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Original Article

Clinical effect of combined western medicine and traditional Chinese medicine on children with Henoch-Schönlein purpura nephritis

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Abstract: Objective: To investigate the efficacy of combined Chinese and western medicine in the treatment of children with Henoch-Schönlein purpura nephritis (HSPN) and its effects on immune function, interleukin (IL)-16, and IL-18 expressione. Methods: The clinical data of 91 children with HSPN were retrospectively collected and divided into two groups according to the treatment regimen. Group A (n=45) was treated only with western medicine, while group B (n=46) was treated with combined Chinese and western medicine. The clinical efficacy, traditional Chinese medicine (TCM) syndrome points before and after treatment, immune function indices, urinary indices, levels of IL-16 and IL-18, and the recurrence rate were compared between the two groups. Results: The total effective rate was 95.65% in group B, higher than 75.56% in group A (P<0.05). The TCM scores after treatment in group B was lower than that in group A (P<0.05). The levels of immunoglobulin IgA and IgM after treatment were lower while IgG levels were higher in group B than those in group A (P<0.05); Urinary microalbumin, urinary beta$_2$ microglobulin, 24 h urine protein elimination, and red blood cells (RBC) in the urine were lower in group B after treatment than in group A (P<0.05). The serum levels of IL-16 and IL-18 in group B were lower than those in group A after treatment (P<0.05). The recurrence rate was 4.35% in group B, lower than 26.67% in group A (P<0.05). Conclusion: Combined regimen of western and Chinese medicine in children showed significant efficacy on improving immune function and reducing recurrence rate and IL-16 and IL-18 levels in patients with HSPN.

Keywords: HSPN, combination of western and Chinese medicine, efficacy, immune function, IL-16, IL-18

Introduction

Clinically, Henoch-Schönlein purpura nephritis (HSPN), also known as self-limiting bleeding, is an allergic cutaneous vasculitis that can attack capillaries and arterioles in the skin as well as other organs [1]. Under the influence of allergies, certain drugs, and pathogen factors, IgG- or IgA-type circulating immune complexes can be deposited in the upper capillaries of the dermis, causing vasculitis, which is commonly manifested as kidney failure, joint pain, abdominal pain, and purpura [2, 3]. HSPN refers to allergic purpura with necrotic small vessel inflammation as a pathological manifestation of renal damage, in addition to the appearance of clinical symptoms such as blood in the stool, abdominal pain, arthralgias and skin purpura, but also proteinuria, hematuria, and in severe cases, even impair renal function [4, 5].

The clinical treatment options of HSPN include control of the immune inflammatory response, inhibition of mesangial proliferative lesions, and effective prevention of chronic fibrotic lesions in the kidney [6, 7]. Pharmacotherapy is one of the common modalities for HSPN, and for cases of pathological grade (IIIb and IV), nephrotic syndrome, and severe pathological damage, a combination of hormonal drugs and immunosuppressants is usually prescribed [8, 9]. Although conventional western medical therapy can achieve certain therapeutic effects, it may also trigger adverse reactions and is prone to relapse, seriously affecting the daily life of children [10]. There is no record of HSPN in Chinese medical classics, and the etiology and pathogenesis of the disease can be classified into the category of "emia", "purpura" and "macula". "Yin toxin" and "yang toxin" are the causing factors [11].

In recent years, traditional Chinese medicine (TCM) has been widely used in the treatment of HSPN in China, and synergistic treatment with western medicine can further improve the clinical efficacy. In view of this, the present study aimed to investigate and compare the western and Chinese medicine in the treatment of pediatric allergic purpura nephritis, thereby improving the clinical efficacy and pediatric immune function.

Materials and methods

Baseline data

The clinical data of 91 children with HSPN in our hospital were retrospectively collected and divided into two groups according to the treatment regimen, among which group A (n=45) was treated only with western medicine, and group B (n=46) was treated with a combination of Chinese and western medicine. (1) Inclusion criteria: symptoms of pediatric patients in line with the diagnostic criteria for HSPN of "Diagnosis and Treatment of Purpuric Nephritis (Draft)" [12]; pathological classification: grade IIIb or IV. Informed consent of the parents of the children was obtained. This study was approved by the medical ethics committee. (2) Exclusion criteria: patients who requested to withdraw during the investigation, and those with severe gastrointestinal, respiratory, and hematologic disorders, severe immune dysfunction, congenital organ and tissue development abnormalities, and hypersensitivity to the drugs used in the study were excluded.

