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Full Paper

Clinical study of lactulose combined with acupoint catgut embedding on maintenance hemodialysis patients complicated with functional constipation

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Abstract: This study explores the clinical effect of lactulose combined with acupoint catgut embedding on maintenance hemodialysis (MHD) patients with functional constipation. Patients with MHD complicated with functional constipation in the blood purification centre of Huzhou Central Hospital were enrolled and randomly divided into a control group and an observation group, with 30 cases in each group. The control group was treated with lactulose oral liquid, and the observation group was treated with lactulose oral liquid + acupoint catgut embedding. The scores of constipation symptoms and the average number of weekly spontaneous complete bowel movement (SCBM) were compared between the two groups before and after treatment. Serum brain-gut peptide-related indicators and indoxyl sulfate indicators were used before and after treatment, and the short-term efficacy of the patients was evaluated. Results showed that after treatment, the scores of stool properties, defecation frequency, difficulty, and defecation time in the observation group were significantly lower than those in the control group ($P<0.01$). The frequency of SCBM in the observation group was significantly more than that in the control group in 2-4 weeks of treatment ($P<0.05$). Compared with the control group after treatment, the serum 5-hydroxytryptamine four receptors level in the observation group significantly increased ($P<0.01$), and the serum somatostatin, vasoactive intestinal peptide, and indoxyl sulfate levels significantly decreased (all $P<0.01$). The results of the curative effect evaluation showed that the total effective rate of the observation group (90.00%) was significantly higher than that of the control group (63.33%, $P<0.05$). Thus, lactulose combined with acupoint catgut embedding can achieve a good curative effect in the treatment of functional constipation complicated by MHD, relieve the symptoms of constipation, increase the frequency of SCBM, mediate the level of serum

brain-gut peptide-related indicators, and promote the recovery of intestinal-kidney function. Thus, this method can alleviate defecation troubles, thereby improving the quality of life of MHD patients.

Keywords: lactulose, acupoint catgut embedding, maintenance hemodialysis, functional constipation

INTRODUCTION

At present, hemodialysis is the primary renal replacement therapy for patients with end-stage renal disease. Dialysis technology has rapidly progressed in recent years, significantly improving patients' survival rates. With the prolongation of hemodialysis time, the residual renal function gradually disappears, and the complications caused by it seriously threaten the quality of life and long-term prognosis of maintenance hemodialysis (MHD) patients. Functional constipation is one of the common long-term complications of MHD patients and is an essential challenge for every dialysis centre [1]. Currently, most hemodialysis patients in China suffer from constipation [2, 3]. A cross-sectional observational study found that the incidence of constipation in hemodialysis patients was 52.7%. Diabetic nephropathy with renal failure and an age of 65 or older were independent risk factors for constipation in hemodialysis patients [4]. Long-term constipation can lead to headache, dizziness, restless sleep, upset and irritability, and can aggravate the accumulation of uremic toxins, leading to the occurrence and aggravation of various complications and affecting patients' work and quality of life. Currently, the clinical treatment of MHD complicated with functional constipation often adopts conventional methods including dietary guidance, defecation training, laxatives, etc. However, the effect is often not good enough, and laxatives lead to more disordered intestinal function and absorption of a large amount of water and electrolytes, leading to other diseases. Therefore, how to choose a treatment method suitable for functional constipation in MHD patients is extremely meaningful.

Regarding western medicine treatment, lactulose is a commonly used drug for treating constipation. It belongs to a disaccharide with osmotic activity. Moisture softens the stool and produces a cathartic effect [5, 6]. In addition, lactulose can be decomposed and utilised by lactic acid bacteria and bifidobacteria in the colon and converted into low molecular weight organic acids, which provide a suitable environment for the growth of beneficial probiotics in the colon, repair the intestinal mucosal barrier, and promote defecation.

MHD functional constipation can be classified as ‘constipation,’ ‘obstructed stool,’ ‘dry stool,’ ‘spleen contraction,’ and other disease names in traditional Chinese medicine. The aetiology of this disease is the conduction failure of the large intestine and the abdominal gas obstruction. Although the disease's location is in the large intestine, it is closely related to the lungs, spleen and kidneys. In recent years acupuncture and moxibustion have achieved good results in treating functional constipation, and clinical research and reports on its treatment have been continuously enriched [7]. Different acupuncture treatment methods include ordinary acupuncture, electroacupuncture, warm needling moxibustion, acupoint catgut embedding, acupoint sticking and ear point embedding. As an extension of acupuncture and moxibustion, catgut embedding at acupoints has a definite curative effect. It can supplement the long-term curative effect of

acupuncture and moxibustion, shorten the time-consuming nature of acupuncture and moxibustion, and improve the sustained curative effect [8].

