

Original Article

Investigation of the effect of Huaiqihuang granules via adjuvant treatment in children with relapsed systemic lupus erythematosus

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Abstract: Objective: To investigate the therapeutic effect of Huaiqihuang granules in children with relapsed systemic lupus erythematosus (SLE), and analyze its impact on the regulation of inflammatory factors, immune function, and recurrence rate. Methods: Seventy-six children with relapsed SLE were evenly divided into two groups, the control group with conventional SLE treatment and the observation group which was treated with Huaiqihuang granules on the basis of the conventional treatment. After 8 weeks of treatment, the positive rate of antinuclear antibody (ANA) titer, 24-hour urine protein (24 h Upro), serum inflammatory factors, monocyte chemoattractant protein 1 (MCP-1), receptor for advanced glycation end products (RAGE) level and systemic lupus erythematosus disease activity index (SLEDAI) score were compared. The recurrence rate of SLE between the two groups was also analyzed at the 6-month follow-up. Results: Compared with before treatment, the positive rate of ANA titer, 24 h Upro, and serum interleukin-10 (IL-10) and tumor necrosis factor family B cell activating factor (BAFF) levels in the two groups of children were decreased after treatment; in addition, levels of these parameters in the observation group were significantly lower than those of the control group. The interleukin-2 (IL-2) level of both groups was significantly increased after treatment, and the observation group showed a significantly higher level of IL-2 than that of the control group (all $P < 0.05$). After treatment, serum MCP-1 and RAGE levels of the two groups were considerably lower compared with that before treatment, which were significantly lower in the observation group than those of the control group (all $P < 0.05$). SLEDAI scores of the two groups were significantly decreased after treatment, which were notably lower in the observation group than those of the control group (all $P < 0.05$). The six-month follow-up demonstrated that the recurrence rate of SLE in the observation group was remarkably lower than that of the control group ($P < 0.05$). Conclusion: The adjuvant treatment by Huaiqihuang granules can effectively reduce the inflammatory response, decrease the disease activity of SLE, and lower the recurrence rate in children with SLE relapse, which is worthy of clinical application.

Keywords: Systemic lupus erythematosus, children, relapse, Huaiqihuang granules

Introduction

Systemic lupus erythematosus (SLE) is a common autoimmune disease. The main pathological changes with SLE include excessive production of autoantibodies and Th1/Th2 imbalance; ultimately leading to the dysfunction of the immune system in the body [1]. SLE can affect multiple tissues and organs, such as the kidney, joints, skin, blood system, etc., and as

such it has a large impact on health [2]. Although SLE occurs more commonly among women of childbearing age, the incidence of SLE in children is also high, accounting for approximate 15% to 20% of the total number of SLE cases, in which it presents with atypical symptoms [3]. Thus, the treatment of children with SLE is more challenging. Conventional treatment for this disease include the use of glucocorticoids and immunosuppressive

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agents, however, some patients have a poor response to hormones, therefore, the therapeutic effect is limited [4].

Huaiqihuang granules are usually applied in the adjuvant treatment of nephropathy, mycoplasma pneumoniae pneumonia, etc. [5, 6]. Studies have reported that supplemental administration of Huaiqihuang granules in combination with glucocorticoid therapy can effectively ameliorate the inflammatory status of children with allergic purpura and relieve the clinical symptoms [7]. Huaiqihuang granules have also been utilized in the treatment of SLE, and it shows a promising outcome, but the therapeutic effect on children with relapsed SLE is still unknown [8]. Therefore, this study mainly aims to explore the effect of Huaiqihuang granules in combination with conventional treatment using glucocorticoids or immunosuppressive agents on the clinical efficacy and recurrence rate in children with relapsed SLE, and to analyze its role in the regulation of the inflammatory response and immune function.

