Clinical Effect of Promoting Growth Patch Combined with Breeding and Strengthening Spleen Ointment on Children with Idiopathic Dwarf Syndrome of Spleen and Kidney Deficiency

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Abstract: Aims: To investigate the clinical effect of promoting growth patch combined with breeding and strengthening spleen ointment on children with Idiopathic Short Stature (ISS)along with syndrome of spleen and kidney deficiency. Method: A total of 80 ISS children from the Department of Child Health of Shandong Provincial Maternal and Child Health Hospital and the Department of Pediatrics of Yantai Hospital of Traditional Chinese Medicine were selected and divided into two groups by simple randomization method. The observation group was treated with the combination of growth promotion patch and breeding and strengthening spleen ointment, while the control group was handled with routine treatment. After 6 months of treatment, the growth status (height, height growth rate (GV), bone age, etc.), and traditional Chinese medicine (TCM) syndrome score were compared between the two groups of children before and after medication. Meanwhile, the expression levels of insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), and 25 hydroxyvitamin D [25-(OH) D] were detected, and the children's sleep questionnaire (PSQ) scores and incidence of adverse reactions were compared. Results: After treatment, the height, weight, bone age and GV of the two groups were significantly increased compared with that before treatment, and the growth rate of the observation group was higher than that of the control group ($P<0.05$). The clinical effective rate of the observation group was 97.5%, which was higher than that of the control group (65%). In addition, the TCM symptom score of the observation group after treatment was significantly lower than that of the control group ($P<0.05$). The levels of IGF-1, IGFBP-3, and 25 (OH) D in the observation group were higher than those in the control group ($P<0.05$). Meanwhile, after treatment, the PSQ scores of the observation group were significantly lower than those of the control group ($P<0.05$), and there was no significant difference in adverse reactions between the two groups of children during treatment ($P>0.05$). Conclusion: The combined application of growth-promoting patch and breeding and strengthening spleen ointment could significantly improve the clinical symptoms of children with ISS, effectively promoted the growth and development of children with ISS, regulated the levels of IGF-1, IGFBP-3 and 25(OH)D, and significantly improved the sleep of children with a low incidence of adverse reactions.

***Keywords*:** Promoting patch, Breeding and strengthening spleen ointment, Idiopathic short stature, Spleen and kidney deficiency, Growth and development

1. Introduction

Short stature refers to children whose height is less than 2 standard deviations from the average height of their peers and whose annual growth rate is less than 5cm with the main symptoms include short stature, slowed growth rate, and abnormal bone metabolism [1]. Idiopathic short stature (ISS) can account for 60% to 80% of children with short stature[2]. Recombinant human growth hormone (rhGH) is a commonly used clinical drug in the treatment of ISS, which has the effect of promoting linear growth in children and improving lifetime growth in children and adults[3]. However, its therapeutic effect varies greatly among individuals, and growth hormone is expensive and may cause some side effects, so its clinical application is limited [4]. Therefore, the search for a more effective treatment has become a hot topic in the medical field.

Traditional Chinese medicine believes that the main cause of ISS is the lack of innate endowments, which is closely related to the spleen and kidney. The kidney is the "foundation of innate development" and growth is influenced by parents.

If the fetus is born with congenital weakness, insufficient kidney essence, reduced bone marrow biochemistry, and slow bone growth, then the body is short. The lack of solid kidney qi in children, also known as "kidney deficiency", can directly affect the development of their bones and organs. The spleen is the "foundation of postnatal life" and the source of qi and blood biochemistry. If a child suffers from eating disorders, with food accumulation inside and milk and food stagnation, it can lead to deficiency due to illness, weak spleen and stomach, insufficient qi and blood, and loss of nourishment in the five organs, resulting in slow growth and development of the child. This study is based on the theoretical basis of "the kidney is the foundation of the innate and the spleen is the foundation of the acquired". The spleen and kidney are supplemented together, and the combination of oral and external treatment is used to develop a self-formulated growth promoting patch and breeding and strengthening spleen ointment formula to treat children with spleen and kidney deficiency type idiopathic short stature and short stature. The aim is to explore a scientific and reasonable traditional Chinese medicine characteristic treatment method for short stature children.