Functional constipation in MHD patients is a common and challenging disease. This study aims to objectively evaluate the clinical efficacy of lactulose combined with acupoint catgut embedding in treating MHD patients with functional constipation and provide a theoretical basis for the standardised diagnosis and treatment of MHD patients with functional constipation.

MATERIAL AND METHODS

Clinical Information

Sixty patients with MHD complicated by functional constipation in the blood purification centre of Huzhou Central Hospital from January to December 2022 were included in the study. Inclusion criteria — the patients met the diagnostic criteria for functional constipation in Rome IV [9]; all selected patients had stable blood pressure and blood sugar with no infection, heart failure, or active immune disease; they were more than 18 years old, had more than 6 months of regular dialysis (three times a week, 4 hr each time); they agreed to accept and obey the research arrangement and signed the informed consent form. Exclusion criteria — patients with organic diseases of the digestive system, such as malignant tumours of the digestive tract and intestinal polyps, and those with a history of digestive tract surgery; patients with primary severe diseases such as those of the heart, brain, liver, and respiratory and hematopoietic systems; patients with mental illness or cognitive impairment; pregnant patients and lactating women; those who had recently taken drugs that affect gastrointestinal function or received other treatments. This study was approved by the Ethics Committee of Huzhou Central Hospital and Affiliated Central Hospital, Hozhou University (Approval no. 2020GY21).

According to the above criteria, 60 patients were divided into control and observation groups by random number table method, with 30 cases in each group. In the control group there were 17 males and 13 females; their mean age was 58.35±8.10 years and the disease duration was 3.04±1.13 years. In the observation group there were 14 males and 16 females; their mean age was 59.37±9.33 years and the disease duration was 2.78±1.26 years. There was no significant difference in the general data between the two groups ($P>0.05$).

Treatment Method

For control group, lactulose oral solution (Duphalac, Fresenius Kabi Austria GmbH) was administered regularly for four weeks (two 15-mL doses daily with suspended dialysis). For observation group, combined treatment with lactulose oral liquid + acupoint catgut embedding was given. The lactulose oral liquid method was the same as before. As for acupoint catgut embedding method, the following acupoints were selected: Tianshu, Dachangshu, Shangjuxu, Zusanli, Qihai, Zhigou, Guanyuan and Pishu. A disposable spring-loaded special no. 8 embedding needle (Dr. Sun, Zhenjiang Gaoguan Company) was used. The thread embedding material was absorbable polyglycolide lactide (Johnson & Johnson, Germany) and cut to 3 cm for later use. For operation method, the doctor washes his hands, wipes with iodophor and puts on sterile gloves. The patient chooses a suitable body position to expose the area where the acupoints are located. The catgut embedding points are sterilised with povidone-iodine cotton balls. The doctor uses disposable sterile tweezers to take out the absorbable protein thread and inserts it into the tube of the embedding needle from the needle tip, paying attention that the thread end does not exceed the needle tip and

leak out of the tube. The needle tip is aimed at the acupoint and is penetrated quickly. After the acupuncture is invigorated, the needle core is pushed forward to embed the protein thread into the deep muscle layer or subcutaneous tissue of the acupoint. The needle tube is then withdrawn, attention being paid not to leak the thread end and the needle hole is pressed with sterile gauze for a while. Then the pinhole is covered with a sterile dressing after there is no bleeding. The whole treatment is given once every two weeks for four weeks.

OBSERVATION INDICATORS

Main Efficacy Indicators

Constipation symptom score

The scores of constipation symptoms in the two groups were compared before and after treatment. The scores were mainly evaluated from four aspects: stool characteristics (Bristol stool characteristics atlas type), defecation frequency, difficulty and defecation time. The score of each observation was 0-3, with higher scores indicating more severe constipation in patients [10, 11].

Average weekly spontaneous complete bowel movement (SCBM)

During the treatment period, the SCBM of the patients in the first, second, third and fourth weeks were recorded, and SCBM ≥ 3 times were considered as normal defecation.

Secondary Efficacy Indicators

Related indicators of serum brain-gut peptide

The serum 5-hydroxytryptamine four receptors (5-HT4R), vasoactive intestinal peptide (VIP) and somatostatin (SS) levels were detected by enzyme-linked immunosorbent assay before and after treatment. 5-Hydroxytryptophan (5-HT) and 5-HT4R kits were purchased from Nanjing Kamiluo Bioengineering Co.(China) and SS and VIP kits were purchased from Shanghai Jianglai Biological Co. (China).

Serum Indoxyl Sulfate (IS) Index

Detection of IS was done with high-performance liquid chromatography (LC-30AD ultra-HPLC-fluorescence detector coupled system (UPLC-FLD, Shimadzu Corporation, Japan). After thawing at room temperature, the serum 5-HT4R was vortexed for 15 sec. and 100 μL of the serum was added with 900 μL of acetonitrile to precipitate protein, vortexed for 60 sec. and centrifuged at 12000 r/min. for 8 min. Five hundred μL of the supernatant was drawn into a 2-mL sample bottle, and 5 μL was taken to UPLC-FLD system for analysis. The standard curve equation of IS is: Y=87769.7X-127213 (r=0.9993), where x is the IS peak area; the IS concentration (mg/L) was calculated.

