

Umbilicus application with Chinese medicine for chronic diarrhea due to food intolerance in kids: a multicenter randomized trial

中药敷脐治疗食物不耐受型儿童慢性腹泻多中心随机观察

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Abstract

Objective: To observe the clinical efficacy of umbilicus application with Chinese medicine in treating children's chronic diarrhea due to food intolerance and the value of healthy diet education.

Methods: Eighty kids with chronic diarrhea due to food intolerance were recruited from multiple centers and divided by using the random number table into a treatment group of 40 cases and a control group of 40 cases. For both groups, based on the level of serum food-specific immunoglobulin G (Ig-G), the patients were given unified diet following the healthy diet guidance: safe, alternate, and forbidden, while the treatment group was additionally given umbilicus application with Chinese medicine. The therapeutic efficacy and symptom score of traditional Chinese medicine (TCM) were observed and compared respectively after 1-week, 2-week, 4-week, and 12-week treatment.

Results: The diarrhea symptoms and coupled symptoms scores dropped significantly in the two groups after treatment (all $P < 0.05$), and the inter-group comparisons also showed statistical significances ($P < 0.05$). The total effective rate was 97.5% in the treatment group versus 77.5% in the control group, and the inter-group difference was statistically significant ($P < 0.05$).

Conclusion: The healthy diet guidance based on the food intolerance test is effective in helping treat diarrhea, while umbilicus application with Chinese medicine works better in treating diarrhea for kids with chronic diarrhea due to food intolerance and can significantly enhance the therapeutic efficacy.

Keywords: Acupoint Therapy; Point, Shenque (CV 8); Drugs, Chinese Herbal; Application Therapy; Administration on Umbilicus; Diarrhea; Children, Preschool

【摘要】目的: 观察中药脐部贴敷对食物不耐受型儿童慢性腹泻患者的临床疗效及饮食健康教育价值。**方法:** 将来自多中心的80例食物不耐受型儿童慢性腹泻患者根据随机数字表分为治疗组40例和对照组40例。两组均根据患儿血清中食物特异性IgG抗体浓度,分别采取统一的“安全进食”、“轮替”、“忌食”的健康饮食指导,治疗组患儿给予中药脐部贴敷治疗。治疗1星期、2星期、4星期及12星期后观察并比较两组疗效及中医症状评分变化。**结果:** 治疗后两组患者的症状评分均明显下降,与本组治疗前有统计学差异(均 $P < 0.05$),组间差异亦具有统计学意义($P < 0.05$)。对照组总有效率为77.5%,治疗组总有效率为97.5%,两组总有效率差异有统计学意义($P < 0.05$)。**结论:** 根据食物不耐受检测结果对患儿进行健康饮食指导止泻有效,中药脐部贴敷对食物不耐受型儿童慢性腹泻具有更好的止泻作用,可显著提高疗效。

【关键词】 穴位疗法; 穴, 神阙; 中草药; 敷贴疗法; 敷脐; 腹泻; 儿童, 学龄前

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Chronic diarrhea is a common and difficult disease in kids, and also a main cause of malnutrition, rickets, and anemia. According to the data stipulated by the World Health Organization (WHO) in 2002, diarrhea occupied

13.2% of children's fatal diseases, and 50% of the cases were chronic diarrhea.

With the development of medicine and varieties of food, human body can get various nutrient substances from the rich dietary pattern. However, influenced by genetic factor, dietary pattern, and cooking method^[1], food allergy or food intolerance is generated, bringing long-term harmful effect on the health of people, which

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has become a global public health problem^[2-3]. Especially to little kids, food intolerance will induce gastrointestinal and dermal symptoms, affecting their growth and development^[4].

Although there are numerous clinical studies on diarrhea-predominant irritable bowel syndrome^[5-7] and a few laboratory studies on the effect of food ingredients on gastrointestinal function^[8-10], gastrointestinal allergy induced by food proteins is difficult to describe^[11]. So far, we don't have sufficient clinical studies about kid's chronic diarrhea caused by food intolerance, not to mention the randomized controlled trials. Meanwhile, we find that umbilicus therapy with Chinese medicine is easy-to-operate, and easier to be accepted by children compared with oral administrations and vascular injections; furthermore, kid's skin has better penetration and absorption, and thus the medicine can quickly enter blood circulation and acts efficiently.

To objectively further evaluate the therapeutic efficacy of umbilicus application with Chinese medication in treating children's chronic diarrhea caused by food intolerance, we studied 80 cases by following the principle of multicenter randomized controlled trial design to preliminarily evaluate the treatment result.