2. Material and methods

2.1 Research objects

A total of 80 children from the Children's Health Department of Shandong Provincial Maternal and Child Health Hospital and the Department of Pediatrics of Yantai Hospital of Traditional Chinese Medicine were selected as the study objects. A simple randomization method was used to divide 80 children into two groups with 40 cases in each group. The general data of children in the observation group and the control group are shown in Table 1. There is no significant difference in clinical data between the two groups, which is comparable. This study was approved by the Ethics Committee of our hospital, and the families of the children signed the informed consent.

Table 1. Comparison of general data between the two groups

Groups	Gender		Age (years)	Height (cm)	Bone age (Year)
	Male	Female			
Observation group(n=40)	21	19	4.68±1.02	99.19±6.70	2.91±1.10
Control group(n=40)	22	18	4.73±0.93	99.28±5.86	2.65±0.94

2.2 Inclusion and exclusion criteria

(1) According to the latest growth standards for children aged 0-7 years released in March 2023, patients whose height is lower than the average normal height of the same race, age, and sex, between minus one standard deviation (-1SD) and minus two standard deviations (-2SD), or family members below minus two standard deviations (-2SD) refuse to use growth hormone.

(2) Children with age of 3-6 years old.

(3) The children's chromosome was normal.

(4) The patient's cranial and pituitary magnetic resonance examinations are normal.

(5) Excluding short stature caused by Turner syndrome, hypothyroidism, liver and kidney dysfunction, etc.

(6) Without skeletal system diseases and genetic metabolic diseases.

(7) Growth hormone stimulation test for children with a height of less than 2SD shows a GH peak of≥10 ng/mL.

(8) IGF-1, IGFBP-3>-2SD.

(9) According to the fourth edition of Pediatrics of Chinese Medicine of Human Health, the syndrome differentiation of Chinese medicine is spleen and stomach weakness, kidney qi deficiency.

(10) No relevant interventions were taken during the first 8 weeks of enrollment.

Criteria for removal, shedding and termination tests are as follows.

2.2.1 Exclusion criteria

(1) Children who use growth hormone;

(2) Children with severe heart, liver, kidney and hematopoietic system diseases, malignant tumors, mental illness, mental retardation;

(3) Children with a history of allergy to the drugs in this study;

(4) Combining digestive system diseases affects food intake and nutrient absorption;

(5) Other participants participated in the study during the observation period.

2.2.2 Standard for detachment

(1) During the experiment, poor compliance of the subjects affected the evaluation of effectiveness and safety;

(2) Serious adverse events, complications and special physiological changes should not continue to accept the experiment;

(3) Those who automatically withdraw from the experiment during the process and those who are lost to follow-up due to various other reasons;

(4) Incomplete information affects the validity and security of the judgment.

2.2.3 Termination test criteria

(1) Those who experience serious adverse reactions during the treatment process;

(2) When significant errors are found in the clinical trial protocol or during implementation, making it difficult to evaluate drug efficacy.