Efficacy Criteria

Criteria for cure were: 1 defecation in 2 days; moist stool, unobstructed during the solution; no recurrence in a short period (drug withdrawal for one month). Criteria for improvement were: defecation once in more than three days, moist stool; bowel movement not smooth. Unhealed condition was: no change in symptoms. Effective rate = [(cured + improved) /n]× 100%.

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Statistical Analysis

Statistical analysis was processed by SPSS21.0 statistical software. The measurement data were first tested for normality, the normality was satisfied, expressed as mean ± standard deviation ($x \pm s$), and the paired t-test was used for comparison between groups. The measurement data were defined as the number of cases, and Fisher's exact test was used for comparison between the two groups. In all statistical tests, $\alpha = 0.05$; $P \leqslant \alpha$ means a difference in the trial; $P > \alpha$ implies no difference in the test.

RESULTS

Constipation Symptom Scores

There is no statistical difference in the scores of constipation symptoms between the two groups before treatment (all P's >0.05). The scores of stool properties, defecation frequency, defecation difficulty, and defecation time in both groups are significantly reduced after treatment (P<0.01). However, after treatment, the scores of all indicators in the observation group are significantly lower than those in the control group, and the difference is statistically significant (P<0.01) (Table 1).

Table 1. Scores of constipation symptoms in two groups before and after treatment (x±s)

Group	Time Point	Stool properties	Defecation frequency	Defecation difficulty	Defecation time
Control Group （n=30）	Before Treatment	2.33±0.67	2.42±0.68	2.21±0.68	2.05±0.79
	After Treatment	1.19±0.52	1.07±0.64	1.00±0.57	0.90±0.60
	t	7.362	7.918	7.469	6.349
	P	<0.0001	<0.0001	<0.0001	<0.0001
Observation Group （n=30）	Before Treatment	2.52±0.46	2.30±0.53	2.40±0.68	2.11±0.77
	After Treatment	0.84±0.59*	0.76±0.43*	0.73±0.45*	0.63±0.37*
	t	12.30	12.36	11.22	9.489
	P	<0.0001	<0.0001	<0.0001	<0.0001

* P<0.05 cf control group ; t = statistical value

Comparison of SCBM

When the SCBM of the two groups after treatment are compared, the results show no significant difference in SCBM between the two groups in the first week of treatment (P>0.05). Compared with the control group, the frequency of SCBM in the observation group in the 2nd, 3rd, and 4th week significantly increases (P<0.05) (Table 2).

Table 2. Comparison of SCBM between two groups after treatment (x±s)

Group	Week 1	Week 2	Week 3	Week 4
Control Group （n=30）	1.36±0.50	1.90±0.63	2.64±0.60	3.33±0.84
Observation Group （n=30）	1.47±0.50	2.25±0.55	3.18±0.54	3.85±0.76
t	0.8521	2.292	3.664	2.514
P	0.3977	0.0255	0.0005	0.0147

Note: t = statistical value

Changes in Serum Brain-gut Peptide-related Index and Serum IS Index

For each index, no statistical difference was found between the two groups before treatment (all P's > 0.05). After treatment, the serum 5-HT4R levels in the two groups are significantly higher than those before treatment (P<0.01), and the serum VIP, SS and IS levels are considerably lower than those before treatment (all P's <0.01) (Table 3). Compared with the control group after treatment, the serum 5-HT4R level in the observation group significantly increases (P<0.01), and the serum VIP, SS and IS levels significantly decrease (all P's <0.01) (Table 3).

Table 3. Changes in serum brain-gut peptide-related index and serum IS index (x±s)

Group	Time point	5-HT_4R（μg/L）	VIP（ng/L）	SS（ng/L）	IS（μg/mL）
Control Group（n=30）	Before treatment	2.58±0.71	312.55±41.34	54.17±8.78	31.12±15.64
	After treatment	3.67±0.93	173.75±27.27	36.70±4.81	20.91±8.98
	t	5.103	15.35	9.558	3.101
	P	<0.0001	<0.0001	<0.0001	0.0030
Observation Group（n=30）	Before treatment	2.35±0.84	322.05±41.58	53.69±9.61	34.96±16.13
	After treatment	4.20±1.04*	130.03±19.35*	29.44±5.25*	15.54±4.34*
	t	7.580	22.93	12.13	6.368
	P	<0.0001	<0.0001	<0.0001	<0.0001

* P<0.05 cf control group; t = statistical value

Comparison of Clinical Curative Effects

The results of curative effects show that after treatment, the total effective rate in the observation group is 90.00% (27/30), and that in the control group is 63.33% (19/30). The total effective rate of the observation group is significantly higher than that of the control group (P<0.05) (Table 4).

