

Original Article

Effect of integrated traditional Chinese medicine therapy in the treatment of children with dyspeptic diarrhea

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Abstract: Objective: To inquire into the effect of integrated traditional Chinese medicine (TCM) therapy on alleviating diarrhea and improving immune function in children with dyspeptic diarrhea. Methods: One hundred and seventy-three children with dyspeptic diarrhea treated in the Henan Provincial Hospital of Traditional Chinese Medicine from May 2017 to February 2019 were selected. 78 cases in the control group (CG) were given western medicine treatment, and 95 cases in the research group (RG) were given integrated TCM therapy. The symptom improvement time, clinical indicators and efficacy of the two groups were observed and recorded. The improvement of gastrointestinal function and the expression of inflammatory factors were measured before and after treatment. The trace element detector was utilized for trace element content detection, and FACSCalibo flow cytometry for the peripheral blood T lymphocyte subsets determination. Hamilton anxiety scale (HAMA) was used to evaluate the anxiety of the two groups before and after treatment. Results: RG showed evidently less recovery time and better clinical indexes than CG. The improvement of abdominal distension, abdominal pain and diarrhea was significantly better in RG than in CG. Compared with CG, the concentrations of motilin and gastrin were significantly lower in RG. The IL-6 and TNF- α levels in RG were significantly lower than those in CG. The improvement of trace elements and immune function in RG was significantly superior to that in CG. RG presented significantly lower HAMA scores and an evidently better total effective rate than CG. Conclusions: Integrated TCM therapy is a feasible treatment scheme for children with dyspeptic diarrhea. It can reduce the frequency of diarrhea, improve gastrointestinal function, reduce inflammatory factors and enhance the immune function of children.

Keywords: Integrated traditional Chinese medicine therapy, pediatric dyspeptic diarrhea, effect exploration

Introduction

Dyspeptic diarrhea in children, as one of the common digestive system diseases in pediatrics, is caused by many factors and most of it stems from improper feeding and food allergy, which lead to malnutrition and growth disorders in children [1, 2]. Clinical presentations of dyspeptic diarrhea mainly range from vomiting, white watery to fever or egg-like stool, and in severe cases, may accompany with water and electrolyte disturbance [3, 4]. At present, micro-ecological therapies such as oral probiotics are often used to improve the intestinal flora of children, but due to the complex etiology, the treatment lags behind [5]. Therefore, finding safe and effective treatment has become the primary clinical task.

Traditional Chinese medicine (TCM) believes that dyspeptic diarrhea is triggered by spleen deficiency in children, which leads to spleen and stomach injury, thus causing diarrhea [6]. Conditioning with TCM, on the other hand, can help strengthen spleen, remove dampness and stop diarrhea [7]. In recent years, TCM massage has been proved to be effective and safe through its application in the treatment of other diseases [8, 9], so this study applied it to children with dyspeptic diarrhea. Through manipulation, TCM can not only dredge meridians, eliminate pathogen and strengthen vital qi, but also strengthen body resistance, regulate qi and blood and adjust zang-fu organs. Besides, it can also be used to strengthen spleen and stomach, clear the small intestine, facilitate defecation and urination through massage,

abdomen-kneading massage and back kneading massage, so as to achieve the effect of activating spleen and checking diarrhea [10, 11]. Studies have shown that massage can improve defense function through nerves, body fluids and reflexes; moreover, it can clear some chemical substances to improve blood circulation and accelerate the removal of inflammatory substances and acidic metabolites [12, 13]. For example, in the study of Wang et al. [14], the treatment of children with splenasthenic diarrhea by activating qi and collateral massage can improve the cure rate and has a good curative effect.

At present, there is little research on the effect of integrated TCM therapy on dyspeptic diarrhea in children. Therefore, this study aimed to provide a better reference for the treatment of children with dyspeptic diarrhea by observing the improvement of diarrhea and immune function of children with this treatment.

Materials and methods

General information

This study included 173 cases of children with dyspeptic diarrhea treated in the Henan Provincial Hospital of Traditional Chinese Medicine from May 2017 to February 2019. 78 cases in the control group (CG) were given western medicine treatment, and 95 cases in the research group (RG) were given integrated TCM therapy. Inclusion criteria: Children in both groups were confirmed to have dyspeptic diarrhea [15] and received follow-up treatment in our hospital after diagnosis, with complete clinical general data, no antibiotic treatment, and no symptoms of dehydration and poisoning. The hospital Ethics Committee of the Henan Provincial Hospital of Traditional Chinese Medicine approved the study protocol, and the guardians of the participants had been informed and signed the fully informed consent. Exclusion criteria: children with hearing impairment; children with severe malnutrition; children complicated with primary diseases in cardio-cerebrovascular, liver, kidney, or hematopoietic system; children with gastrointestinal and immune dysfunction; children who dropped out of the experiment; children who lost to follow up. The inclusion criteria were applicable to all enrolled participants.

