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Original Article

Efficacy of Sheng Xuexiaoban capsules combined with glucocorticoids in treating primary immune thrombocytopenia

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Abstract: Objective: To explore the efficacy of Sheng Xuexiaoban capsules combined with glucocorticoids in treating primary immune thrombocytopenia (PITP). Methods: Eighty-two patients with PITP were allocated into an observation group and a control group by a random number table, with 41 cases in each group. Patients in the observation group were treated with Sheng Xuexiaoban capsules combined with glucocorticoids, while those in the control group were treated with glucocorticoids alone. After 3 months of treatment, platelet count, clinical efficacy, regulatory T (Tr) cells and inflammatory factors in the peripheral blood were compared. Results: The platelet count increased in both groups after treatment (P<0.05), and was higher in the observation group (P<0.05). The total effective rate in the observation group (95.12%) was significantly higher than in the control group (70.73%; P<0.05). After treatment, percentage of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ all increased in both groups (P<0.05), while $CD8^+$ decreased (P<0.05). The observation group showed higher $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$, but lower $CD8^+$ percentage than the control group (all P<0.05). After 3 months of treatment, IL-10 in both groups was higher than that before treatment (P<0.05), and IL-17 in the observation group was higher than that in the control group (P<0.05). Conclusion: Sheng Xuexiaoban capsules combined with glucocorticoids is superior to glucocorticoids alone in treating PITP; which regulates immune function *in vivo* and inhibits inflammation. Therefore, it is worthy of further clinical application.

Keywords: Sheng Xuexiaoban capsule, glucocorticoid, primary immune thrombocytopenia, efficacy observation

Introduction

Primary immune thrombocytopenia (PITP) is a disease characterized by destruction and underproduction of platelets, and results in hemorrhage; with an annual morbidity of 1.9-6.4/100,000 in children and 3-4/100,000 in adults [1, 2]. This disease shows a polarization trend, that is, it occurs mostly in people under 14 and over 60 years old, and 9/10 of patients over the age of 75 are male [3]. Although PITP is benign, it has an acute attack and can cause severe bleeding or even death. Moreover, repeated and protracted PITP is easily transformed into chronic ITP, which seriously affects the physical and mental health and life quality of patients [4]. The mechanisms of PITP still remain unknown, but a large number of studies have shown that the pathogenesis of PITP is closely related to the dysfunction of the immune system [5, 6]. The most recognized pathogenesis of PITP is antibody-mediated humoral immunity, and the key to the pathogenesis is the production of antibodies against platelet membrane glycoproteins *in vivo* [7, 8]. Antigen-antibody complexes, formed by the combination of antibody and platelet membrane glycoproteins, bind to macrophage Fcy receptors and are phagocytized and cleared by macrophages [9]. Based on the above mechanisms, glucocorticoids are recommended by the Chinese Society of Hematology in 2016, which can reduce the generation of antibodies and complexes while inhibiting the phagocytic system of macrophages, and thus will increase capillary permeability, thereby stimulating bone marrow hematopoiesis and the release of peripheral blood [10]. At present, the treatment of PITP focuses on the correction of the immune disorder and regulation of cytokines to improve immune function so as to relieve clinical symptoms [11]. As the preferred drug

for PITP, glucocorticoids are capable of suppressing the immune system and inhibiting the production of platelet antibodies to increase platelets. However, there are side effects and adverse reactions in their clinical application and even recurrence of PITP during the withdrawal of treatment [12-14]. In traditional Chinese medicine, the pathogenesis of PITP is explained as "blood-heat and inordinate bleeding", thus, the treatment takes cooling blood and stopping bleeding as its principle. Previous studies have found that traditional Chinese medicine combined with hormones has a significant effect on reducing toxicity and increasing efficiency in the treatment of PITP [15]. Sheng Xuexiaoban capsules are composed of indigo naturalis, cortex moutan, forsythia, hairyvein agrimony and licorice; which achieve efficacy by clearing heat, cooling blood, and stopping bleeding. According to two domestic studies, the total effective rate of Sheng Xuexiaoban capsules plus glucocorticoids in the treatment of PITP was higher that of glucocorticoids alone (96.67% vs 70.00%, 85.70% vs 73.30%) [16, 17]. Therefore, it's more effective for Sheng Xuexiaoban capsules combined with glucocorticoids to treat PITP. Previous studies have shown that this treatment has the functions of anti-inflammation, sterilization, inhibition of capillary infiltration and regulation of immune function, but the specific immunoregulatory mechanisms have not been made clear [18]. In this study, besides the clinical efficacy, the immune mechanisms of Sheng Xuexiaoban capsules combined with glucocorticoids for PITP were further studied and discussed.