Materials and methods

General information

A total of 76 children with SLE (from February 2019 to January 2020) were selected as research subjects, they were divided into the observation group and the control group, with 38 children in each group, using a random number table. Inclusion criteria: aged 2 to 13 years old; diagnosis in accordance with the diagnostic criteria in the "Chinese Guidelines for the Diagnosis and Treatment of Systemic Lupus Erythematosus" [9]; children with relapsed SLE; children with a positive rate of antinuclear antibody (ANA) titer; signature of informed consent by family members. Exclusion criteria: recently treated children; other autoimmune diseases; allergic to the medications in this study; participation in other projects at the same time. This study was approved by the Ethics Committee of the Affiliated Municipal Hospital of Taizhou University.

Methods

The control group was given conventional treatments, such as glucocorticoids or immunosuppressants including sodium hydrocortisone succinate (Fuan Pharmaceutical (Group) Hubei People's Pharmaceutical Co., Ltd., China, 50

mg) which were diluted with saline solution and intravenously injected, 50 mg/d; cyclophosphamide (Jiangsu Hengrui Pharmaceutical Co., Ltd., China, 0.5 g) that was intravenously injected for pulse therapy and administered at a dose of 10 mg/(kg·d), once a week, for 8 weeks. The observation group was administered Huaiqihuang granules (Qidong Gaitianli Pharmaceutical Co., Ltd., China, 10 g) based on the conventional treatment, half bag/time for children under 3 years old, 1 bag/time for 3-15 years old, 2 times/d, for 8 weeks.

Observation indices

Major indices: (1) Five milliliters of venous blood was collected from children, of which 2 mL was let coagulate and centrifuged, and the serum was collected for further use. The positive rates of serum ANA titer before and after treatment were compared between the two groups. ANA detection was carried out by Western blotting, the kit was purchased from Oumeng Company, Germany. Briefly, this experiment was conducted as follows: Hep-2 cells were used as the substrate, the serum to be tested was prepared by serial dilution as 1:100, 1:320, 1:1000, 1:3200, 1:10000, and ANA titer $\geq 1:100$ was considered as positive.

(2) Patient's 24-hour urine was collected, which was used to quantify the 24-hour urine protein (24 h Upro) by the biuret method using an ultraviolet-visible spectrophotometer (Shanghai Puyuan Instrument Co., Ltd., China).

(3) ELISA was applied to detect serum levels of interleukin-2, 10 (IL-2, IL-10) and tumor necrosis factor family B cell activating factor (BAFF). The kits were all purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd., China, and all experiments were carried out according to the instructions of the kits.

(4) ELISA was utilized to detect serum monocyte chemoattractant protein 1 (MCP-1) and receptor for advanced glycation end products (RAGE) levels. The kits were all purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd., China, and all experiments were performed in accordance with the instructions of the kits.

Minor indices: (1) The systemic lupus erythematosus disease activity index (SLEDAI) score was applied to evaluate the SLE activity of the

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Table 1. Comparison of general information of the two groups of children (n, $\bar{x} \pm sd$)

Index	Observation group (n=38)	Control group (n=38)	χ^2/t	P
Gender			0.396	0.529
Male (n)	7	5		
Female (n)	31	33		
Age (years)	9.8±2.2	10.1±2.8	0.519	0.605
Disease course (years)	4.7±1.0	4.9±1.2	0.789	0.432
ANA titer positive (n)	38	38	/	/

Note: ANA: antinuclear antibody.

Table 2. Comparison of the positive rate of ANA titer between the two groups of children before and after treatment

Group	Time	Positive rate of ANA titer (%)
Observation group (n=38)	Before treatment	38 (100.00)
	After treatment	12 (31.58)*.#
Control group (n=38)	Before treatment	38 (100.00)
	After treatment	22 (57.89)*

Note: Compared with before treatment, *P<0.05; compared with control group, #P<0.05. ANA: antinuclear antibody.