Treatment methods

Children in CG were given montmorillonite powder (Fangsheng Pharmaceutical Co., Ltd., Hunan, China, H20094210, specification: 3 g/bag) and Combined Bacillus Subtilis and Enterococcus Faecium Granules with Multivitamines, Live (Hanmi Pharm Co., Ltd., Beijing, China, S20020037). Medication method: montmorillonite powder: ≤ 1 year old (1/3 bag per time, 3 times daily), 1-2 years old (1/3-2/3 bag per time, 3 times daily), > 2 years old (2/3 bag per time, 3 times daily); Combined Bacillus Subtilis and Enterococcus Faecium Granules with Multivitamines, Live: 1 bag per time, 3 times daily. The treatment lasted for 15 days.

Children in RG were treated with antidiarrheal prescription made by our hospital (9 g each Radix Pseudostellariae, Poria cocos, Scutellaria baicalensis Georgi and Pueraria lobata; 5 g each Herba Perilliae and Medicine Terminalia Fruit; 4 g each agastache rugosa, Largehead Atractylodes Rh and coptis chinensis; and 3 g of liquorice). The antidiarrheal prescription was given 1 dose per day. After decocting in water, 500 mL of decoction was taken in two divided doses. For children with yellow greasy furred tongue, 4 g each of forsythia suspensa, Honysuckle Flower and Radix Bupleuri were added; In case of abdominal pain, 4 g each of Rhizoma Corydalis and Radix Paeoniae Alba were added; And 5 g each of dried tangerine peel, ginger and Pinellia ternata were added if there was vomiting. Massage therapy: Abdomen massage: the doctor spreads both hands flat, with the thumb perpendicular to the palm, and pushes the thumb down from the xiphoid point to the child's abdomen for about 50-100 times. Abdomen-kneading massage: the doctor's palm faces the child's abdomen and kneads counterclockwise 50-100 times to promote gastrointestinal lubrication. Back kneading massage: The doctor spreads both hands while bringing the limbs together. Then separate the thumb from the thumb, press the thumb against both sides of the child's spine, and push it from top to bottom until the skin on both sides of the spine appears reddish and feverish. Massage therapy was performed every 3 days for 25 min for 15 d. Enema treatment: 1 mL/kg Houttuynia cordata injection (Yixiang Pharmaceutical Co., Ltd., Guangdong, China, Z14020479) and 60 mL/kg Shuang-

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huanglian injection (Fusen Pharmaceutical Co., Ltd., Henan, China, Z41020750) were used for enema administration. The sterile catheter was inserted in 10 cm, heated to 37°C, and the mixture was introduced to ensure a retention time of 15 min before the successful enema was determined. The treatment duration was 5 days.

Outcome measures

The recovery time of stool frequency, stool character and body temperature after treatment and the hospitalization time of the two groups were observed.

The changes in the scores of abdominal distension, abdominal pain and diarrhea were observed before and after treatment. According to the severity of symptoms, the score was divided into zero, mild, moderate and severe, with scores of 0, 1, 2 and 3 respectively.

Detection of gastrointestinal function indexes and inflammatory factor indexes: Before and after treatment, 5 mL venous blood was drawn from children in both groups, centrifuged at 1500×g at 4°C for 10 minutes, and stored in a low-temperature refrigerator at -70°C for later use. Enzyme-linked immunosorbent assay (ELISA) [16] was applied to detect gastrin and motilin (Yipu Biotechnology Co., Ltd., Wuhan, China, MM-1174H1, MM-1510H1), and interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (Saihongrui Biotechnology Co., Ltd., China), strictly following the instructions provided with the kits.

Trace element detector (Zeguan Medical Devices Co., Ltd., Zhangqiu, China, 11111) was utilized for the determination of iron, calcium, zinc and selenium concentrations in the two groups of children.