Methods

Group A was treated with hormone drugs combined with immunosuppressive agents, and given oral prednisone (H41025342, Shanghai Quanyu Biotech Queshan Pharmaceutical Co., Ltd.) The dosage was 2 mg/(kg.d), and the maximum dosage was controlled at 60 mg/d. After 4 weeks, the dosage was gradually reduced while 10 mg/(kg.d) cyclophosphamide was administrated (H20160467: Baxter Oncology GmbH Specification). 2 days of intravenous drip and 2 weeks of interruption was a course of treatment. Continuous 6-8 courses of treatment were performed and the cumulative amount of cyclophosphamide was controlled below 150 mg/kg, if the pathology showed diffuse distortion or crescent formation, methylprednisolone 15-30/(kg.d) (H20103047, Tianjin Jinyao Pharmaceutical Industry Co., Ltd) was prescribed every other day or once a day, and the maximum dose was controlled <1 g/d.

In group B, western medical treatment was applied the same as Group A. Meanwhile, Chinese herbals were prepared with the following prescriptions: Chinese yam 15 g, herba cirsii 15 g, Amur Corktree Bark 10 g, Polygonatum sibiricum 10 g, Yetbadetajo Hert extract 10 g, hairyvein agrimonia 10 g, Salvia miltiorrhiza 10 g, Fengyi 15 g, Achyranthes aspera 30 g, Gordon Euryale seed 10 g, Hedyotis diffusa 10 g, and Rehmannia glutinosa 10 g. 400 ml decoction of the above herbs was prepared and orally taken in the morning and evening, respectively, for 3 months.

Outcomes measurement

Therapeutic efficacy criteria [13]: If clinical symptoms were completely disappeared and the results of RBCs in urine sediment and 24-hour urine protein quantitation were normal, it was considered to be clinically controlled; if the urine protein decreased by "++", RBCs and 24 h urine protein decrease by 40% or more, it was considered to be improvement; if the urine protein decreased by "+", RBCs and 24 h urine protein decreased by less than 40%, it was considered to be effective; if the results of all tests had not improved or even worsened, it was considered to be ineffective. Effective + improved + clinically controlled = total effective.

TCM symptoms points [14]: Before and after treatment, TCM symptoms points were calculated according to the severity of symptoms, with primary symptoms calculated according to a 0-6 point scoring system and secondary symptoms calculated on a 0-3 Likert scale, and the severity of symptoms was proportional to the points.

Immune function indices: Before and after treatment, 2 ml of morning fasting venous blood was collected from both groups of children, and plasma immunoglobulin IgA, IgM and IgG levels were measured by immunoscattering turbidimetry and operated in strict accordance with the kit instructions. IgA, IgM and IgG kits (Item No. K15183B-1) were all purchased from Beijing Sino-uk Institute of Biological Technology.

Table 1. Comparison of baseline data between the two groups [n (%)]/($\bar{x}$ ± s)

Baseline data		Group A (n=45)	Group B (n=46)	t/X^2	P
Gender (cases)	Male	31 (68.89)	33 (71.74)	0.089	0.766
	Female	14 (31.11)	13 (28.26)		
Age (years)		10.25±0.15	10.28±0.13	1.020	0.310
Duration of illness (months)		1.85±0.13	1.88±0.09	1.282	0.203
Pathological typing (cases)					
Class IIIb		29 (64.44)	31 (67.39)	0.088	0.767
Class IV		16 (35.56)	15 (32.61)		

Table 2. Comparison of the efficacy [n (%)]

Group	Cases	Clinically controlled	Improvement	Effective	Ineffective	Total effective rate
Group A	45	9 (20.00)	12 (26.67)	13 (28.89)	11 (24.44)	34 (75.56)
Group B	46	13 (28.26)	16 (34.78)	15 (32.61)	2 (4.35)	44 (95.65)*
X^2						7.503
P						0.006

Note: *indicates the comparison with group A, P<0.05.

Table 3. Comparison of TCM points between the two groups ($\bar{x}$ ± s, min)

Group	Pre-treatment	Post-treatment
Group A (n=45)	51.58±5.68	32.15±1.05#
Group B (n=46)	51.62±5.62	20.12±1.02#,*
t	0.034	55.439
P	0.973	0.000

Note: #indicates comparison with pre-treatment, P<0.05; *indicates comparison with group A, P<0.05.

