ORIGINAL ARTICLE

Systemic Lupus Erythematosus Complicated with Femoral Head Ischemic Necrosis Treated by Chinese Medicine Therapy for Activating Blood and Dredging Collaterals Method

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ABSTRACT **Objective**: To observe the effect and mechanism of Chinese medicine therapy for activating blood and dredging collaterals (ABDC) on treating systemic lupus erythematosus complicated with avascular necrosis of the femoral head (SLE-ANFH). **Methods**: Thirty-four patients (51 joints) with SLE-ANFH were assigned by a random number table to two groups: 22 patients (32 joints) in the treatment group and 12 patients (19 joints) in the control group. All received Western medical conventional treatment for anti-inflammation and immunosuppression, but an additional Chinese medicine decoction prescribed based on ABDC principle was administered to patients in the treatment group. The observation on the patients' condition and therapeutic effect lasted for 3 years. **Results**: The patients' conditions in the two groups, as assessed by Association for Research Circulation Osseous (ARCO) staging, were similar before treatment. After treatment, comparison between groups showed significant difference ($P<0.05$), and the raised Harris functional scores in the treatment group were higher than that in the control group ($P<0.01$). The post-treatment symptom improving rate in the treated group was 72.73%, which was higher than that in the control group (50.00%, $P<0.05$). Moreover, the former was superior in improving hematologic and hemorrheologic parameters in terms of prolonging activated partial thromboplastin time, lowering whole blood middle/low shear viscosity, and plasma viscosity ($P<0.05$ or $P<0.01$). Two patients in the control group but none in the treatment group received hip joint replacement operation during the observation period. **Conclusions**: Chinese medicine ABDC therapy could effectively alleviate clinical symptoms and improve joint function of patients with SLE-ANFH. The mechanism may be related to its effects on improving high coagulation manner and trend for getting embolism.

KEYWORDS systemic lupus erythematosus, femoral head ischemic necrosis, Chinese medicine, activating blood and dredging collaterals

Systemic lupus erythematosus (SLE) is a kind of autoimmune disease. Due to the advancement of diagnosis and treatment levels, the prognosis of SLE patients has improved in recent years. However, the complicated avascular necrosis of the femoral head (ANFH) that occur in patients caused by glucocorticoid treatment is still a nuisance. ANFH would progress to femoral head collapse 1 to 4 years later in about 80% of patients when they do not undergo effective treatment[1]. In most of these patients, the illness would further develop in several years to severe osteoarthritis, necessitating for joint replacement. It was found that Chinese medicine treatment for activating blood and dredging collaterals (ABDC) could obviously improve the quality of life (QOL) in patients with SLE complicated with ANFH (SLE-ANFH), the results are reported as follows.

METHODS

Diagnostic Standard

Diagnosis of SLE was performed according to the standard issued by American Association of Rheumatology (revised in 1882)[2].

The stage of ANFH was differentiated by adopting the installation method of Association for Research Circulation Osseous (ARCO)[3], that is, stage 0: all examinations, including X-ray, computed tomography (CT), bone scanning, show normal outcomes, or with insufficient evidence for diagnosis; stage Ⅰ: normal results of X-ray film and CT, but abnormal outcomes could be found in bone scanning or magnetic resonance imaging (MRI); stage Ⅱ: abnormalities (bone sclerosis, trabecula deficit, and local saccate formation) found in X-ray film but

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without meniscus sign; stage Ⅲ: X-ray film shows meniscus sign and/or joint surface deformation involving the lateral side of femoral head; and stage Ⅳ: osteoarthritis with narrowed gap, acetabular change, and joint destruction. The function of hip joint was evaluated by Harris scoring[4] with 100 scores in total, where pain had 44, activity had 47, malformation had four, and moving scope had five.

Inclusion and Exclusion Criteria

Patients between 15 and 60 years old matching the diagnostic standards of SLE and ANFH were included. Patients who had the following conditions were excluded: (1) pregnant or lactating women; (2) complications of mental disease; (3) ANFH caused by tumor, osteomyelitis, bone tuberculosis, hematopathy, trauma, or excessive drinking; (4) perthes disease; and (5) unfitting to the inclusion criteria or with incomplete materials.