1 Materials and Methods

1.1 Diagnostic criteria

By referring the diagnostic criteria of diarrhea from the *Practical Pediatric of Zhu Fu-tan*^[12] and the *Criteria of Diagnosis and Therapeutic Effects of Diseases and Syndromes in Traditional Chinese Medicine*^[13]: alterations of stool, including loose stool, liquid stool, or mucus stool; defecation times more than normal; the feces examination detected fat globules and undigested food; repeated microscopic studies and cultures excluded parasites and bacterial infection; 14 kinds of food allergen-specific immunoglobulin G (IgG) antibodies positive in serum.

The detection of specific IgG antibody: Venous blood 2 mL was withdrawn on an empty stomach and placed in vacuum blood collection tubes and then examined by using the enzyme-linked immunosorbent assay (ELISA) to detect the 14 kinds of food allergen-specific IgG antibodies (Biomerica, USA) in serum. The test results were divided into 4 levels according to the instructions about IgG antibody level: level 0 standing for negative; level +1 for mild allergy or mild intolerance; level +2 for moderate allergy or moderate intolerance; level +3 for severe allergy or severe intolerance.

1.2 Inclusion criteria

Alterations of feces, manifested by loose, liquid, or mucus feces; increased defecation times; examination of feces found fat globules and undigested food;

parasites and bacterial infection were excluded by repeated microscopic examinations and cultures; food intolerance confirmed by test of food allergy-specific IgG; subjects aged 1-5 years old, no sex predilection; disease duration ≥ 14 d.

1.3 Exclusion criteria

Accompanied by severe primary diseases such as liver or kidney dysfunction, severe cardiac or pulmonary diseases; severe dehydration or coma; with a history of drug allergy; blood stool, without intensive stomachache, and body temperature over 39 °C; using antibiotics prior to the recruitment.

1.4 Statistical analysis

The Microsoft Excel and SPSS 17.0 software were adopted for data analyses. The measurement data conforming to normal distribution were expressed as mean \pm standard deviation ($\bar{x} \pm s$), the intra-group comparisons were performed by paired *t*-test, and inter-group comparisons were by *t*-test; for the data of homogeneity of variance, the *t*-statistics were calculated by Cochran method. The measurement data of non-normal distribution were described by medial and percentile. The inter-group comparisons of numeration data were analyzed by Chi-square test, and the symptom and sign scores of traditional Chinese medicine (TCM) were by rank-sum test. $P < 0.05$ was considered to have a statistical significance.

1.5 General data

Totally 80 kids with chronic diarrhea were recruited from Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine and its Baoshan Branch from July 1 of 2012 to October 31 of 2014. The recruited kids were diagnosed with food intolerance by the food allergy-specific IgG test. They were randomized into a treatment group and a control group by following the principle of multicenter randomized controlled trial design with 2012 as the random number seed, 40 cases in each group. The disease duration ranged from 14 d to 42 d.

2 Intervention Methods

2.1 Treatment group

2.1.1 Healthy diet guidance

Based on the content of serum food allergy-specific IgG antibody, the kids from the two groups were asked to follow the corresponding diet: safe, alternate, and forbidden.

Safe: Kids with negative test result were asked to take ordinary food.

Alternate: Kids were asked to take the food with at least a 4-day interval if the food caused mild intolerance. If there were many foods requiring alternation, these foods would be prepared on the same day.

Forbidden: Foods causing moderate or severe intolerance were asked to be avoided for 1-3 months.

When the disease condition was improved or the symptoms were gone, the forbidden foods could be labeled as alternate, while only one type of forbidden food could be taken at once, and the interval was at least 1 week.

2.1.2 Umbilicus application with Chinese medicine

Medications: *Wu Bei Zi* (*Galla Chinensis*), *Duan Mu Li* (*Calcined Concha Ostreae*), and *Qian Shi* (*Semen Euryales*) were mixed at 1:1:1, and the medications were decoction-free granules provided by Shenzhen 999 Pharmaceuticals Company (ground into powder). The medication powder 3 g was applied to umbilicus and fixed by adhesive plaster (Taizhou Jingwei Medical Appliance Co., Ltd., China), lasting for 4 h, once a day, for successively 3 d, with an interval of 4 d, which was taken as a treatment course. Two treatment courses were given during a month.

2.2 Control group

Kids in the control group were only asked to follow

the dietary education.

The therapeutic efficacies and the changes of TCM symptoms and signs were observed and compared respectively after 1-week, 2-week, 4-week, and 12-week treatment.

3 Results Observation

3.1 Criteria of therapeutic efficacy

The diarrhea symptoms and coupled symptoms were scored based on the *China Diagnostic and Treatment Protocol for Diarrhea*^[14] and the *Guiding Principles for Clinical Study of New Chinese Medicines*^[15]. The major symptoms were scored 16 as the highest score and 10 for the secondary symptoms, and the sum of the two scores was taken as the global score. The higher the score, the severer the disease condition (Table 1 and Table 2).