Table 3. Comparison of 24 h Upro and BAFF levels before and after treatment in the two groups ($\bar{x} \pm sd$)

Group	Time	24 h Upro (g)	BAFF (mg/L)
Observation group (n=38)	Before treatment	2.33±0.76	0.83±0.20
	After treatment	0.96±0.27*.#	0.32±0.12*.#
Control group (n=38)	Before treatment	2.42±0.80	0.87±0.21
	After treatment	1.36±0.38*	0.49±0.15*

Note: Compared with before treatment, *P<0.05; compared with control group, #P<0.05. BAFF: tumor necrosis factor family B cell activating factor; 24 h Upro: 24-hour urine protein.

two groups of children before and after treatment [10]. The SLEDAI score included 99 points, 0-4 points represented no activity, and equal or above 15 points represented severe activity.

(2) Follow-up at 6 months was used to assess the recurrence rate of SLE between the two groups.

Statistical analysis

SPSS 20.0 was utilized to analyze the data. The counting data was presented by %, and the comparison analysis was done by χ^2 test. The quantitative data was presented as mean \pm standard deviation ($\bar{x} \pm sd$), and the comparison was conducted by t test. P<0.05 indicated

that the difference was statistically significant between groups.

Results

Comparison of general information between the two groups of children

There was no statistically significant difference between the two groups of children regarding general information including gender, age, and disease course (P>0.05). Indices were comparable between these 2 groups (**Table 1**).

Positive rate of ANA titer

Compared with before treatment, the positive rate of ANA titer of the two groups of children were both significantly decreased after treatment, and the observation group showed a significantly lower rate than that of the control group (all P<0.05; **Table 2**).

Comparison of 24 h Upro and BAFF levels

Compared with before treatment, the 24 h Upro and BAFF levels in the two groups of children were notably decreased after treatment, and the levels

in the observation group were significantly lower than those of the control group (all P<0.05; **Table 3** and **Figure 1**).

Inflammatory factor levels

Compared with before treatment, serum IL-2 levels of the two groups of children increased considerably, while serum IL-10 levels were remarkably decreased after treatment, and the changes in the observation group were significantly more obvious (all P<0.05; **Table 4** and **Figure 2**).

Serum MCP-1 and RAGE levels

After treatment, serum MCP-1 and RAGE levels in the two groups of children were significantly

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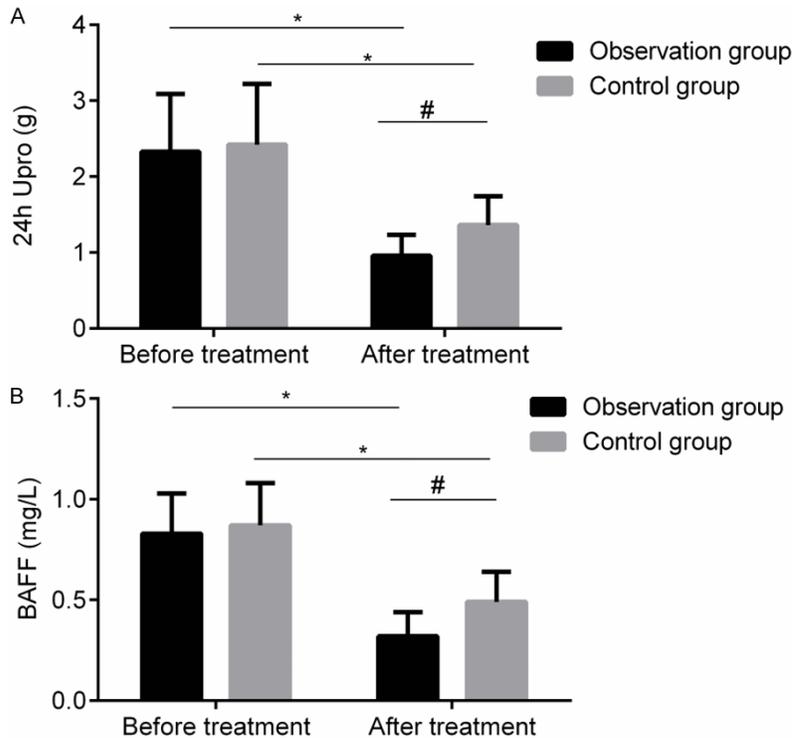