T lymphocyte subsets in peripheral blood of two groups of patients were determined by FACSCalibur flow cytometry (Exxon Technology Co., Ltd., Beijing, China, BD FACSCALIBUR), and CD3+, CD4+, CD8+ and CD4+/CD8+ values in peripheral blood were read. The experimental procedures were carried out in strict accordance with the product instructions.

Hamilton Anxiety Scale (HAMA) [17]: There were 14 items in the scale, all of which were scored using a five-point scoring method of 0-4 points:

0 was classified as asymptomatic, 1 as mild anxiety, 2 as moderate anxiety, 3 as severe anxiety, and 4 as extremely severe anxiety. The score was in proportion to the severity of the child's anxiety.

Efficacy judgment: If the frequency of defecation was reduced within 1-2 days after treatment, the symptoms of defecation became better and the clinical symptoms disappeared completely, it was rated as markedly effective. If the frequency of stools decreased within 2-3 days after treatment, the fecal character was observed to be improved, water decreased, and the clinical symptoms disappeared, it was rated as effective. If the number of diarrhea did not decrease after treatment and the stool character did not change, it was rated as ineffective. Total effective rate was calculated as number of (markedly effective + effective) cases/total number of cases × 100%.

Statistical methods

SPSS22.0 (EasybioTechnology Co., Ltd., Beijing, China) was used for statistical analysis. The counting data were denoted by number of cases/percentage [n (%)] and compared by the Chi-square test between groups. Continuous correction Chi-square test was applied when the theoretical frequency in Chi-square test was less than 5. The measurement data were represented by mean ± standard error of the mean (SEM); the inter-group comparison was performed by independent-sample t-test, and the successive comparison within groups was performed by paired t-test. When P < 0.05, the difference was statistically significant.

Results

General information

There was no statistically significant difference in general baseline data such as gender, body weight, average age, average course of disease, place of residence, mode of delivery, low birth weight, and parental smoking history between RG and CG (P > 0.05) (**Table 1**).

Comparison of symptom improvement time between the two groups

Compared with CG, the recovery time of stool frequency, stool character and, body tempera-

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Table 1. Comparison of general information between the two groups [n (%)] (x ± sd)

Classification	Research group (n=95)	Control group (n=78)	t/ χ^2 value	P value
Gender			0.081	0.776
Male	52 (54.74)	41 (52.56)		
Female	43 (45.26)	37 (47.44)		
Body mass (kg)	8.04±1.54	8.13±1.57	0.379	0.705
Average age (years old)	2.46±0.32	2.51±0.35	0.980	0.328
Average course of disease (years)	8.43±1.34	8.25±1.37	0.870	0.385
Residence			0.549	0.459
Han	47 (49.47)	43 (55.13)		
Ethnic minorities	48 (50.53)	35 (44.87)		
Birth mode			0.596	0.440
Caesarean section	48 (50.53)	44 (56.41)		
Natural labor	47 (49.47)	34 (43.59)		
Low birth weight			0.134	0.714
Yes	28 (29.47)	25 (32.05)		
No	67 (70.53)	53 (67.95)		
Parents' smoking history			0.679	0.409
Yes	32 (33.68)	31 (39.74)		
No	63 (66.32)	47 (60.26)		

Table 2. Comparison of symptom improvement time between the two groups (mean ± SEM)

Groups	n	Recovery time of stool frequency	Recovery time of stool character	Recovery time of body temperature	Hospitalization time
Research group	95	1.03±0.04	2.54±0.14	3.23±0.18	3.72±0.38
Control group	78	2.14±0.09	3.73±0.23	5.43±0.35	5.24±0.57
t	-	108.000	41.870	53.300	20.940
P	-	< 0.001	< 0.001	< 0.001	< 0.001

Table 3. Improvement of clinical indicators before and after treatment in the two groups (mean ± SEM)

Groups	n	Abdominal distension		Abdominal pain		Diarrhea	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research group	95	3.24±0.32	0.93±0.12	3.12±0.12	1.04±0.09	3.27±0.32	1.04±0.07
Control group	78	3.31±0.31	1.69±0.18	3.15±0.11	1.34±0.14	3.19±0.36	1.79±0.14
t	-	1.452	33.160	1.698	17.040	1.546	45.730
P	-	0.148	< 0.001	0.091	< 0.001	0.123	< 0.001

ture, and the hospitalization time were evidently less in RG after treatment ($P < 0.05$) (**Table 2**).