Table 1. Scoring criteria of diarrhea symptoms

Item	Score (point)				
	0	1	2	3	4
Defecation frequency	No	Loose stool, and the shortest interval between two defecations >3 h	Loose stool, and the shortest interval between two defecations >2 h	Mushy stool, and the shortest interval between two defecations >1 h	Liquid stool, and the shortest interval between two defecations <1 h
Total times	No	<3 times a day	3-4 times a day	5-10 times a day	Over 10 times a day
Diarrhea-ceasing time	No	Within 12 h	Within 24 h	Within 72 h	Over 72 h
Defervescence time	No	Within 12 h	Within 24 h	Within 72 h	Over 72 h

Table 2. Scoring criteria of coupled symptoms

Item	Score (point)	
	0	1
Stomachache	No	Yes
Abdominal distension	No	Yes
Tenesmus	No	Yes
Poor appetite	No	Yes
Nausea and vomiting	No	Yes
Lassitude	No	Yes
Ache in limbs/Heaviness in limbs	No	Yes
Insomnia/dreaminess	No	Yes
Spontaneous/night sweating	No	Yes
Drowsiness	No	Yes

The symptoms were scored and the global symptom scores were calculated based on Table 1 and 2. The improvement rate of the global symptom score was calculated by the Nimodipine method: Improvement rate of total symptom score = (Pre-treatment total

score — Post-treatment total score) ÷ Pre-treatment total score × 100%.

Recovery: Diarrhea was gone, and the improvement rate of the total symptom score ≥95%.

Markedly effective: Feces and defecation frequency were normal, and the improvement rate of the total symptom score ≥70%, <95%.

Effective: Feces showed obvious improvement, defecation frequency dropped, the general symptoms were significantly improved, and the improvement rate of the global symptom score ≥30%, <70%.

Invalid: Feces, defecation frequency, and general symptoms were not improved or even worse, and the improvement rate of the global symptom score <30%.

3.2 Results

3.2.1 Comparison of the baseline data

During the whole study, there were no dropouts or rejected cases in the two groups. There were no significant differences in comparing the data of gender, average age, average disease duration, mean global symptom score, and level of food-specific IgG between the two groups before intervention ($P>0.05$), indicating the comparability (Table 3 and Table 4).

Table 3. Comparison of the baseline data

Group	<i>n</i>	Gender (case)		Average age ($\bar{X} \pm s$, year)	Average duration ($\bar{X} \pm s$, day)	Average total symptom score ($\bar{X} \pm s$, point)
		Male	Female			
Treatment	40	15	25	5.5±1.1	25.9±2.13	13.56±8.50
Control	40	18	22	5.7±1.3	26.0±2.12	14.39±8.05

Table 4. Pre-treatment comparison of food-specific IgG to 14 kinds of food (case)

Food	Level +3		Level +2		Level +1		Sum	
	Treatment group	Control group	Treatment group	Control group	Treatment group	Control group	Treatment group	Control group
Milk	19	18	6	7	4	5	29	30
Egg white/yolk	18	17	5	4	4	4	27	25
Rice	11	11	4	5	3	2	18	18
Wheat	5	3	3	6	2	1	10	10
Bean	3	1	2	2	1	2	6	5
Crab	1	0	2	4	1	0	4	4
Beef	0	1	0	0	1	0	1	1
Tomato	0	0	1	1	1	0	2	1
Shrimp	0	0	1	3	1	1	2	4
Mushroom	0	0	1	2	1	1	1	3
Corn	1	0	0	0	0	1	1	1
Codfish	0	0	1	1	1	1	2	2
Chicken	0	0	0	0	2	1	2	1
Pork	0	0	0	0	1	0	1	0

3.2.2 Comparison of symptom score

Before treatment, there were no significant differences in comparing the diarrhea symptoms and coupled symptoms scores between the two groups ($P > 0.05$). The diarrhea symptoms and coupled symptoms scores dropped significantly in the two groups after treatment ($P < 0.05$), and the inter-group comparisons also showed statistical significances ($P < 0.05$), indicating that the symptoms were improved in both groups, and the improvement was more significant in the treatment group (Table 5).

3.2.3 Comparison of the clinical efficacy after 1-week treatment

After 1-week treatment, the total effective rate was

85.0% in the treatment group versus 57.5% in the control group, and the inter-group difference was statistically significant ($P < 0.05$), indicating that the dietary education is effective in ceasing diarrhea, and the efficacy is better in the treatment group (Table 6).