Figure 1. Comparison of 24 h Upro and BAFF levels before and after treatment in the two groups. A: 24 h Upro level; B: BAFF level. Compared with before treatment, * $P < 0.05$; compared with control group, # $P < 0.05$. BAFF: tumor necrosis factor family B cell activating factor; 24 h Upro: 24-hour urine protein.

Table 4. Comparison of the levels of inflammatory factors between the two groups of children before and after treatment ($\bar{x} \pm sd$)

Group	Time	IL-2 (pg/mL)	IL-10 (pg/mL)
Observation group (n=38)	Before treatment	32.48±3.09	26.60±4.86
	After treatment	35.50±3.44*#	18.98±3.20*#
Control group (n=38)	Before treatment	32.03±4.15	27.02±5.49
	After treatment	33.87±3.20*	22.37±4.40*

Note: Compared with before treatment, * $P < 0.05$; compared with control group, # $P < 0.05$. IL-2: interleukin-2; IL-10: interleukin-10.

lower than those before treatment, and those in the observation group were significantly lower in comparison to the control group (all $P < 0.05$; **Table 5**).

SLEDAI score

After treatment, the SLEDAI scores of the two groups of children were significantly lower than those of before treatment, with levels in the observation group being notably lower compared with the control group (all $P < 0.05$; **Table 6** and **Figure 3**).

Recurrence rate

The six-month follow-up revealed that the recurrence rate of SLE in the observation group was 2.63% (1/38), which was significantly lower than that of the control group, 15.79% (6/38; $P < 0.05$). The recurrence time of 1 case in the observation group was 4 months post-discharge; whereas 1 relapsed case was found in the control group 2 months post-discharge, 3 cases were recorded 3 months post-discharge, and 1 case was found 4 months and 5 months post-discharge, respectively.

Discussion

In this study, the serum IL-2 levels in the two groups of children were significantly increased after treatment, while the levels of IL-10 and BAFF were notably decreased, and the differentials were larger in the observation group. BAFF can stimulate the rapid proliferation and differentiation of B cells in our body and produce a large amount of autoantibodies and cytokine IL-10, in which the autoantibodies can activate

the complement system and this results in tissue and organ damage; while IL-10 plays an immunomodulatory role [11]. When there is INF- α in our body, the role of IL-10 can be switched from anti-inflammatory to pro-inflammatory [12]. Garić et al. have found that mice with elevated plasma BAFF levels may be accompanied with neutropenia and other clinical manifestations that are similar to SLE [13]. Geginat et al. have reported that the elevated level of serum IL-10 in patients with SLE positively correlates with the ANA antibody titer and disease activity of SLE [14]. Our results have

