itching and reduce inflammatory response of the skin lesions.

At present, Western medicine treatment of AD, includes systemic and topical treatment, it avoids using systemic glucocorticoids in principle. There is no "atopic dermatitis" appellation Chinese medicine, but it can be attributed to areas of "infantile eczema" "eczema" "acute eczema" "f atopic dermatitis

" and others, which can be seen in the records of the Golden mirror of medicine. In the understanding of pathogenesis, more people think that result of the inherent endowment intolerance and acquired dystocia in combination, and that was in accordance with the pathogenesis of modern medicine. As for the systematic and local treatment, they are mainly based on the situation of skin lesions to syndromes differentiation for treatment, and the modern physicians have to achieved a good clinical efficacy through experiences or self-prescription prescription for oral administration, such as the use of Cangyi soup, moistening dryness method, f atopic dermatitis soup, Shengui (ginseng and Angelica sinensis) apozem and soup to invigorating spleen to remove dampness [9,10].

The components of Chinese medicine bath given to the patients in research group of this study: dittany bark, caltrop, Kuh-seng, golden cypress, fructus kochiae, rhubarb, caulis spatholobi, radix stemonae and radix clematidis. Among them, dittany bark can heat-clearing and damp-drying drug, caltrop can promoting blood circulation by removing wind, Kuh-seng has diuretic property, golden cypress can relieve internal heat or fever, fructus kochiae can dispel

wind and arrest itching, Chuanjun, also called rhubarb, has function of promoting blood circulation to remove blood stasis, so does the caulis spatholobi, radix stemonae can induce sweat to dispel heat and radix clematidis can dredge the meridians and relieve pain. Through the whole prescription, all the components achieve function of heat-clearing and detoxifying, nourishing blood and promoting blood flow and Moisturizing skin to stop itching. The results showed that the effective rate of research group was 89.3%, which was significantly higher than that in the control group of 69.6%, ($P < 0.05$). The incidence of adverse reactions of former one was 3.6% that was significantly lower than that in the later one of 10.7%, ($P < 0.05$). After 3 weeks of treatment, the EASI and DLQI scores of the research group were all significantly lower than those of the control group ($P < 0.05$). It is suggested that the efficacy of traditional Chinese medicine bath combined with tacrolimus in the treatment of AD patients is superior to that of tacrolimus ointment alone, and in accordance with high quality of life and less adverse reactions.

Previous studies have shown [11,12] that T helper cells are divided into two subgroups of Th1 and Th2. Th1 secretes IL-4 and IL-5, Th2 secretes IFN- γ , and IgE belongs to antibody of allergy-mediation of type , its level is related to IL-4. Existing studies have shown [13-15] that T lymphocyte subsets imbalance is the major performance of atopic dermatitis immune dysfunction. The results indicates that in the prior treatment, the differences about levels of serum inflammatory factors IgE, IL-4 and IL-5 of two groups had no statistically significance ($P > 0.05$); After 3 weeks of treatment, theirs in research group was obviously lower than those of control group ($P < 0.05$), which suggesting that traditional Chinese medicine bath combined with tacrolimus treatment can regulate T lymphocyte subsets cytokine expression of AD patients and balanced to help control the inflammatory response, so we speculate that the traditional Chinese medicine bath combined with tacrolimus treatment Mechanism is related to it.

Recent follow-up also showed that the recurrence rate of research group was low, which suggesting that traditional Chinese medicine bath combined with tacrolimus ointment coating may have a better synergistic effect. Because the sample

size was so small in this study and with a short follow-up time, the differences in the recurrence rate between the two groups were not significant, which may be related to the above factors, further expanding the sample size and prolonging the follow-up time may be expected to significantly distinguish Chinese medicine bath combined with tacrolimus and tacrolimus treatment alone.

In summary, traditional Chinese medicine bath combined with tacrolimus treatment has a good effect on AD, which effectively eliminating the skin lesions, reducing serum IgE, IL-4, IL-5 levels, improving patient-related quality of life, and with a lower incidence of adverse reactions and recurrence rate, it is superior to effect of simple treatment of tacrolimus ointment coated alone.

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