General Materials

The 34 SLE-ANFH patients (with 51 diseased hip joints) who were enrolled came from the Department of Rheumatology and Immunology in the authors' hospital from 1995 to 2005. They were assigned by a random number table to two groups. The 22 patients (32 joints) in the treated group were 2 males and 20 females, 19 to 60 years old, 39.73 ±11.87 years on average, and with illness duration between 1 month and 3 years, 15.36±10.53 months on average. Diagnosis of ANFH was confirmed in 13 patients at first visit. Twenty patients had received large-dose steroid hormonal pulse therapy. The mean oral dosage of hormone at enrollment (scaled by prednisone) was 24.09±7.50 mg/d. The 12 patients (19 joints) in the control group were 1 male and 11 females, 21 to 58 years old, 42.25±9.98 years on average, and with illness duration between 5 months and 2.5 years, 14.85±9.68 months on average. Diagnosis of ANFH was confirmed in 6 patients at first visit. Ten patients had received hormonal pulse therapy. The mean oral dosage of hormone at enrollment (scaled by prednisone) was 25.63±5.75 mg/d. The two groups were insignificantly different in the terms of sex, age, illness duration, cases who received hormonal pulse therapy, and oral dosage of hormone at enrollment (P>0.05).

Treatment

All patients were treated by conventional Western medical treatment. Patients were asked to limit the motion of diseased hip joint or reduce the up-stand burdened time for bilateral joint involvement patients. The drugs administered for SLE were the immunosuppressive agents other than the hormone, such as oxychloroquine and cyclophosphamide, to replace the hormone therapy. The dose of the hormone was reduced to ⩽ 0.2 mg/(kg·d) gradually according to the patients' condition. In cases where the patients' SLE condition becomes aggravated, short-time pulse therapy with methylprednisolone might be applied. The drugs administered for ANFH were prescribed as follows: for patients with osteoporosis, activated vitamin D3 0.25 to 0.5 μg/d and Caltrate D tablet 0.6 g/d to supplement calcium, and the patients' blood and urinary calcium levels were reexamined every three months. For patients with hyperlipidemia, the blood lipid-reducing agents (atorvastatin or Fenofibrate) were given. Dipyridamole was given to all patients to antagonize platelet aggregation.

Additionally, Chinese medicine ABDC therapy was administered to patients in the treated group. The decoction was prescribed based on Shentong Zhuyu Decoction (身痛逐瘀汤), which consists of (in one dose) *Radix Gentianae Macrophyllae* 10 g, *Rhizoma Ligusticum wallichii* 15 g, *Semen Juglandis* 9 g, *Flos Carthami* 9 g, *Radix Glycyrrhizae* 6 g, *Rhizoma et Radix Notopterygii* 10 g, *Myrrha* 10 g, *Radix Angelicae sinensis* 15 g, *Faeces Trogopterori* 15 g, *Rhizoma Cyperi* 10 g, *Radix Achyranthis Bidentatae* 15 g, and *pheretima* 10 g. A large dosage (30 g) of *Radix Astragali* was added. The prescription was modified according to the syndrome revealed in patients. For patients with excessive heat toxin, drugs for clearing heat, such as *Radix Scrophulariae*, *Rhizoma Anemarrhenae*, *Cortex Mori radicis*, etc., were added. For patients with yin deficiency and fluid insufficiency, drugs for nourishing yin-blood and dispersing Fei (肺)-qi, such as *Radix Asparagi*, *Radix Ophiopogonis, Radix Paeoniae Alba, Radix Platycodi, Bulbus fritillariae Thunbergii*, etc., were added. The drugs were prepared into decoction. One dose was medicated every day.

Items and Methods of Observation

The observation lasted for 3 years, and outcomes of the following items before and after completed the observation course were compared.

ARCO Stage and Harris Function Scores

ARCO stage[3] and Harris function scores[4] in patients were assessed to evaluate the joint function improving rate. The effectiveness on symptoms was evaluated based on Harris function scoring.

Determination of Levels of Lipids

Levels of lipids in 12 h fasting blood were measured, including total cholesterol (TC), which was measured by COD-PAP method with apparatus made by Hitachi type 7180 and photo-test kit, and triglyceride (TG), which was measured by GPO-PAP method with the same apparatus and test kit of Germany Holma Co.