Materials and methods

Clinical data

Eighty-two patients with PITP admitted to the People's Hospital of Quzhou from March 2017 to December 2018 were divided into an observation group and a control group by a random number table, with 41 cases in each group. Patients in the observation group were treated with Sheng Xuexiaoban capsules combined with glucocorticoids, while those in the control group were treated with glucocorticoids alone. All patients enrolled were aged 18-75 years old, with an average age of 64.5±6.0 years old. This study was approved by the Ethics Committee of People's Hospital of Quzhou. All patients included in this study signed an consent form.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients diagnosed with PITP according to the Hemostasis and Thrombology Group of Chinese Society of Hematology in 2016 [19]; (2) Patients over 18 years old. Exclusion criteria: (1) Patients with severe heart and lung diseases; (2) Patients with hepatic and renal insufficiency; (3) Patients with previous thrombotic diseases; (4) Patients taking other thrombopoietic drugs during treatment; (5) Patients allergic to drugs; (6) Pregnant and lactating women; (7) Patients with malignant tumors; (8) Patients with osteoporosis.

Methods

Patients in the control group took prednisolone acetate tablets (1 mg/kg/d) (Harbin Pharmaceutical Group Fourth Pharmaceutical Factory, China) orally on an empty stomach in the morning, while those in the observation group were additionally treated with Sheng Xuexiaoban capsules (0.45 g each, Hao Qi Jun Pharmaceutical Co., Ltd., Shaanxi, China), three times a day, half an hour after meals, 4 capsules each time. Withdrawal of glucocorticoids: The platelets of the patient were detected every 3 days. If the platelets increased more than 2 times or reached a normal level, the total amount of glucocorticoids was reduced by 10% each time by 5-10 mg/d, for 6 consecutive courses (2 weeks/course). The patients were followed up for 3 months to evaluate the clinical efficacy.

Outcome measures

Platelet count: At admission and 3 months after treatment, the fasting venous blood from the elbow was collected in the morning from all patients and sent to the testing room, where platelets were detected by a hematology analyzer.

Efficacy evaluation: Markedly effective: no bleeding after treatment and the platelet count $\geq 100*10^9$/L; effective: no bleeding after treatment and the platelet count $\geq 30*10^9$/L; ineffective: bleeding after treatment and the

Table 1. Comparison of general data and baseline data ($\bar{x}$ ± sd, n)

Item	Observation group (n=41)	Control group (n=41)	χ^2/t	P
Gender (male/female)	24/17	26/15	0.205	0.651
Age (year)	64.7±6.6	64.3±5.4	0.291	0.772
Platelets count at admission (10^9/L)	17.73±6.64	16.93±7.16	0.582	0.599
Bleeding site			0.672	0.995
Skin	15	16		
Gingiva	7	6		
Oral cavity	6	7		
Increased menstrual volume	4	3		
Nose	3	2		
Face region	3	3		
No external bleeding	3	4		

platelet count <30*10^9/L. The total effective rate = the number of (markedly effective + effective) cases/total number of cases *100% [20].

Detection of regulatory T cells (Tr cells) and inflammatory factors in peripheral blood: 5 mL of fasting blood was collected from all patients in the morning at admission and 3 months after treatment. FACSCanto II flow cytometer (BD Company, USA) was used to detect the expression of FITC-labeled anti-human CD3, CD4 and CD8 monoclonal antibodies. Serum and plasma were separated using a centrifuge at 3,300 rpm/min. The separated plasma was mixed with 40 μL phosphate buffer solution containing protease inhibitor (Haibiao Technology Co., Ltd., Xiamen, China) and was stored in a freezer at -80°C. Interleukin-10 (IL-10) and interleukin-17 (IL-17) levels were determined by enzyme-linked immunosorbent assay (Bio RAD Biotechnology Co., Ltd., Shanghai, China) with a full-automatic multifunctional microplate reader (Thermo Company, USA).

Side effects of glucocorticoids: Infection, osteoporosis, Cushing's syndrome, gastric ulcer, elevated blood pressure and blood glucose may occur after treatment.