Improvement of clinical indicators before and after treatment in the two groups

There were no significant differences in abdominal distension, abdominal pain and diarrhea between the two groups before treatment ($P > 0.05$). Whereas, the above symptoms were im-

proved after treatment in both groups ($P < 0.05$), and the improvement in RG was significantly higher than that in CG ($P < 0.05$) (**Table 3**).

Comparison of gastrointestinal function between the two groups before and after treatment

Motilin and gastrin levels differed insignificantly between the two groups before treatment (P

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Table 4. Comparison of gastrointestinal function between the two groups before and after treatment (mean ± SEM)

Groups	n	Gastrin (ng/L)		Motilin (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment
Research group	95	584.23±59.32	401.43±45.54	145.35±30.43	81.43±9.84
Control group	78	594.12±59.45	463.75±45.85	138.54±31.24	95.65±10.54
t	-	1.090	8.929	1.447	9.159
P	-	0.277	< 0.001	0.149	< 0.001

Table 5. Comparison of inflammatory factors between the two groups before and after treatment (mean ± SEM)

Groups	n	IL-6 (pg/mL)		TNF-α (pg/mL)	
		Before treatment	After treatment	Before treatment	After treatment
Research group	95	25.43±2.76	10.32±1.43	30.54±3.04	12.43±1.26
Control group	78	25.28±2.74	16.23±1.56	30.85±3.02	21.43±2.03
t	-	0.356	25.960	0.669	35.660
P	-	0.722	< 0.001	0.504	< 0.001

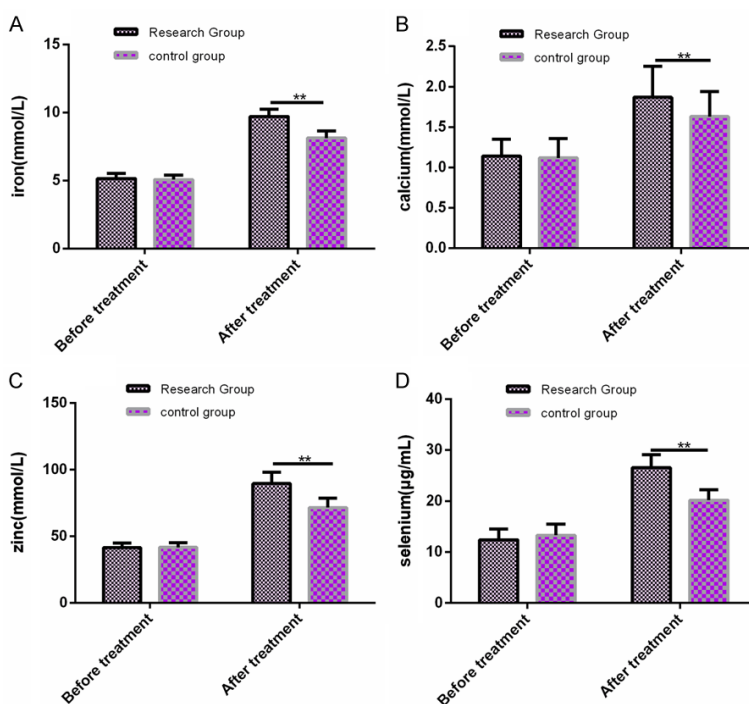


Figure 1. Comparison of trace elements between the two groups before and after treatment. A: There was no significant difference in the iron level between the two groups before treatment, but after treatment, the iron level in research group was significantly higher than that in control group. B: There was no significant difference in the calcium level between the two groups before treatment, but after treatment, the calcium level in research group was significantly higher than that in control group. C: There was no significant difference in the zinc level between the two groups before treatment, but after treatment, the zinc level in research group was significantly higher than that in control group. D: There was no significant difference in the selenium level between the two groups before treatment, but after treatment, the selenium level in research group was significantly higher than that in control group. Note: * indicated $P < 0.05$ vs before treatment; ** indicated $P < 0.01$ vs control group after treatment.

> 0.05). After treatment, motilin and gastrin levels reduced remarkably in both groups ($P < 0.05$), and the decline was more notably in RG than in CG ($P < 0.05$) (Table 4).