Routine Tests of Blood Coagulation

Prothrombin time (PT) was determined by one-stage method and activated partial thromboplastin time (APTT) was determined by coagulation method with Acl-TOP test kit (product of System Co. of Instrument, USA).

Hemorrheologic Parameters

Hemorrheologic parameters, including whole blood viscosity (in high, middle, and low shears) and plasma viscosity, were determined with Precil automatic viscosimeter by rotary method.

Case of Endpoint Hip Joint Replacement

The case of endpoint hip joint replacement was calculated at the end of observation.

Evaluation of Effectiveness on Symptoms

The effectiveness on symptoms was evaluated according to the self-formulated criteria: improved denoted that Harris score improved by 30% or more, unchanged denoted that Harris score improved by less than 30%, and worsened denoted that Harris score was lowered.

Statistical Analysis

SPSS software 11.5 was adopted. The measurement data were analyzed by *t*-test. The enumeration data were analyzed by rank-sum test or *Ridit* method. $P<0.05$ was considered statistically significant.

RESULTS

Follow-up

The follow-up study on patients was carried out for 3 years, and observation was completed in all patients. Sixteen patients had ever paused to take Chinese medicine drug medication for < 2 months, four patients had paused for 2 to 4 months and two had paused for 6 to 12 months.

Comparisons of ARCO Stage Distribution and Harris Scores

Before treatment, the ARCO stage distribution and Harris functional scores in the two groups were insignificantly different ($P>0.05$). After treatment, it was shown by *Ridit* analysis that patients in the treatment group had improved ARCO stages and had Harris scores better than those in the control group ($P<0.01$, Table 1).

Comparison of Therapeutic Effectiveness on Symptoms

The symptoms were improved in 16 patients (72.73%) of the treatment group and five patients (41.67%) of the control group. The improving rate was significantly higher in the former ($\chi^2=19.67$, $P<0.05$, Table 2).

Table 2. Comparison of Therapeutic Effectiveness on Symptoms [Case (%)]

Group	Case	Improved	Unchanged	Worsened
Control	12	5 (41.67)	3 (25.00)	4 (33.33)
Treatment	22	16 (72.73)*	4 (18.18)	2 (9.09)

Note: *$P<0.05$, compared with the control group

Comparisons of Blood Lipids and Coagulation-Associated Parameters

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Table 1. Comparisons of ARCO Stage Distribution and Harris Functional Scores

Group	Case/Joint	Time	ARCO stage distribution [No. of Joint (%)]				Harris function score (Score, $\bar{x}\pm s$)
			Ⅰ	Ⅱ	Ⅲ	Ⅳ	
Control	12/19	Pre-treat.	2 (10.53)	8 (42.11)	6 (31.58)	3 (15.79)	40.74±8.91
		Post-treat.	0 (0.00)	3 (15.79)	9 (47.37)	5 (26.32)	42.37±11.52
Treatment	22/32	Pre-treat.	4 (12.50)	13 (40.63)	9 (28.13)	6 (18.75)	42.11±9.32
		Post-treat.	3 (9.38)	11 (34.38)	10 (31.25)	8 (25.00)	60.15±8.83*

Note: *$P<0.01$, compared with post-treatment in the control group

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Table 3. Comparisons of Blood Lipids and Coagulation-Associated Parameters ($\bar{x} \pm s$)

Group	Case	Time	TC (mmol/L)	TG (mmol/L)	PT (s)	APTT (s)
Control	12	Pre-treat.	5.51 ± 0.59	1.41 ± 0.41	11.98 ± 1.12	29.49 ± 3.59
	10	Post-treat.	4.24 ± 0.68*	1.21 ± 0.38	11.97 ± 1.14	28.26 ± 2.67
Treatment	22	Pre-treat.	5.54 ± 0.75	1.54 ± 0.49	11.98 ± 1.10	28.93 ± 3.19
	22	Post-treat.	4.21 ± 0.86*	1.28 ± 0.28	12.51 ± 0.60	32.76 ± 3.59*△

Notes: *P<0.01, compared with pre-treatment in the same group; △P<0.01, compared with post-treatment in the control group

Table 4. Comparisons on Changes of Blood Viscosity ($\bar{x} \pm s$)