2.3 Experimental method

All children were given dietary guidance, exercise, sleep, vitamin D routine height management, and oral administration of five-dimension lysine granules. Children in control group received intervention treatment with Life and Five-Dimensional Lysine Granules (Yanbian University Caoxian Pharmaceutical Co., Ltd.) twice a day, one bag at a time. Based on the treatment of the control group, the observation group was given the treatment of promoting growth patch and breeding Jianpi ointment. Growth promoting patch formula [Codonopsis pilosula (Franch.) Nannf (1g), Rhizoma Atractylodis Macrocephalae (1g), Sparganium stoloni erum (0.5g), Radix Bupleuri (1g), Ligusticum chuanxiong hort. (1g), Ageratum cornyzoides (0.5g), Angelicae Sinensis Radix (0.5g), Borneolum (2g), Asarum insigne Diels (1g), Evodiae Fructus (1g), and Cinnamomum cassia Presl (1g)] was made by mixing sesame oil into a paste and applying it to the Shenque, Zhongwan, Guanyuan, Zusanli (both sides), and Spleen acupoints (both sides) for 4-6 hours each time, 2-3 times a week. Formula for breeding and strengthening spleen ointment: Dioscorea oppositifolia L. (240g), Stir fried malt (180g), Semen Nelumbinis (180g), Dolicho Lablab L. (180g), Glycyrrhiza uralensis Fisch. (30g), Pogostemon cablin (Blanco)Benth. (60g), Stir fried Liu Shen Qu (120g), Scorched hawthorn (120g), Tangerine peel (120g), Tuccoia (180g), Codonopsis (180g), stir-fried white art (180g), Gox seed (180g), Coix seed (180g), platycodon (30g), alisma platycoicum (60g), Dan peel (60g), cooked ground (120g), dogwood (60g), and Coptis (20g). The above medicines were soaked for 12 h, then decocted for 3 times and filtered, then the medicinal juice was concentrated into extract, 180 g of turtle gum was injected into the medicinal liquid, and 200g of malt sugar was added to the final refining. After making the medicinal paste, it was cooled for 12 h for treatment, 2 bags a day, and taken half an hour after meals. The above treatment lasted for 3 months as 1 course, and both groups were treated for 2 courses.

2.4 Observation indexes

2.4.1 Clinical effect

Basic developmental indicators, including height and body mass, were measured before treatment and 6 months after treatment, and the growth rate (GV) of the two groups were compared. According to the clinical efficacy evaluation criteria formulated in accordance with the "Guidelines for Clinical Research of Traditional Chinese Medicine New Drugs (Trial)" [5], significant effect: the increase in height of the child per month is greater than 0.7 cm; Effective: The child's monthly height growth rate is greater than 0.5 cm; Invalid: The child's monthly height increase is less than 0.5 cm.

2.4.2 TCM symptom and curative effect

The single symptom score of spleen and kidney deficiency weakness syndrome[6], includes indicators such as sparse hair, thin and weak body, soft muscles, pale complexion, poor appetite, and loose stools. A 4-point scoring method is used to evaluate normal, mild, moderate, and severe symptoms, with scores of 0, 2, 4, and 6, respectively. The score reduction rate of syndrome = (total score of single symptoms of spleen and kidney deficiency before treatment - total score of single symptoms of spleen and kidney deficiency after treatment)/total score of single symptoms of spleen and kidney deficiency before treatment x 100%.

(1) Basic recovery: symptoms and signs basically disappeared, syndrome score decreased by≥95%;

(2) Obvious effect: the symptoms and signs were significantly improved, and the syndrome score was reduced by≥70%;

(3) Improvement: Symptoms and signs have improved, and the syndrome score has decreased by≥30%;

(4) Invalid: Symptoms and signs show no significant improvement or even worsen, and the reduction in syndrome score is less than or equal to 30%.

2.4.3 Laboratory indexes

2-3 mL fasting venous blood was collected before and after treatment in the morning, centrifuged at 3000 RPM for 15min, the supernatant was taken and refrigerated, and the serum levels of IGF-1, IGFBP-3 and 25 (OH) D were determined by electrochemical luminescence method with automatic biochemical analyzer.

2.4.4 Pediatric sleep questionnaire (PSQ)

The scores of children's sleep questionnaire (PSQ) before treatment, 3 months and 6 months after treatment were compared between the two groups, which included breathing, sleep, behavior and 4 other sleep-related dimensions, with a total of 22 items, all of which were classified as "yes" and "no" options. If you answered "yes", you would get 1 point, and if you answered "no", you would get no score. Finally, the total scores of each item were calculated. Out of 22 points, the higher the score, the more serious the condition, and >7 points that there may be sleep quality problems.

2.4.5 Safety evaluation

To evaluate the discomfort and adverse reactions of patients during medication.

2.5 Statistical analysis

All data were processed by SPSS26.0 statistical software. t test was used for measurement data, $\chi 2$ test for counting data and rank sum test for rank data.

3. Results

3.1 Comparison of clinical efficacy between two groups of children

Compared with before treatment, the height, weight, bone age and growth rate of children in the observation group and the control group were significantly improved (Table 2), but the clinical efficacy of the observation group was significantly better than that of the control group (Table 3).