Statistical methods

The SPSS 17.0 was applied to analyze the data. Continuous variables were expressed as mean ± standard deviation ($\bar{x}$ ± sd), Data consistent with a normal distribution and variance homogeneity were analyzed by the independent samples t-test. Paired t test was used for comparison before and after treatment. The counting data were expressed as percentage and analyzed by Pearson chi-square test. P<0.05 was considered statistically significant.

Results

General data and baseline data

There was no statistical difference in sex, age, platelet count and bleeding site between the two groups, indicating group comparability (P> 0.05), as shown in **Table 1**.

Comparison of platelet count

There was no statistical difference in platelet count between the two groups before treatment (P>0.05). The platelet count was significantly increased after 3 months of treatment, and the observation group was higher than the control group (P<0.05). The difference before and after treatment in the observation group was more significant than that in the control group (P<0.05). See **Table 2**.

Comparison of clinical curative efficacy

Comparison of the curative efficacy showed that the total effective rate in the observation group (95.12%) was significantly higher than that in the control group (70.73%; P<0.05), as shown in **Table 3**.

Comparison of Tr cell subsets in peripheral blood

Before treatment, there was no statistical difference in $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$

Table 2. Comparison of platelet count ($\bar{x}$ ± sd)

Item	Platelets count (10^9/L)
Before treatment	
Observation group (n=41)	17.73±6.64
Control group (n=41)	16.93±7.16
t	0.582
P	0.599
Three months after treatment	
Observation group (n=41)	130.44±56.47[a]
Control group (n=41)	94.73±51.40[a]
t	2.747
P	0.007
Difference before and after treatment	
Observation group (n=41)	112.71±58.84
Control group (n=41)	77.80±44.25
t	12.264
P	<0.001

Note: [a]P<0.05, compared within the same group before treatment.

percentage between the two groups (P>0.05). After 3 months of treatment, $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ all increased in both groups (P< 0.05), and $CD8^+$ decreased (P<0.05). The observation group showed higher $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ than the control group (P< 0.05), and lower $CD8^+$ than the control group (all P<0.05). In addition, the difference before and after treatment in the observation group was more significant than those in the control group (P<0.05). See **Table 4** and **Figure 1**.

Comparison of IL-10 and IL-17

Before treatment, there was no significant difference in IL-10 and IL-17 between the two groups (P>0.05). While after 3 months of treatment, IL-10 was significantly higher than that before treatment in both groups (P< 0.05), and IL-17 was significantly higher than that before treatment in the observation group (P<0.05). After treatment, IL-10 and IL-17 in the observation group were significantly higher than those in the control group, and the difference before and after treatment in the observation group was more significant than that in the control group (P<0.05). See **Table 5**.

Comparison of complications after treatment

Comparison showed that the incidence of complications in the observation group was lower than that in the control group (P<0.05), as shown in **Table 6**.

Discussion

Glucocorticoids achieve more than 70% efficacy in treating PITP, but patients with recurrence and who are refractory to treatment still account for 11-35% [7, 10]. Therefore, reducing the incidence of relapsed and refractory PITP has become a priority. In traditional Chinese medicine, the pathogenesis of PITP lies in blood stasis caused by blood-heat bleeding, and Yin deficiency and internal heat. Therefore, the treatment is based on the principle of cooling blood and stopping bleeding, as well as dispersing stasis and eliminating plaque. The effectiveness of Sheng Xuexiaoban capsules is based on the above principles. A study revealed that Sheng Xuexiaoban can directly stimulate megakaryocytes to proliferate, regulate immune function and increase $CD4^+$ *in vivo*. Moreover, Sheng Xuexiaoban plays a pivotal role in cooling blood and stopping bleeding, dispersing stasis and eliminating plaques, and meanwhile raising the number of platelets [21]. The effective ingredients of Sheng Xuexiaoban capsule, paeonol, have been reported to reduce capillary permeability and regulate immune function [22]. A domestic study found that the total effective rate of Sheng Xuexiaoban capsules plus glucocorticoids in the treatment of PITP is higher that of glucocorticoids alone (96.67% vs 70.00%) [16]. In the present study, the combined therapy also achieved a significant curative effect. After treatment, the elevation of platelets in the observation group was statistically higher than that in the control group, and the clinical effective rate (95.12%) was significantly higher than that in the control group (70.73%). This suggests that Sheng Xuexiaoban capsules combined with glucocorticoids improves the clinical efficacy, which is correlated with above mechanisms. In this study, the efficacy of glucocorticoids alone was lower than that in previous clinical reports, which may be related to the smaller sample size enrolled.