Group	Case	Time	Whole blood viscosity (mPa·s)			Plasma viscosity (mPa·s)
			High shear	Middle shear	Low shear	
Control	12	Pre-treat.	4.06 ± 0.71	4.81 ± 0.64	8.38 ± 1.50	1.54 ± 0.53
	10	Post-treat.	3.91 ± 0.63	4.74 ± 0.70	9.06 ± 1.21	1.46 ± 0.29*
Treatment	22	Pre-treat.	4.01 ± 0.63	4.73 ± 0.54	8.59 ± 1.30	1.41 ± 0.30
	22	Post-treat.	3.42 ± 0.65**	4.04 ± 0.24**△△	6.70 ± 0.84**△△	1.21 ± 0.23*△

Notes: *P<0.05, **P<0.05, compared with pre-treatment in the same group; △P<0.05, △△P<0.01, compared with post-treatment in the control group

parameters, including TC, TG, PT, and APTT, were not significantly different between the two groups before treatment (P>0.05). The changes after treatment were as follows: TC levels were lowered in both groups with insignificant difference between groups. APTT was markedly elongated in the treatment group, showing significant difference compared with that before treatment as well as compared with that in the control group (P<0.01, Table 3).

Comparison of Changes in Hemorrheologic Parameters

All hemorrheologic parameters, including whole blood viscosity (high, middle, and low shears) and plasma viscosity were insignificantly different in the two groups before treatment (P>0.05). After treatment, the parameters were significantly lowered in the treatment group (P<0.01), while the changes in the control group, except plasma viscosity (P<0.05), were statistically insignificant (P>0.05). The intergroup differences of all hemorrheologic parameters, except high shear whole blood viscosity, were significant (P<0.05 or P<0.01, Table 4).

Activity of Disease in the Observation Period

In the three years of observation, relapse in SLE occurred in eight of the 34 patients (three in the control group and five in the treatment group) and revealed new skin lesions and large quantity urinary protein (⩾ 3.5 g/24 h). After treatment with short-term prednisolone pulse therapy, aggravation of hip joint pain happened only in one case of the control group.

Case of Hip Joint Replacement

Hip joint replacement was conducted in two cases of the control group, while, in the treatment group, no one underwent an operation in the 3-year observation period.

DISCUSSION

ANFH has a rather high incidence (2.8%–40%) in patients with SLE[5]. For a long time, it was thought that ANFH complication in SLE was mainly related to the chronic application of large-dose glucocorticoid. The report of Li, et al[5] affirmed that the incidence of ANFH was related to the application of high-dose (> 200 mg/d) steroid hormone pulse therapy. The observation of Chen, et al[7] showed that ANFH occurred in 46 out of the 86 atypical pneumonia patients after they have been treated by hormone therapy. The morbidity reached up to 53.5%. However, Colwell, et al[6] reported that no inevitable relation between occurrence of ANFH and hormone therapy could be found in their observation on 1 420 patients who received the hormone therapy for over 10 years due to suffering from asthma or rheumatoid arthritis. The correlation was not expressly analyzed in this study, but the general historical materials showed that, from the 34 patients enrolled, 30 patients had received large-dose hormone pulse therapy, showing a rather high percentage (88.2%), which may embody the intimate relation from another angle.

In Western medical view, the final cause for SLE-ANFH is the obstacle of blood supply. It is in accordance with the Chinese medicine cognition

on "pain is caused by obstruction". Chinese medicine holds that "stasis" appeared in all known pathogenetic processes of ANFH, including lipid metabolism disorder, intravascular coagulation[8], and osteoporosis[9]. It also appeared in the pathologic change (vasculitis) of SLE itself. "Stasis" existed in the whole body of SLE patients, while the application of large-dose hormone could aggravate it further and exhibited emphasis on the femoral head area, thus forming ANFH. Therefore, SLE-ANFH should be treated in view of "stasis" and be put into consideration on ABDC throughout the treatment course with specialties for different phases.