Table 2. Clinical efficacy of children in two groups

Groups	Height (cm)		Weight (kg)		Bone age (years)		Gv	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation group	99.19±6.70	103.90±6.65$^{**\#}$	15.72±1.89	18.32±2.00$^{***\#}$	2.91±1.10	3.42±1.11$^{*\#}$	4.17±0.97	9.47±1.28$^{***\#\#\#}$
Control group	99.28±5.86	101.10±5.82	15.95±1.76	17.42±1.68***	2.65±0.94	2.93±0.93	3.87±0.94	4.60±3.23

*P<0.05, **P<0.01, ***P<0.001, intra-group comparison; #P<0.05, ##P<0.01, ###P<0.001, inter-group comparison.

Table 3. Clinical efficacy of two groups of children

Groups	Significant	effective	ineffective	Total effective rate (%)
Observation group	29	10	1	97.5
Control group	7	19	14	65

3.2 Comparison of TCM symptoms and curative effect between two groups of children

As shown in Table 4, after 6 months of treatment, there was a significant statistical difference in the TCM syndrome scores between the two groups of children (P<0.01), and the observation group was significantly lower than the control group, indicating that the combined use of growth promoting patches and breeding spleen strengthening ointment formula had a significantly better effect than conventional treatment.

Table 4. Comparison of Traditional Chinese Medicine Syndrome Points between Two Groups of Children (Score, $\bar{x}$ ±s)

Groups	n	Pre-treatment	Post-treatment
Observation group	40	13.55±1.77	6.75±1.55***
Control group	40	13.43±1.68	10.88±1.79$^{***\#\#\#}$

*P<0.05, **P<0.01, ***P<0.001, intra-group comparison; #P<0.05, ##P<0.01, ###P<0.001, inter-group comparison.

3.3 Comparison of laboratory indexes between the two groups

After treatment, the levels of IGF-1 and IGF-BP3 in both groups of children were significantly increased compared

to before treatment. The observation group was significantly higher than the control group, and the difference between the two groups was statistically significant (P<0.05). Moreover, the Ghrelin expression level was significantly reduced, with the observation group showing a significantly lower decrease compared to the control group (P<0.05); Compared with before treatment, the bone metabolism index 25 (OH) D of both groups of children significantly increased after treatment, and the elevated level in the observation group was significantly better than that in the control group (P<0.05), as shown in Table 5.

Table 5. Comparison of serum IGF-1, IGFBP-3, Ghrelin, and 25 (OH) D levels between two groups of pediatric patients ($\bar{x}$ ±s)

Groups	IGF-1 (ng/mL)		IGFBP-3 (ng/mL)		Ghrelin(pg/ml)		25(OH)D (ng/mL)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation group	97.38±7.58	160.30±9.06$^{***\#}$	3.27±0.34	4.58±0.38$^{***\#}$	4.39±0.18	3.14±0.13$^{***\#\#\#}$	28.23±2.01	33.60±2.24$^{***\#}$
Control group	98.73±7.90	141.20±8.76*	3.42±0.40	4.23±0.43***	4.37±0.18	3.26±0.19***	27.30±2.28	29.88±2.27***

3.4 Comparison of PSQ scores between the two groups

After treatment, the PSQ scores of both groups of children significantly decreased, and the scores of the observation group were significantly lower than those of the control group (P<0.05, Table 6), indicating a significant improvement in the sleep quality of the children.

Table 6. PSQ scores of children in two groups ($\bar{x}$ ±S)

Groups	Pre-treatment	Post-treatment	T value	P value
Observation group	16.20±1.62	6.53±1.36	28.94	<0.001
Control group	15.95±1.45	10.43±2.52	12.02	<0.001
t	0.727	8.614	-	-
p	0.469	<0.001	-	-

3.5 Comparison of the incidence of adverse reactions between the two groups

After treatment, one child in the observation group experienced joint pain, two had rash, and three had headache, with an adverse reaction rate of 15%; In the control group, there were 3 cases of joint pain, 2 cases of rash, and 17.52 cases of headache, with an adverse reaction rate of 17.5%. There was no significant difference in the occurrence of adverse reactions between the two groups of children (P>0.05).