The occurrence of PITP is not only related to humoral immunity but also to cellular immunity [23]. Besides, Tr cells play an important role in the occurrence and development of autoimmune diseases, with varied number and func-

Table 3. Comparison of curative efficacy (n, %)

Item	Observation group (n=41)	Control group (n=41)	χ^2 Comparison of curative efficacy (n, %)	P
Markedly effective	21 (51.22)	11 (26.83)		
Effective	18 (43.90)	18 (43.90)		
Ineffective	2 (4.88)	12 (29.27)		
The total effective rate	39 (95.12)	29 (70.73)	8.613	0.003

Table 4. Comparison of Tr cell subsets in peripheral blood ($\bar{x} \pm sd$)

Item	$CD3^+$%	$CD4^+$%	$CD8^+$%	$CD4^+$%/$CD8^+$%
Before treatment				
Observation group (n=41)	65.32±3.86	32.84±3.16	28.15±2.74	0.178±0.005
Control group (n=41)	65.48±3.92	32.86±3.12	27.86±2.58	0.19±0.004
t	0.196	0.028	0.498	0.575
P	0.845	0.978	0.620	0.567
Three months after treatment				
Observation group (n=41)	73.34±4.61[a]	42.56±3.84[a]	21.51±1.86[a]	1.978±0.008[a]
Control group (n=41)	69.07±4.23[a]	38.42±3.34[a]	24.35±2.31[a]	1.579±0.013[a]
t	4.361	5.203	6.118	165.821
P	<0.001	<0.001	<0.001	<0.001
Difference before and after treatment				
Observation group (n=41)	8.02±0.75	9.72±0.68	6.64±0.88	0.811±0.010
Control group (n=41)	3.59±0.31	5.57±0.22	3.50±0.26	0.400±0.016
t	68.460	37.079	21.797	139.103
P	<0.001	<0.001	<0.001	<0.001

Note: [a]P<0.05, compared within the same group before treatment.