Shentong Zhuyu Decoction is an ancient recipe that originated from "*Yilin Gaicuo* (医林改错)", in which *Radix Gentianae Macrophyllae, Rhizoma et Radix Notopterygii*, and *earthworm* were used for dispersing blockage to dredging collaterals; *Semen Juglandis, Flos Carthami, Faeces Trogopterori, Myrrha*, and *Rhizoma Ligusticum wallichii* for activating blood, running qi, and dissolving stasis; *Rhizoma Cyperi, Fructus Aurantii*, and *Rhizoma Corydalis* for dispersing Gan (肝)-qi to relieve pain; and *Radix Achyranthis Bidentatae* for moving qi to dredging Meridians. Altogether, they remove the stasis, dredge collaterals, and move qi to relieve the pain. The utilization of large-dose *Radix Astragali* in the Chinese herbal decoction used in this study was prescribed based on the primary modifying method. Based on Chinese medicine view, qi is the impulse force of blood circulation. Since the chronic course of illness has injured the organism, led to qi blood insufficiency, and aggravated the stasis, enhancing qi force by administering drugs for supplementing qi, such as *Radix Astragali*, is a good measure for promoting blood circulation to remove the "dead bone" and regenerate the "new bone", which is the so-called "to regenerate new bone by removing stasis".

Moreover, through modern pharmacological researches, the component of *Flos Carthami*, its total flavine, was proven to have anti-inflammatory, analgesic, and anti-thrombus formation actions. Its flavochrome could prolong PT and blood coagulation time and markedly increase the activity of profibrinolysin activator to enhance the local thrombus dissolved[10]. Water extract of *Pheretima* was found by Hu, et al[11] to be capable of reducing the length of extracorporeal thrombus and its wet and dry weights as well as suppressing erythrocyte aggregation, lowering plasma fibrinogen content, decreasing the whole blood viscosity in all shearings, and improving the deformability of red blood cells. The water decocted and ethanol-settled extracts of *Rhizoma et Radix Notopterygii* were illustrated by Zhang, et al[13] as effective in preventing thrombus formation, platelet aggregation, and fibrino-thrombus formation and its growth velocity to prolong the thrombosis time in rabbit *in vitro*, while *Radix Achyranthis Bidentatae* was proven to have apparent anti-inflammatory analgesic action. Cyperone, an extract from *Rhizoma Cyperi*, was proven as a strong prostaglandin synthetic inhibitor, showing evident analgesic effect *Radix astragali* has an immunoregulating action.

Based on the above-mentioned finding, the Shentong Zhuyu Decoction was taken by the authors as the basic recipe, with additional large dosage of *Radix astragali* for strengthening and activating the power of qi-supplementing, blood-nourishing. The prescription could be modified depending on the different phases of ANFH. At active stage, the disease is dominant in excessive heat toxin. The treatment should be cooling and activating blood with large amount of drugs for clearing heat. At quiescent phase, when yin deficiency and fluid insufficiency are of dominance, treatment should be nourishing and activating blood while using drugs for dispersing Fei and running qi.

The current conservative treatments, both western and Chinese medicines, all target mainly the prevention of osteonecrosis and femoral head collapse, whereas Chinese medicine ABDC therapy used in this study reached, as an additional finding, an effect of retarding the occurrence of osteonecrosis, showing that the post-treatment ARCO stage distribution is better in the treatment group than that in the control group ($P<0.05$). Although the treatment could not reverse the X-ray feature in patients of stage Ⅲ to Ⅳ, it could obviously reduce the local pain, improve the patients' QOL and function of lower limb, and diminish the necessity of joint replacement operation (two cases in the control group received the operation but none in the treatment group). Therefore, treatment must be continued even during cases of illness worsening. Moreover, the results of the observation showed that ABDC treatment could be effective to prolong APTT and decrease whole

blood and plasma viscosity, which could facilitate to reduce the possibility of intravascular micro-thrombus formation and improve the blood circulation in hip joint area.

In the observation period, the hormonal pulse therapy was applied for eight patients (three cases in the control group and five cases in the treatment group) with developing SLE disease. After pulse therapy, aggravation of joint pain was found in one case of the control group but none in the treatment group, suggesting that, when SLE-ANFH becomes active, short-term application of the hormone pulse therapy is necessary to avoid loss of time of treating the primary disease due to misgiving on ANFH by any means. At the same time, ABDC therapy should be stressed to prevent the aggravation of ANFH.

In sum, ABDC treatment is a beneficial measure for patients with SLE-ANFH, even for those being confirmed to have late-stage femoral head necrosis. It could effectively delay the progress of the illness, improve the QOL in the patients, and thus have the potential to diminish the possibility of joint replacement operation. It might realize the effect by way of correcting, in multiple orientations and multiple targets, blood hypercoagulation and thrombus formation in patients.

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