The Efficacy and Mechanism of Xuefu Zhuyu Decoction Combined with Tenofovir Dipyrfurate Fumarate Tablets in The Treatment of Liver Depression and Blood Stasis Type Hepatitis B Cirrhosis

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Abstract Background: Cirrhosis is a chronic progressive liver disease. Hepatocyte injury leads to liver dysfunction. At present, antiviral drugs are mainly used to inhibit the replication of hepatitis virus to block liver fibrosis. Tenofovir disoproxil fumarate is a novel nucleotide reverse transcriptase inhibitor, which can eliminate hepatitis B virus and control the deterioration of chronic hepatitis B. Objective To investigate the efficacy and mechanism of Xuefu Zhuyu Decoction combined with tenofovir disoproxil fumarate tablets in the treatment of hepatitis B cirrhosis of liver depression and blood stasis. Methods A total of 150 patients with hepatitis B cirrhosis who were treated in our hospital from January 2019 to June 2021with the dialectical type of "liver stagnation and blood stasis" were selected and divided into groups according to their treatment plan. 75 cases in the control group were given Fu Tenofovir disoproxil marate tablets were treated, and 75 patients in the observation group were treated with Xuefu Zhuyu Decoction combined with tenofovir disoproxil fumarate tablets. Count the total effective rates and adverse reactions of the two groups, record the scores of TCM syndromes, liver hemodynamics, fibrosis, liver function, hepatitis B virus deoxyribonucleic acid (HBV-DNA), MMP1, TIMP1, TIMP1/MMP1 changes. Results The curative effect of the observation group was higher than that of the control group, which was statistically significant (P<0.05). Compared with before treatment, the portal vein flow rate (PVV) and intrahepatic circulation time (HV-HA) of the two groups increased (P<0.05), the portal vein congestion index (PV-CI) decreased (P<0.05), and the portal vein diameter (PVD) Compared with before treatment, the difference was not statistically significant (P>0.05). After treatment, PVV and HV-HA in the observation group were higher than those in the control group (P<0.05), and PV-CI was lower than that in the control group (P<0.05). Compared with the control group, the difference was not statistically significant (P>0.05). Compared with before treatment, the scores of the two groups of chest and hypothermia distended, abdominal distension, mental fatigue, depression, irritability, and amitrati decreased (P<0.05). The scores of TCM syndromes of the observation group were lower than those of the control group (P<0.05). P<0.05). Compared with before treatment, the two groups of matrix metalloproteinase 1 (MMP1) increased (P<0.05), laminin (LV), type IV collagen (IV-C), type III procollagen (PCⅢ), hyaluronic acid (P<0.05) HA), tissue inhibitor of matrix metalloproteinase 1 (TIMP1), TIMP1/MMP1, alanine aminotransferase (ALT), aspartate aminotransferase (AST), HBV-DNA decreased (P<0.05), observe After treatment, MMP1 in the group was higher than that in the control group (P<0.05), and fibrosis indexes, liver function indexes, TIMP1, TIMP1/MMP1, and HBV-DNA were lower than those in the control group (P<0.05). The adverse reactions between the two groups were not statistically significant (P>0.05). Conclusion Xuefu Zhuyu Decoction

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combined with tenofovir disoproxil fumarate tablets is effective in treating hepatitis B cirrhosis of liver depression and blood stasis, and its mechanism may be related to improving liver hemodynamics, regulating fibrosis, liver function and other indicators related.

Keywords: Xuefu Zhuyu Decoction; Tenofovir disoproxil fumarate tablets; Liver depression and blood stasis type; Hepatitis B cirrhosis; Liver hemodynamics
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Liver cirrhosis is a chronic progressive liver disease. A large number of liver cell damage and immune function changes can further lead to liver function decline. Early detection and early treatment can reverse the process of liver cirrhosis and liver fibrosis. Liver fibrosis is a necessary process for the development of chronic liver disease into cirrhosis. Inhibition of liver fibrosis is of positive significance for blocking the progress of patients with hepatitis B cirrhosis. Tenofovir disoproxil fumarate is a novel nucleotide reverse transcriptase inhibitor, which can eliminate hepatitis B virus and control the deterioration of chronic hepatitis B. Although drug resistance is low and there are no serious adverse reactions, liver cirrhosis cannot be cured because liver fibrosis may still exist. With the clinical application of syndrome differentiation and treatment of traditional Chinese medicine, the anti-fibrosis effect of traditional Chinese medicine has been fully exerted, which makes up for the deficiency of traditional Western medicine treatment. Traditional Chinese medicine believes that liver disease is related to blood stasis, and advocates the treatment of softening and dispersing blood stasis, promoting blood circulation and removing blood stasis. In order to explore the curative effect and mechanism of Xuefu Zhuyu decoction combined with tenofovir disoproxil fumarate tablets in the treatment of hepatitis B cirrhosis with liver depression and blood stasis type, this study selected patients with hepatitis B cirrhosis with liver depression and blood stasis type treated in our hospital.