4. Discussion

ISS is a growth disorder disease with a high prevalence rate among children at present. At present, the incidence rate of ISS incidence rate is about 3%[7], showing a rising trend year by year. It not only affects the normal growth and development of children, but also can lead to psychological problems of different degrees. Therefore, early intervention and treatment should be carried out. In clinical practice, seeking traditional Chinese medicine methods to treat and improve height in children with ISS is also a research focus in the field of growth and development in the future.

Traditional Chinese Medicine believes that ISS is mainly responsible for the spleen and kidneys. The spleen is the foundation of postnatal development and is the basis for children's growth and development. According to the results of the study on the medication rule of traditional Chinese medicine in the treatment of children with short stature based on big data mining, the efficacy of drugs in the clinical treatment of short stature children is mainly to benefit the kidney and spleen, supplemented by nourishing Yin, nourishing blood and regulating qi [8]. In this study, the treatment of spleen deficiency was selected, and then the formulation of promoting growth paste and breeding Jianpi ointment was made. The results of the study found that the height, weight, bone age and growth rate of the children who were combined with growth-promoting patch and Fei-Jianpi paste recipe were significantly better than those who were treated with conventional treatment, and the Chinese medicine symptom score of the children was significantly improved, indicating that the combined application of growth-promoting patch and Fei-jian pi paste recipe had a significant clinical effect on ISS.

ISS is a type of dwarfism with unknown etiology, and its growth and development are influenced by various factors. At present, abnormal function of the GH IGF-1 axis is considered as the pathogenesis of ISS. Research has shown that there is a positive correlation between height and IGF-1 levels in children with ISS[9], which provides data support for the correlation between IGF-1 and height growth and the incidence of ISS. Another study has shown that after treatment with traditional Chinese medicine, the levels of IGF-1 and IGFBP-3 in the serum of ISS children have been increased, indicating that the

therapeutic mechanism of ISS children may be related to IGF-1 and IGFBP-3. This study confirmed that IGF-1 and IGFBP-3 levels were significantly increased in ISS children after treatment. These results indicated that the combination of growth promotion patch and breeding Jianpi ointment may play a therapeutic role in ISS by regulating the level of hypothalamic-GH-IGF-1.

Vitamin D can regulate the growth and differentiation of human cells and tissues, regulate calcium and phosphorus metabolism. If the human body lacks vitamin D, it can affect calcium absorption and bone formation, which may lead to rickets and osteomalacia in children. And 25- (OH) D levels can reflect the nutritional status of vitamin D in the body, thereby reflecting the overall nutritional status or improvement in growth and development of the child [10]. In this study, the combination of growth promoting patches and nourishing spleen paste formula can significantly increase the level of 25 (OH) D in children's bodies, indicating that the combination of growth promoting patches and nourishing spleen paste formula can promote the absorption or utilization of vitamin D, enhance the effect of promoting growth and development.

In addition to nutrition, exercise and sleep are also important factors affecting children's height growth. Therefore, we evaluated the sleep quality of ISS patients before and after treatment using PSQ questionnaire scores. The results showed that the combination of growth promoting patches and breeding spleen strengthening ointment significantly reduced the PSQ scores of patients and improved their sleep. This study also found that no serious adverse reactions were observed in children treated with the combination of growth promoting patches and nourishing spleen ointment formula, as well as conventional therapy.

In summary, the combination of growth promoting patches and nourishing spleen ointment formula can significantly promote the growth and development of ISS children, improve their clinical symptoms, regulate their levels of IGF-1, IGFBP-3 and 25 (OH) D, and significantly improve their sleep without serious adverse reactions. However, this study lasted for 6 months and did not demonstrate the long-term effect of the combination of growth promoting patches and nourishing spleen ointment formula in treating ISS. Therefore, its long-term effect in improving spleen and kidney deficiency also needs to be observed. Moreover, due to the limited number of observation indicators and the lack of blank controls, this trial has resulted in low reliability. The specific mechanism of the combined use of growth promoting patches and breeding spleen strengthening ointment in the treatment of ISS is still unclear and requires further research.

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