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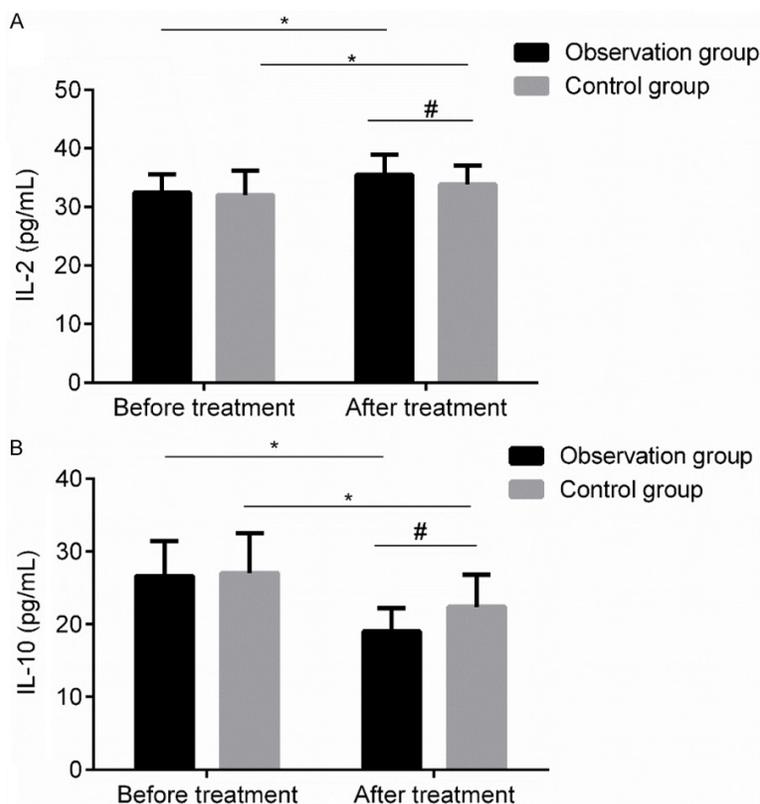


Figure 2. Comparison of the levels of inflammatory factors between the two groups of children before and after treatment. A: IL-2 level; B: IL-10 level. Compared with before treatment, * $P < 0.05$; compared with control group, # $P < 0.05$. IL-2: interleukin-2; IL-10: interleukin-10.

demonstrated that the SLEDAI scores of children in the observation group are significantly lower than those in the control group after treatment, suggesting that supplementation with Huaqihuang granules after conventional treatment, helps diminish the inflammatory response and disease activity of SLE in children with relapsed SLE.

Chemokines play important roles in the initiation and development of autoimmune diseases. Several studies have shown that MCP-1 plays a key role in the SLE kidney and autoimmune damage [15, 16]. RAGE is a receptor for advanced glycation end products, and it is a transmembrane protein belonging to the immunoglobulin superfamily that can amplify and exacerbate immune response. It has been demonstrated that serum RAGE can be used as an auxiliary non-invasive index to estimate the prognosis of SLE and can also serve as an auxiliary indicator for the proliferative and non-proliferative lupus nephritis [17]. This study has

shown that serum MCP-1 and RAGE levels of the two groups of children after treatment were significantly lower than those of before treatment, and the levels in the observation group were significantly lower in comparison to the control group, indicating that supplementation of Huaqihuang granules based on the conventional treatment can effectively reduce the level of chemokines and inhibit an excessive immune response. These effects are attributed to the pharmacological mechanism of Huaqihuang granules. This medication is refined from Polygonatum, Lycium barbarum, Huaier cream, etc., which can benefit Qi and nourish Yin in the perspective of traditional Chinese medicine. Modern pharmacological studies reveal that Huaqihuang granules have anti-inflammatory, immunity enhancing and other benefits [18]. Basic research has also confirmed that Polygonatum Poly-

saccharide, the main component of Polygonatum, has a certain immunomodulatory effect, which can stimulate the production of a variety of cytokines and enhance the immune function in mice [19]. Additionally, Lycium barbarum nourishes the liver, kidneys, Yin, and blood. Modern pharmacology has demonstrated that Lycium barbarum has the effect of strengthening immunity as well [20].

Tanha et al. have reported that SLE can lead to proteinuria and compromise renal function after targeting the kidney [21]. After treatment, proteinuria can be gradually decreased coupled with the recovery of SLE. The data from our study have demonstrated that the positive rate of ANA titer and 24 h Upro in children with relapsed SLE after treatment in the observation group were significantly lower than those in the control group, indicating that supplementation of Huaqihuang granules on the basis of conventional treatment can decrease the ANA titer of children with relapsed SLE and reduce

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Table 5. Comparison of serum MCP-1 and RAGE levels before and after treatment in the two groups of children ($\bar{x} \pm sd$, pg/mL)

Group	Time	MCP-1	RAGE
Observation group (n=38)	Before treatment	213.39±14.33	1830.08±133.33
	After treatment	140.07±12.40*.#	936.60±142.08*.#
Control group (n=38)	Before treatment	212.98±15.05	1870.26±140.04
	After treatment	163.40±14.96*	1130.08±103.75*

Note: Compared with before treatment, *P<0.05; compared with control group, #P<0.05. MCP-1: monocyte chemoattractant protein 1; RAGE: receptor for advanced glycation end products.