Routine urine test [15]: Before and after treatment, routine urinalysis was performed in both groups, and urine microalbumin, urine β_2 microglobulin, 24 h urine protein and red blood cell (RBC) count in urine were all determined by automatic biochemical analyzer.

Interleukin (IL)-16 and IL-18 [16]: Before and after treatment, 2 ml of morning fasting venous blood was collected from both groups, centrifuged at 2000 r/min for 15 min, and serum IL-16 and IL-18 levels were determined by enzyme-linked immunosorbent assay. IL-16 kit (Item No. ZN2652) was purchased from Qingdao Jieshikang Biotechnology Co., Ltd., and IL-18 kit (Item No. XY-SJH-N1511) was purchased from Shanghai Xinfan Biological Technology Co., Ltd.

Disease recurrence rate: The two groups of children were followed up for 3 months after treatment to compare the recurrence rate of disease.

Statistical methods

SPSS 22.0 was used for data analysis. Measurement data were expressed as mean ± standard deviation. t test was used for normally distributed data, while Mann-Whitney U test was used for non-normally distributed data. Count data [n (%)] were compared by X^2 test. P<0.05 indicated statistical significance.

Results

Comparison of baseline data

No statistical significance (P>0.05) (**Table 1**) was found in terms of sex, age, disease duration and pathological type between the two groups.

Comparison of the efficacy

The total effective rate was 95.65% in group B, higher than 75.56% in group A (P<0.05) (**Table 2**).

Comparison of the TCM points

There was no significant difference in pre-treatment TCM points (P>0.05). After treatment, TCM points were decreased in both groups

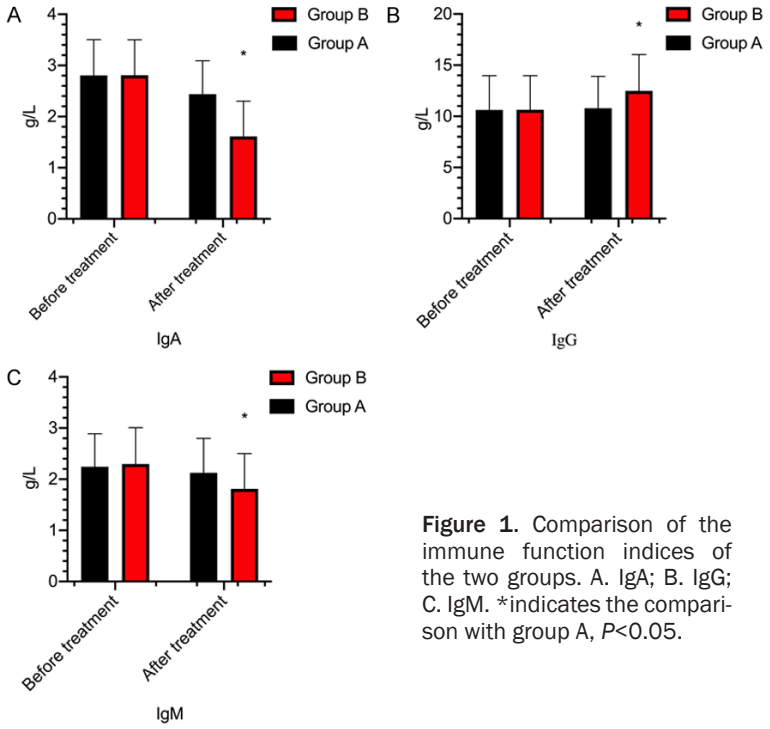

Figure 1. Comparison of the immune function indices of the two groups. A. IgA; B. IgG; C. IgM. *indicates the comparison with group A, $P<0.05$.