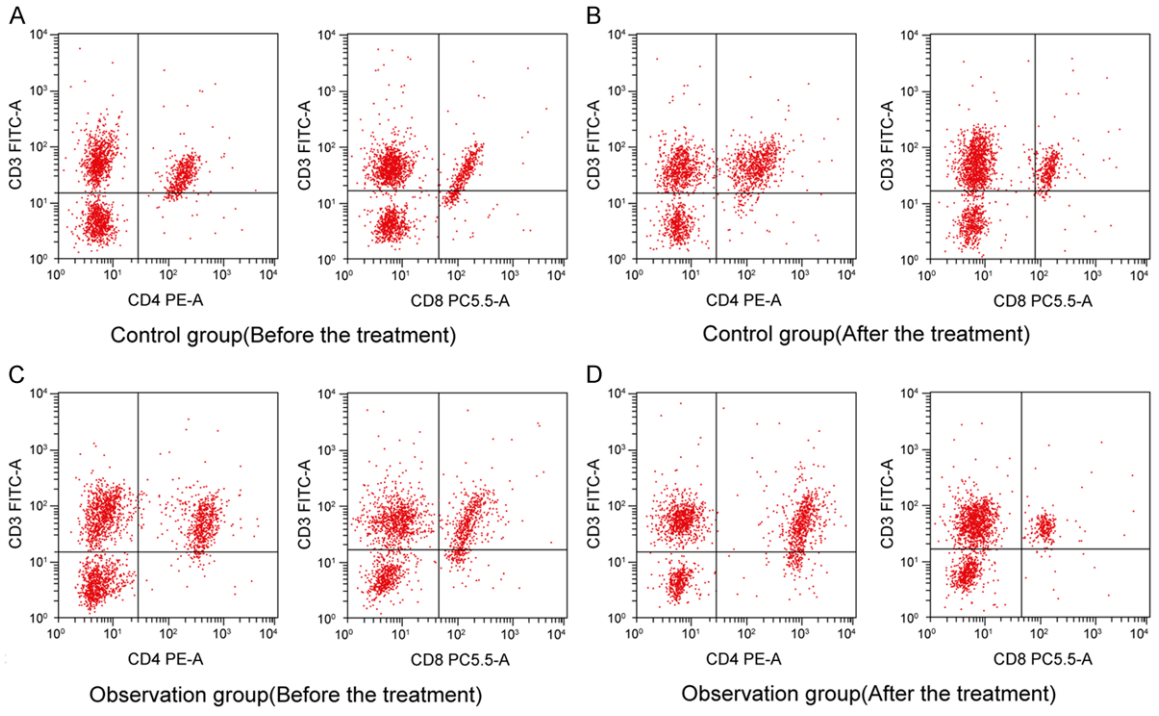

Figure 1. Comparison of flow charts of CD3, CD4 and CD8 before and after treatment. A. Flow chart of control group before treatment; B. Flow chart of control group after treatment; C. Flow chart of observation group before treatment; D. Flow chart of observation group after treatment.

Table 5. Comparison of IL-10 and IL-17 ($\bar{x}$ ± sd)

Item	IL-10 (ng/L)	IL-17 (ng/L)
Before treatment		
Observation group (n=41)	18.14±5.21	14.42±4.72
Control group (n=41)	17.67±3.20	14.41±4.29
t	0.495	0.013
P	0.622	0.989
Three months after treatment		
Observation group (n=41)	35.75±8.19[a]	16.58±5.21[a]
Control group (n=41)	21.42±7.81[a]	13.83±3.05
t	8.111	2.922
P	<0.001	0.005
Difference before and after treatment		
Observation group (n=41)	17.61±2.98	2.16±0.49
Control group (n=41)	3.75±4.61	-0.58±1.24
t	16.162	13.167
P	<0.001	<0.001

Note: [a]P<0.05, compared within the same group before treatment.

Table 6. Comparison of complications after treatment ($\bar{x}$ ± sd)

Complication	Observation group (n=41)	Control group (n=41)	χ^2	P
Infection	0 (0.00)	2 (4.88)		
Osteoporosis	1 (2.44)	2 (4.88)		
Cushing's syndrome	2 (4.88)	3 (7.32)		
Gastric ulcer	0 (0.00)	1 (2.44)		
Elevated blood pressure	1 (2.44)	3 (7.32)		
Elevated blood glucose	2 (4.88)	3 (7.32)		
The total incidence	6 (14.63)	14 (31.15)	4.232	0.040

tions in different autoimmune diseases [24, 25]. The expression of $CD4^+$ Tr cells accounts for 5-15% in the peripheral blood of healthy individual [26, 27]. $CD4^+$ cells assist B cells to produce antibodies, and are the most important cells in the regulation of the immune system in autoimmune diseases [28]. $CD8^+$ T cells mediates platelet destruction and participates in the occurrence of PITP [29, 30]. Besides, $CD3^+$ has been found to be down-regulated in patients with chronic ITP due to the mediation of cytotoxicity-related factors [31]. Above all, $CD3^+$ and $CD4^+$ decrease while $CD8^+$ increases in patients with PITP [21], consistent with our findings. After treatment, the expression of $CD3^+$ and $CD4^+$ increased and $CD8^+$ decreased in the two groups compared with before treatment, and the observation group showed more significant improvement than the control group. Macrophages are important in immune system diseases, and IL-10 and IL-17 exert anti-inflammatory effects *in vivo* [32-34]. A large number of inflammatory factors are secreted due to the immune dysfunction caused by PITP, so the anti-inflammatory factors, IL-10 and IL-17, are present with low expression. We also noticed that decreased IL-10 and IL-17 in patients with PITP became elevated in the two groups after treatment, especially in the observation group. The expression of IL-17 in the observation group was more improved than that in the control group, which may be related to the regulation of immune function and the reduction of immune response by Sheng Xuexiaoban capsules.

A study revealed that the treatment of PITP with traditional Chinese medicine combined with hormones had significant curative effects by reducing toxicity and enhancing treatment efficiency [15]. The evident increase of platelet count and the fast withdrawal of hormones after treatment with Sheng Xuexiaoban capsules combined with glucocorticoid contribute to lower incidence of side effects in the observation group.

The sample size of this study is small and needs to be further expanded. In addition, it is necessary to prolong the observation duration to study the long-term recovery in both groups.

To sum up, Sheng Xuexiaoban capsules combined with glucocorticoids improves the clinical treatment efficacy, regulates the immune

function and inhibits inflammation, which is worthy of clinical application.

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Disclosure of conflict of interest

None.

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