3.2.4 Comparison of the clinical efficacy after 12-week treatment

After 12-week treatment, the total effective rate was 97.5% in the treatment group versus 77.5% in the control group, and the inter-group difference was statistically significant ($P < 0.05$), suggesting that the dietary education is effective in ceasing diarrhea, and the efficacy is more significant in the treatment group (Table 7).

Table 5. Comparison of symptom score ($\bar{X} \pm s$, point)

Group	<i>n</i>	Diarrhea symptom score		<i>t</i> -value	<i>P</i> -value	Score of the coupled symptoms		<i>t</i> -value	<i>P</i> -value
		Pre-treatment	Post-treatment			Pre-treatment	Post-treatment		
Treatment	40	10.35±4.00	5.24±0.37	8.04	0.001	10.17±4.03	4.91±0.87	8.07	0.001
Control	40	9.62±3.69	5.38±0.21	7.25	0.001	9.48±4.20	5.39±0.98	5.99	0.001
<i>t</i> -value		0.840	2.081			1.010	2.317		
<i>P</i> -value		0.399	0.040			0.315	0.023		

Note: Between-group comparison of the total effective rate, $\chi^2=7.314$, $P=0.014$

Table 6. Comparison of the clinical efficacy after 1-week treatment (case)

Group	<i>n</i>	Recovery	Markedly effective	Effective	Invalid	Total effective rate (%)
Treatment	40	23	8	3	6	85.0
Control	40	12	7	4	17	57.5

Note: Between-group comparison of the total effective rate, $\chi^2=7.384$, $P=0.013$

Table 7. Comparison of the clinical efficacy after 12-week treatment (case)

Group	<i>n</i>	Recovery	Markedly effective	Effective	Invalid	Total effective rate (%)
Treatment	40	28	8	3	1	97.5
Control	40	16	7	8	9	77.5

Note: Between-group comparison of the total effective rate, $\chi^2=7.314$, $P=0.014$

4 Discussion

Over the past decades, studies on the correlation between kid's chronic diarrhea and food allergy/food intolerance have achieved certain progress, and most studies hold that food allergy induces gastrointestinal dysfunction and the aggravated diarrhea symptoms are related to food allergy/food intolerance^[16]. Dietary regulation is economical and effective, and the patients can control it by themselves^[17]. Clinical studies show that dietary control benefits the improvement of diarrhea. Nevertheless, in reality, dietary control alone is not enough to treat kid's chronic diarrhea induced by food intolerance.

It's found that umbilicus application with Chinese medication is effective in treating diarrhea^[18]. TCM holds that umbilicus is connected to the internal organs, and is the joint area of the meridian qi of the Thoroughfare and Conception Vessels. During the development of embryo, abdominal wall is finally closed at the umbilicus. Therefore, the umbilicus can better absorb the medication during the medicinal application as it has the thinnest epidermal layer, no subcutaneous fat, weakest barrier function, and rich vessel distribution. In the current study, the standardized decoction-free granules of *Wu Bei Zi* (*Galla Chinensis*), *Duan Mu Li* (*Calcined Concha Ostreae*), and *Qian Shi* (*Semen Euryales*) were ground and mixed at 1:1:1 for umbilicus application. Modern studies show that *Wu Bei Zi* (*Galla Chinensis*) contains tannin, which has an astringent function and can mitigate intestinal inflammation to stop diarrhea. Furthermore, when tannin is extracted by aether, the rest fluid of *Wu Bei Zi* (*Galla Chinensis*) can still inhibit bacteria. The component of *Duan Mu Li* (*Calcined Concha Ostreae*), calcium carbonate, also produces astringent and analgesic effects. That's why *Duan Mu Li* (*Calcined Concha Ostreae*) is often used together with *Qian Shi* (*Semen Euryales*) to tonify spleen and cease diarrhea. One thing we need to notice is that *Sheng Mu Li* (*Raw Concha Ostreae*) shouldn't be used, as it possibly contains Norovirus, which can induce gastrointestinal inflammation. When the three

medications used together to apply to Shenque (CV 8), the functions of the medications and acupoint are united to cease diarrhea.

Kid's chronic diarrhea caused by food intolerance is a progressive disease. To explore a safe effective treatment protocol for this disease, the current study observed the efficacy of umbilicus application with Chinese medication by following the principle of multicenter randomized controlled trial design, and the results showed that dietary education was effective in treating this disease, while umbilicus application with Chinese medication enhanced the efficacy, and it's safe without adverse reactions. Therefore, this method can be adopted as the optimal protocol in treating kid's chronic diarrhea caused by food intolerance.

Conflict of Interest

The authors declared that there was no potential conflict of interest in this article.

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Statement of Informed Consent

Informed consent was obtained from the guardians of the recruited children in this study.

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