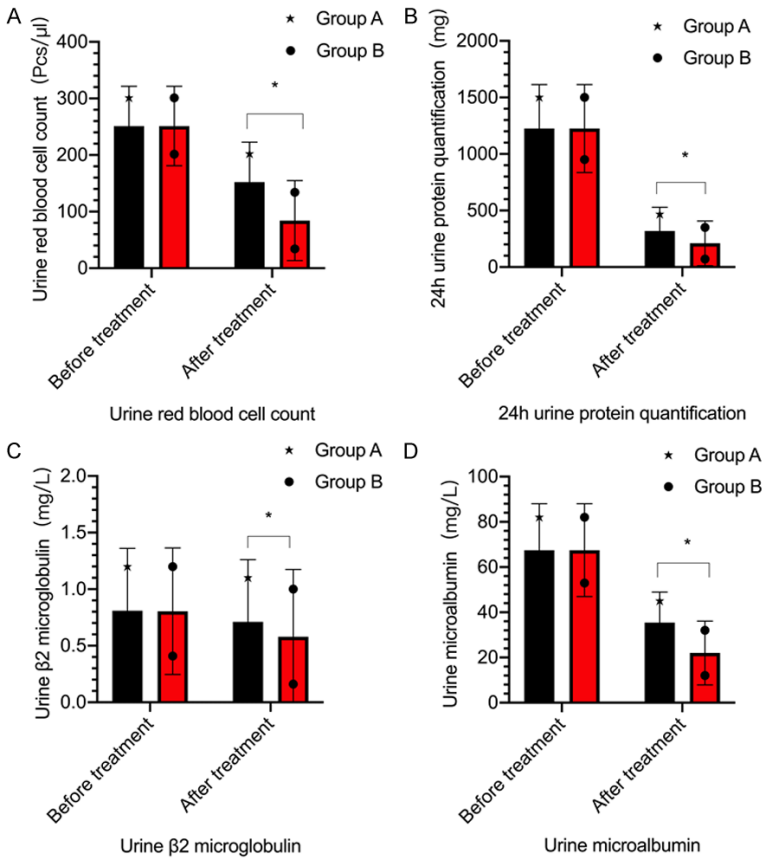

Figure 2. Comparison of routine urinary parameters between the two groups. A. Urine RBCs; B. 24 h urine protein quantification; C. Urinary β_2 microglobulin; D. Urinary microalbumin. *indicates the comparison with group A, $P<0.05$.

($P<0.05$) and were lower in group B than in group A ($P<0.05$) (**Table 3**).

Comparison of immune function indices

The levels of IgA, IgM, and IgG showed no significant difference between the two groups before treatment ($P>0.05$). Compared with those before treatment, the levels of IgA and IgM were abnormally lower and the levels of IgG were increased ($P<0.05$). Group B exhibited lower the levels of IgA and IgM and higher levels of IgG than group A ($P<0.05$) (**Figure 1**).

Comparison of urinary routine parameters

There was no significant difference in urine routine indices between the two groups before treatment ($P>0.05$). Compared with before treatment, urine microalbumin, urine β_2 microglobulin, 24 h urine protein, and RBC count were all decreased after treatment ($P<0.05$). Compared with group A, group B had lower indices above after treatment ($P<0.05$) (**Figure 2**).

Comparison of IL-16, IL-18

The two groups showed no significant difference in pretreatment serum IL-16 and IL-18 levels ($P>0.05$). Both serum IL-16 and IL-18 levels were decreased after treatment ($P<0.05$). The serum IL-16 and IL-18 levels of group B were lower than those of group A after treatment ($P<0.05$) (**Figure 3**).

Comparison of disease recurrence rates

There were 12 children of relapses in group A and 2 chil-

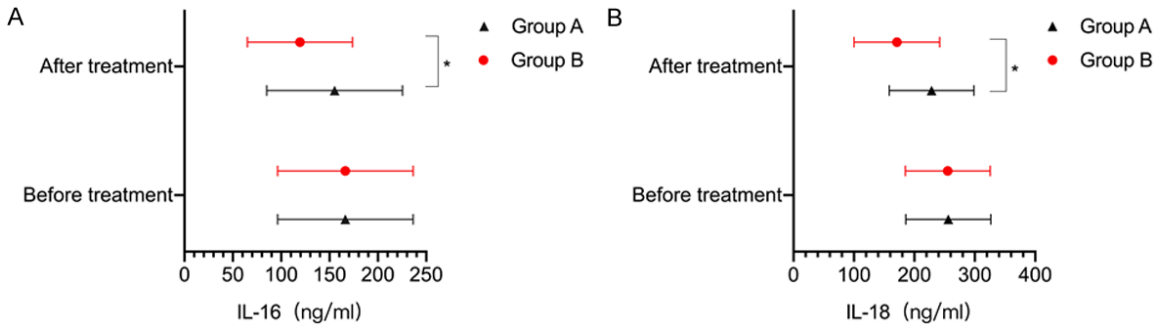

Figure 3. Comparison of IL-16 and IL-18 levels between the two groups. A. IL-16 levels; B. IL-18 levels. *indicates the comparison with group A, $P<0.05$.