DATA AND METHODS

General information

From January 2019 to June 2020, 150 patients with hepatitis B cirrhosis of liver stagnation and blood stasis type were selected and divided into two groups according to the treatment plan. 75 patients in the control group were treated with tenofovir disoproxil fumarate tablets, including 43 males and 32 females. The age was 18-74 years old, with an average of (53.26±11.95) years old.The course of hepatitis B was 3 to 28 years, with an average of (10.69± 2.74) years. The course of liver cirrhosis was 1 to 21 years, with an average of (7.44±2.12) years. 75 cases in the observation group were treated with Xuefu Zhuyu decoction combined with tenofovir disoproxil fumarate tablets, of which 39 cases were male and 36 cases were female. aged 19 – 74 years old, with an average of (52.78±12.85) years old. The course of hepatitis B was 3 to 28 years, with an average of (11.02±2.82) years. The course of liver cirrhosis ranged from 1 to 21 years with an average of (7.36±2.28) years. There was no significant difference in general data between the two groups (P > 0.05).

Inclusion of exclusion criteria

Inclusion criteria: (1) Hepatitis B cirrhosis in line with the 《Guidelines for prevention and treatment of chronic hepatitis B》 decompensated standard: 1 a clear history of chronic viral hepatitis. 2 Positive serum viral markers. 3 Both imaging diagnosis and transient elastography were diagnosed as cirrhosis. 4 has typical clinical manifestations of liver cirrhosis, such as fatigue, loss of appetite. (2) Age≥ 18 years, ≤75 years. (3) The dialectical classification of traditional Chinese medicine conforms to the standard of ' liver stagnation and blood stasis type ' in 《Guiding Principles of Clinical Research on New Drugs of Traditional Chinese Medicine》: ① Main syndromes: chest pain, abdominal distention, anorexia, fatigue. ② Secondary syndrome: emotional depression or irritability, irritability, pain in the ribs, and excessive interest. ③ Tongue veins: dark purple tongue or ecchymosis, fine

number of veins or smooth number of veins. (4) Liver reserve function according to Child-Pugh classification < 7 points (grade A). (5) Fibroscan diagnoses S ≥3/APRI=40U/L. (6) Complete clinical data.

Exclusion criteria: (1) Hepatitis caused by other hepatotropic viruses. (2) Pregnant women. (3) Sensitive constitution. (4) Severe brain, cardiovascular, kidney and other important organ diseases. (5) Mental abnormality. (6) With other system diseases, such as blood, urinary system, etc.

Method

Control group : oral tenofovir disoproxil fumarate tablets (manufacturer : Zhengdatianqing Pharmaceutical Group Co., Ltd., specification : 300 mg / tablet, production batch number 20181206), 300 mg / time, 1 time / d.Observation group : on the basis of the control group, combined with Xuefu Zhuyu decoction, Basic prescriptions: Rubra Radix Paeoniae 20 g, Radix Rehmanniae 20 g, Radix Angelicae Sinensis 20 g, Flos Carthami 20 g, Semen Persicae 20 g, Radix Bupleuri 20 g, Rhizoma Chuanxiong 15 g, Fructus Aurantii 15 g, Radix Glycyrrhizae 15 g. Dialectical addition and subtraction: abdominal distension plus wood 15 g, areca nut 20 g. Liver and spleen blood stasis joins Pangolin, Turtle shell, Pberetima each 20 g, Ezhu, Sanling each 15 g. Annoyed people with Danpi 25 g, Gardenia 20 g. Night sleep dreamers added fried jujube kernel 25 g, Caulis polygoni multiflori 25 g.Take juice 200 mL after decoction, 1 dose a day, 2 times a day, 1 month for a course of treatment. Both groups were treated for 4 consecutive weeks.

Test method

Two groups of portal vein index (PVV), portal venous flow velocity (PVV), intrahepatic circulation time (HV-HA), portal venous congestion index (PV-CI), portal venous diameter (PVD) using GE 730 color Doppler ultrasound. Before and after treatment, 4 mL of fasting venous blood was extracted in the next morning and liver function was tested using a Hitachi 7600 - 120 fully automated biochemical analyzer. The levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bin (TBIL), and albumin (ALB) were recorded.

The liver fibrosis indexes [laminin (LV), type IV collagen (IV-C), type III procollagen (PC III), hyaluronic acid (HA)], blood matrix metalloproteinase 1 (MMP1), tissue inhibitor of matrix metalloproteinase 1 (TIMP1) were detected by ELISA. The corresponding ELISA test kits were purchased from Shanghai Enzymatic Biotechnology Co., Ltd. Access 2 automatic immunoassay analyzer (Beckman Coulter, USA) and supporting reagents were used for determination by solid-phase chemiluminescence immunoassay. HBV-DNA determination using AG-9900 automatic fluorescence quantitative PCR detector, the reagent by Sun Yat-sen University Da ' a Gene Co., Ltd.The APRI index calculates = [(AST/ULN) / PLT (109 / L)] * 100 with ULN is the upper AST normal

Efficacy criteria and scoring criteria

Efficacy criteria: Refer to 《 Guidelines for Diagnosis and Treatment of Liver Fibrosis by Integrated Traditional Chinese and Western Medicine 》 evaluation, clinical symptoms disappeared, liver fibrosis serological markers returned to normal or decreased by more than 50 % for effective. Liver function close to normal or lower than before treatment > 25 %, liver fibrosis serological markers decreased more than or equal to 25 % is effective. No improvement or aggravation is invalid.