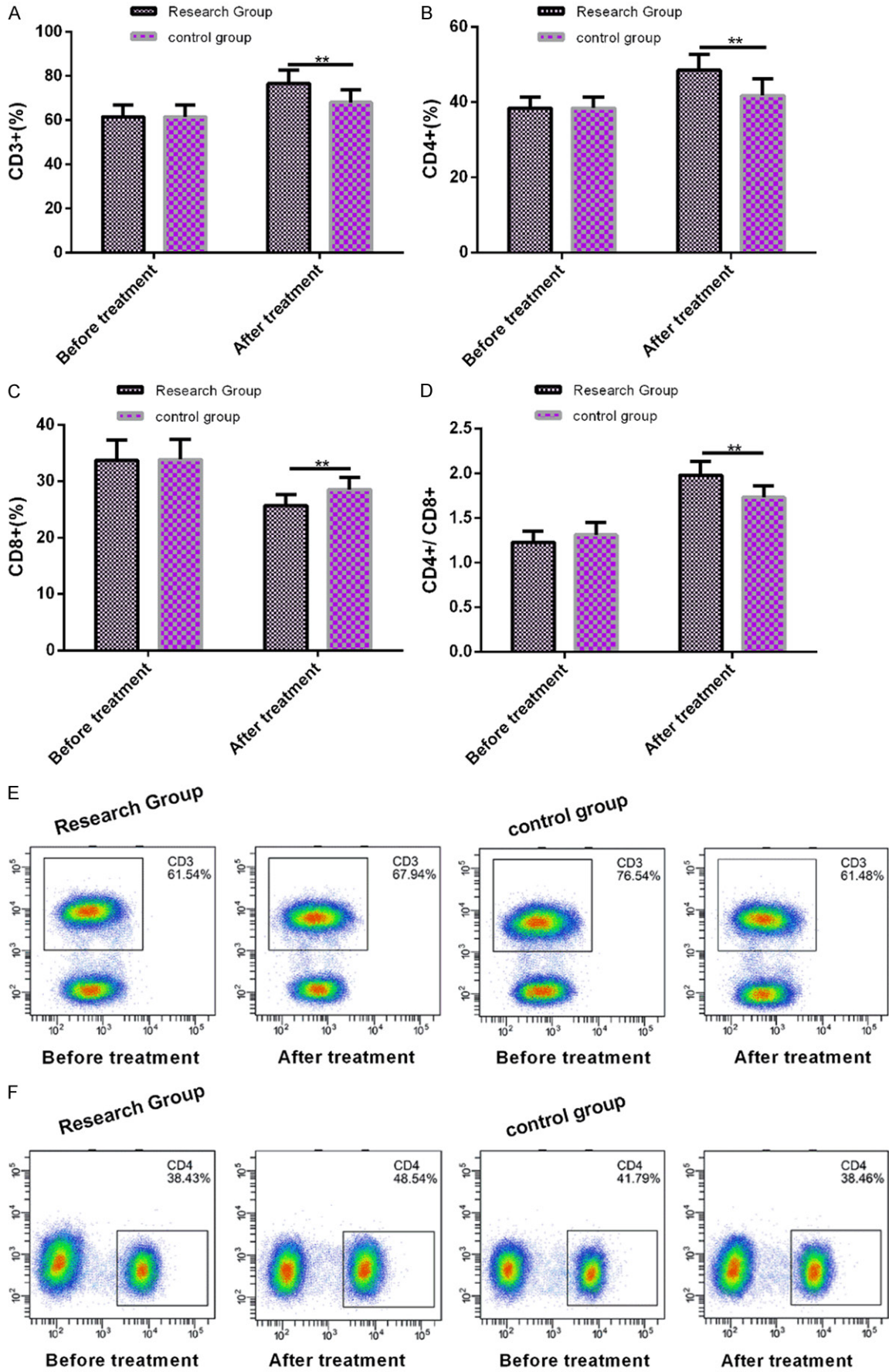
Comparison of inflammatory factors between the two groups before and after treatment

The pre-treatment IL-6 and TNF-α identified no marked differences between the two groups ($P > 0.05$), while their post-treatment levels reduced notably both in RG and CG ($P < 0.05$), and the decrease was more profound in RG than in CG ($P < 0.05$) (Table 5).

Comparison of trace elements between the two groups before and after treatment

Iron, calcium, zinc and selenium contents showed no marked differences between the two groups before treatment ($P > 0.05$). However, their post-treatment contents increased notably in both groups ($P < 0.05$), and the increase was more profound in RG than in CG ($P < 0.05$) (Figure 1).