Table 4. Comparison of recurrence rate [n (%)]

Grouping	Cases	Disease recurrence rate
Group A	45	12 (26.67)
Group B	46	2 (4.35)*
X^2		8.704
P		0.003

Note: *indicates the comparison with group A, $P<0.05$.

dren of relapses in group B, and the disease relapse rate was 4.35% in group B, lower than 26.67% in group A ($P<0.05$) (**Table 4**).

Discussion

The pathogenesis of HSPN may include abnormal coagulation mechanisms, flood of inflammatory mediators, inflammatory cell infiltration, and abnormal cellular and humoral immunity [17]. In general, children with HSPN show markedly elevated levels of IgA in the early stage and deposit in multiple tissues, mainly in the skin and kidneys [18]. The high levels of IgA are caused by allergens-mediated immune metamorphosis, which promotes B-cell dysfunction and impairs immune function, resulting in urinary protein and hematuria symptoms [19, 20]. Secondly, the inflammatory response of capillary wall will increase capillary permeability, causing bleeding, edema, which significantly reduces the IgG level and increases IgM level [21]. In this study, IgA and IgM levels of children in group B were lower than those in group A, and IgG levels were higher, suggesting that combined western and Chinese medicine could improve the immune function. The mechanism may be that hormonal drugs could bind to intracellular hormone receptors, form dimers and inhibit the exudation of inflammatory cells. Immunosuppressants, on the other hand, can effectively prevent infections, thus improving cellular and humoral immune functions [22]. In this study, decoction of amur corktree bark has the effect of eliminating evil spirits and strengthening the righteousness; Hairyvein agrimonia helps stop bleeding; Yetbadetajo Hert extract nourishes the kidneys and yin; Hedyotis diffusa clears heat and detoxifies toxins, promotes water retention and blood circulation; Herba cirsii stops bleeding, induces diuresis and clears stasis; Salvia miltiorrhiza improves blood circulation, and resolves blood stasis; Gordon Euryale seed and Chinese yam nourish yin; Achyranthes aspera invigorates blood, disperses blood stasis, clears heat and detoxifies toxins; Polygonatum sibiricum cools blood; Rehmannia glutinosa strengthens the spleen and protects the kidneys and nourishes yin. Modern studies also have shown that polygonatum sibiricum can increase the rate of lymphocyte softening and promote the formation of antibodies, thus improve the immune function [23].

The present study found that the overall treatment efficiency, urinary routine parameters, disease recurrence rate, serum levels of IL-16 and IL-18 were better in the combined Chinese and western medicine group than in the western medicine group alone, suggesting that the combined Chinese and western medicine treatment could improve the clinical efficacy, inflammation and immune function status. The study of Shi [24] also found that the total effective rate of the combined Chinese and western medicine group was significantly higher than that of the western medicine group alone,

which was highly consistent with the results of this study. This may be attributed to the synergistic effect of the combined Chinese and western medicine treatment. IL-16 is one of the cytokines secreted by activating cells, also be secreted by respiratory epithelial cells, neutrophils, eosinophils, and monocytes/macrophages after activation in early stage of onset of inflammation. Besides, IL-16 can stimulate B cells to produce a large number of immunoglobulins and antibodies binding antigens to form circulating immune complexes, which are deposited in the blood vessel wall and activate complement, leading to inflammation in the walls of small vessels and around capillaries and improving the permeability of the blood vessel wall, which may damage the kidney [25]. IL-18 is an important member of the IL-1 cytokine family and also belongs to an important immune response regulator, which is capable of sensitizing the inflammatory response of the body and activating macrophages and T cells, resulting in the production of a series of cytokines that play a crucial role in the development of inflammation [26]. In this study, serum levels of IL-16 and IL-18 were lower in group B after treatment, suggesting that combined western and Chinese medicine could exert the desirable therapeutic effect by suppressing IL-16 and IL-18 levels.

However, there are certain limitations in this study and the efficacy of combined Chinese and western medicine treatment is not investigated from the aspect of blood clotting mechanism, which needs to be further investigated.

Disclosure of conflict of interest

None.

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