Table 4. Comparison of clinical curative effects

Group	Cure	Improvement	Unhealed	Effective rate（%）
Control Group（n=30）	5	14	11	63.33
Observation Group（n=30）	11	16	3	90.00
P				0.0303

DISCUSSION

The results of this study clearly show that compared with lactulose oral liquid treatment alone, when combined with acupoint catgut embedding of traditional Chinese medicine in the treatment of MHD patients with functional constipation, the latter treatment can lead to a better curative effect as indicated from improvement in the scores of constipation symptoms of patients and a significant increase in the patients' SCBM. Thus, acupuncture and moxibustion in traditional Chinese medicine seems to significantly affect the treatment of functional constipation. As a grade-1 disease spectrum of acupuncture treatment, constipation can be treated with acupuncture and moxibustion alone to achieve the purpose of cure [12]. The latest acupoint catgut embedding therapy refers to the use of embedding needles to embed the polyglycolide lactide thread in the

selected acupuncture point for some time under strict disinfection conditions. Acupoint catgut embedding therapy stimulates the corresponding meridians and acupoints of the body for a more extended period, thereby curing the disease [12].

The 'brain-gut axis' is a bidirectional pathway connecting the enteric nervous system, neuroendocrine system, immune system and central nervous system, and regulates gastrointestinal motility. The brain-gut peptide in the brain-gut axis is a small-molecule polypeptide substance essential for the brain-gut axis. Under physiological conditions, the brain-gut peptide passes through the central nervous system and gastrointestinal smooth muscle cells and regulatory gastrointestinal motility is affected [13, 14]. The imbalance of brain-gut axis regulation will lead to pathogenesis of functional constipation, and the levels of brain-gut peptide-related indicators can reflect the state of the body's brain-gut axis. As a G protein-coupled receptor, 5-HT4R can promote the contraction of gastrointestinal smooth muscle and increase the secretion of digestive juice after activation, thereby improving stool properties and promoting excretion [15]. VIP and SS are inhibitory neurotransmitters. VIP can inhibit the contraction of smooth muscle in the digestive tract, reduce intestinal motility, reduce the secretion of gastrointestinal mucosal glands, and cause constipation. SS can reduce gastrointestinal blood flow, inhibit gastrointestinal motility, and reduce the secretion of various digestive juices and hormones [16, 17]. Our study shows that before treatment, the serum levels of 5-HT4R in patients with MHD complicated with functional constipation are lower, while the levels of VIP and SS are higher. VIP and SS decrease significantly and the changes in index levels are more evident in the combined treatment group. This shows that a combination therapy can effectively regulate the levels of related indicators of brain-gut peptide, balance the function of the brain-gut axis and promote the return of patients' defecation function to normal.

Insufficient dialysis is one of the causes of functional constipation in patients. Changes in one organ in the intestinal tract and kidneys will have adverse effects on the other organ and can cause and affect each other, causing and/or exacerbating each other. This effect is called the 'gut-kidney axis.' IS is a crucial uremic toxin, which is derived from tryptophan ingested in food, decomposed by intestinal bacteria into indole, transported to the liver through the portal vein, and then metabolised by cytochrome P4502E1 [18, 19]. When renal function is normal, IS is mainly secreted and excreted through renal tubules; when renal function is impaired, the serum concentration increases significantly [20]. Serum IS is a small molecular toxin with a binding rate of over 90% to plasma proteins, making it extremely difficult to remove by ordinary dialysis [21]. The removal of IS by hemodialysis is intermittent, while the removal by residual renal function is continuous. Therefore, residual renal function is vital in IS clearance; patients with end-stage renal disease with adequate dialysis have a lower serum IS concentration. In our study IS levels of the two groups of patients after treatment are significantly lower than those before treatment and the IS levels of the observation group are significantly lower than those of the control group. We infer that lactulose combined with acupoint catgut embedding therapy can help restore the intestinal function of the patient, further enhance the patient's renal function under the influence of the gut-kidney axis, promote the clearance of serum IS and reduce the level of IS.

CONCLUSIONS

Lactulose combined with acupoint catgut embedding can achieve a good curative effect in the treatment of functional constipation complicated by MHD by relieving constipation symptoms, increasing the frequency of SCBM, mediating the levels of serum brain-gut peptide-related indicators, promoting the recovery of intestinal-kidney function, reducing defecation troubles in

patients with blood MHD, thereby improving the quality of life of patients. However, the number of cases enrolled in this study is relatively small. Multi-centred, large-sample clinical studies are still needed in future work, as in the study on the impact of the treatment on patients.

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