Table 6. Comparison of SLEDAI scores between the two groups of children before and after treatment ($\bar{x} \pm sd$, score)

Group	Time	SLEDAI score
Observation group (n=38)	Before treatment	35.75±5.49
	After treatment	22.20±4.35*.#
Control group (n=38)	Before treatment	36.04±6.33
	After treatment	28.70±4.49*

Note: Compared with before treatment, *P<0.05; compared with control group, #P<0.05. SLEDAI: systemic lupus erythematosus disease activity index.

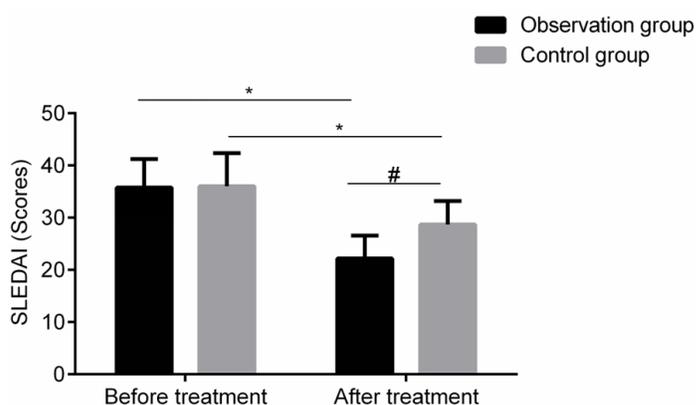


Figure 3. Comparison of SLEDAI scores between the two groups of children before and after treatment. Compared with before treatment, *P<0.05; compared with control group, #P<0.05. SLEDAI: systemic lupus erythematosus disease activity index.

urine protein concentration. ANA antibody is a representative autoantibody in SLE, and the positive rate of ANA titer can reflect the progress of SLE to a certain extent [22]. SLE affects multiple tissues and organs, of which the kidney is one of the most sensitive ones. After the kidneys are compromised, proteinuria, hematuria, tubular urine and other manifestations can appear, in which proteinuria is the most common symptom [23]. Twenty-four-hour Upro is an indicator that reflects the protein content in the urine within 24 hours in our body. The higher the value, the more severe the proteinuria and

the worse the kidney function. The research by Guo et al. have also revealed that Huaiqihuang granules show a protective effect on kidney function [24]. Li et al. have suggested that Huaiqihuang granules prevent proteinuria by targeting p-ERK/CHOP pathway to inhibit the damage of MPC5 podocytes [25]. Finally, our study has analyzed the recurrence rate of SLE 6 months post-discharge. The results have shown that the recurrence rate of SLE in the observation group is significantly lower than that in the control group, indicating that the supplementary treatment with Huaiqihuang granules on the basis of conventional treatment can effectively reduce the recurrence rate of relapsed SLE in children post-discharge. However, the sample size of this study is limited, and the follow-up time is only 6 months. Thus, the effect of adjuvant Huaiqihuang granules on the long-term efficacy and recurrence rate of relapsed SLE in children warrants further studies.

In summary, supplementation of Huaiqihuang granules on the basis of conventional treatment can effectively alleviate the inflammatory response in children with relapsed SLE, improve their immune function, reduce the disease activity of SLE, and decrease the recurrence rate, which is worthy of clinical application.

Disclosure of conflict of interest

None.

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