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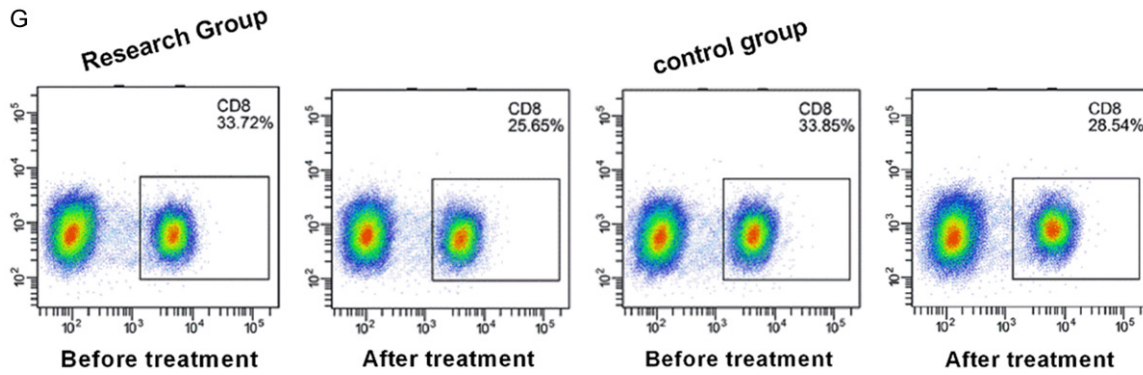


Figure 2. Comparison of immune function between the two groups before and after treatment. A: There was no significant difference in the expression of CD3+ between the two groups before treatment, but the expression of CD3+ in research group was significantly higher than that in control group after treatment. B: There was no significant difference in the expression of CD4+ between the two groups before treatment, but the expression of CD4+ in research group was significantly higher than that in control group after treatment. C: There was no significant difference in the expression of CD8+ between the two groups before treatment, but the expression of CD8+ in research group was significantly lower than that in control group after treatment. D: There was no significant difference in the ratio of CD4+/CD8+ between the two groups before treatment, but the CD4+/CD8+ ratio in research group was significantly higher than that in control group after treatment. E: Flow cytometry of CD3+ in the research group and the control group before and after treatment. F: Flow cytometry of CD4+ in the research group and the control group before and after treatment. G: Flow cytometry of CD8+ in the research group and the control group before and after treatment. Note: * indicated $P < 0.05$ vs before treatment; ** indicated $P < 0.01$ vs control group after treatment.

Table 6. Comparison of HAMA scores between the two groups before and after treatment (mean \pm SEM)

Groups	n	HAMA scores	
		Before treatment	After treatment
Research group	95	18.43 \pm 1.65	8.31 \pm 1.03
Control group	78	18.24 \pm 1.62	11.34 \pm 1.43
t	-	0.759	16.170
P	-	0.448	< 0.001

Comparison of immune function between the two groups before and after treatment

The levels of CD3+, CD4+, CD8+ and CD4+/CD8+ were not significantly different before treatment between the two groups ($P > 0.05$). The above indicators improved in both RG and CG after treatment, and in comparison with CG, CD3+, CD4+ and CD4+/CD8+ were higher ($P < 0.05$) while CD8+ was lower in RG ($P < 0.05$) (Figure 2).

Comparison of HAMA scores between the two groups before and after treatment

The HAMA score before treatment showed no significant difference between the two groups ($P > 0.05$). After nursing intervention, the HAMA score reduced noticeably in both RG and CG ($P < 0.05$), and the score was noticeably lower in RG than in CG ($P < 0.05$) (Table 6).

Comparison of efficacy between the two groups before and after treatment

The total effective rate of RG after treatment was 94.74%, which was remarkably higher than 82.05% of CG ($P < 0.05$) (Table 7).

Discussion

Diarrhea is a digestive tract syndrome characterized by changes in stool character and increased frequency, which usually occurs in infants and young children [18]. While dyspeptic diarrhea is mainly caused by improper diet of children, it easily leads to water and electrolyte disorders. Without prompt and effective treatment, it may further destroy the physical function of children, causing malnutrition or stunting, thus affecting the growth and development of children, and even threatening the life safety of children in severe cases [19, 20]. For the treatment of indigestion diarrhea, the current clinical intervention is mostly based on Western medicine [21], while the research on TCM intervention is scanty.

In this study, integrated TCM therapy was applied to treat dyspeptic diarrhea in children, and it was found that the condition of children improved enormously after intervention. Being an external therapy with a long history, TCM massage has been used to treat a variety of

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Table 7. Comparison of efficacy between the two groups before and after treatment [n (%)]

Groups	n	Markedly effective	Effective	Ineffective	Total effective rate (%)
Research group	95	66 (69.47)	24 (25.26)	5 (5.26)	90 (94.74)
Control group	78	29 (37.18)	35 (44.87)	14 (17.95)	64 (82.05)
χ^2	-	-	-	-	7.050
P	-	-	-	-	0.008

diseases. As an important therapeutic method with significant curative effect and high cost efficiency, it has been extensively used clinically for the treatment of functional constipation [22]. The results of the present study identified that the recovery time of stool frequency, stool character and body temperature, and the hospitalization time of the children in RG were significantly less than those in CG, suggesting that integrated TCM therapy could improve the secretion of digestive enzymes in children and improve their stool characters. Other evidence has indicated that [23], giving massage treatment to children with acute diarrhea can improve the clinical cure rate, reduce the frequency of stools and shorten the time of acute diarrhea. In line with the preceding research, this study revealed a significantly better improvement in abdominal distension, abdominal pain and diarrhea in RG than in CG after treatment, demonstrating that effective intervention can improve the clinical symptoms of children, and the comprehensive treatment of integrated TCM therapy can better alleviate abdominal pain in children and more efficiently resolve the clinical symptoms. Clinically, it has been shown that all major systems of infants are not well developed, and dyspeptic diarrhea will lead to disorders of spleen, stomach and intestinal function [24]. As vital gastrointestinal hormones, motilin and gastrin can promote gastrointestinal motility and regulate the transport of water and electrolyte in patients' gastrointestinal tract [25]. A large number of studies have identified that motilin and gastrin increase significantly during diarrhea. For example, He et al. [26] reported that plasma motilin and serum gastrin levels in patients with chronic diarrhea were significantly higher than those in the healthy group, while their levels reduced significantly in patients after TCM treatment, with significantly improved clinical symptoms. Our research showed that motilin and gastrin levels in RG were remarkably lower than those in CG, which is similar to the results of He et al.,

indicating that effective TCM treatment can improve the gastrointestinal function of children, but integrated TCM therapy renders higher safety and efficiency. Also, there was a clinical research showing that [27] serum IL-6, IL-10 and TNF- α elevated evidently in patients with diarrhea-predominant irritable bowel syndrome. In our study, the expression levels of IL-6 and TNF- α in RG were significantly lower than those in CG, which indicated that integrated TCM therapy could reduce the inflammatory reaction caused by diarrhea in children.

Severe diarrhea can lead to malnutrition, dehydration and even electrolyte imbalance in children, and can result in abnormal level of trace elements and immune function in patients [28]. The research of Wang and Feng et al. showed that [29], the treatment for acute diarrhea in children can effectively shorten the duration of diarrhea and hospitalization time, reduce the frequency of diarrhea, and enhance cellular immune function. Here, we identified that children in RG presented statistically higher concentrations of iron, calcium, zinc and selenium than CG, which proved that the integrated TCM therapy can improve the gastrointestinal function of children and slow down the loss of trace elements. Further, the observation of immune function indexes of children in the two groups revealed remarkably higher CD3+, CD4+ and CD4+/CD8+ levels while noticeably lower CD8+ level in RG as compared to CG, suggesting that integrated TCM therapy can effectively improve the immune function of children, enhance their immunity and improve the therapeutic effect. Diarrhea also affects the behavior and mood of children [30]. Our results showed that HAMA scores reduced remarkably in both groups after treatment, and the reduction was more significant in RG, indicating that integrated TCM therapy can significantly relieve anxiety in children, thus reducing the frequency of diarrhea. Finally, the total effective rate was observed to be significantly

higher in RG than in CG, which indicated that the symptoms of children with dyspeptic dyspepsia resolved more quickly and the clinical effect was more significant after the integrated TCM therapy.

Although this study confirmed that integrated TCM therapy is a feasible treatment scheme for children with dyspeptic diarrhea, there are still some shortcomings. For example, the study had neither analyzed the quality of life of the children nor evaluated their family satisfaction. In the future research, it is necessary to extend the research time and further prove the results of this research.

Collectively, integrated TCM therapy is a feasible treatment scheme for children with dyspeptic diarrhea, which can reduce the frequency of diarrhea, improve gastrointestinal function, reduce inflammatory factors and bolster the immune function of children.

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Disclosure of conflict of interest

None.

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