TCM syndrome score: referring to the evaluation of 《Guiding Principles of Clinical Research on New Drugs of Traditional Chinese Medicine》, including chest pain, abdominal distention, mental fatigue, emotional depression or irritability, and euphoria. The first three symptoms were scored 0, 2, 4, and 6 points according to the Likert 4 rating method, and the last two were scored 0, 1, 2, and 3 points according to the Likert 4 rating method.

Statistical Methods

The data were processed by SPSS19.0. The measurement indexes were described by ($\bar{\chi}\pm s$). The t test was used for comparison. The enumeration data were described by the number of cases (percentage). The χ^2 test was used for comparison. The test level was 0.05.

RESULTS

Comparison of the efficacy of the two groups

The observation group showed 31, 38, total efficiency of 92.00%, higher than the control group (22, 38, total 80.00%) and statistically significant (P< 0.05). See Table 1

Comparison of liver hemodynamic indicators in the two groups

Before treatment, differences were compared between liver hemodynamic indicators, statistically significant (P> 0.05), PVV、HV-HA (P< 0.05), PV-CI (P< 0.05), PVD (P> 0.05), and after treatment, PVV、HV-HA was higher than control (P< 0.05), PV-CI below control (P< 0.05), and PVD (P> 0.05). See Table 2

Comparison Chinese medicine syndrome scoresof the two groups

Before treatment, there was no significant difference in TCM syndrome scores between the two groups (P > 0.05). Compared with before treatment, the scores of chests hypochondriac pain, epigastric fullness, fatigue, emotional depression or irritability and joy in the two groups decreased (P < 0.05). After treatment, the scores of TCM syndrome in the observation group were lower than those in the control group (P < 0.05). See table 3

Comparison of two groups

Before treatment, the difference was statisinsignificant between fibrosis groups (P> 0.05), compared with LV、IV-C、PCIII、HA before treatment (PP> 0.05), and after treatment, the observed group was lower than the control group (PP> 0.05). See Table 4

Comparison of the liver function indexes of the two groups

Before treatment, the difference was statisinsignificant between the two groups (P> 0.05), ALT、AST (P< 0.05) and after treatment, the observed group was lower than the control group (P< 0.05). See Table 5

Comparison of Two Group MMP1、TIMP1 and TIMP1/MMP1

Before treatment, differences between MMP1、TIMP1 and TIMP1/MMP1 (P> 0.05), pre - treatment MMP1 increase (P< 0.05), TIMP1、TIMP1/MMP1 decrease (P< 0.05), and post - treatment comparison that observed MMP1 was higher than the control group (P< 0.05) and TIMP1、TIMP1/MMP1 below the control group (P< 0.05). See Table 6

Comparison of the two groups of HBV-DNA

Before treatment, differences were statistically significant (P> 0.05), lower before treatment (P< 0.05) and after treatment were lower than the control group (P< 0.05). See Table 7

Comparison of adverse reactions in the two groups

The incidence of adverse reactions (8.00%) was not compared with the control group (9.33%) (P> 0.05). See Table 8

DISCUSSION

At present, antiviral drugs are mainly used in the treatment of compensated hepatitis B cirrhosis, which can inhibit the development of cirrhosis and reverse liver fibrosis by inhibiting the replication of hepatitis B virus, and improve the survival rate and quality of life of patients. Tenofovir dipyrfurate fumarate is a new type of oral nucleoside (acid) analogue, which has strong anti-HBV effect and can be combined with other antiretroviral drugs to treat chronic hepatitis B.However, the single use of viral drugs cannot improve the compliance of patients, and the curative effect is poor. Chinese medicine can be combined for treatment. Xuefu Zhuyu Decoction in Qing Dynasty is a typical prescription for promoting blood circulation and removing blood stasis. Based on this prescription and according to the clinical manifestations of patients, this study dialectically modified Xuefu Zhuyu Decoction.In the prescription, safflower can promote blood circulation, remove blood stasis, and relieve tendon dredging. Safflower yellow and safflower quinone glycoside in safflower can enhance human fibrin dissolution, and effectively inhibit the massive aggregation of platelets in vivo. Peach kernels promote blood circulation, eliminate blood stasis, expelling wind pain, promote blood circulation. At the same time, Chuanxiong has a certain expansion effect on small arteries, which can

effectively inhibit the proliferation of fibroblasts. Rehmannia nourishing yin, nourishing body fluid, clearing heat and detoxification. Fructus Aurantii Immaturus and Radix Bupleuri can soothe liver and relieve depression, and Radix Achyranthis bidentata can promote blood circulation. The whole side can eliminate blood stasis, neglect the liver and relieve depression without consuming gas.At the same time, it can fight tumor and antioxidant, and inhibit inflammatory reactions, which can prevent the large release of inflammatory cytokines, regulate immune function, and effectively remove oxygen free radicals.

The results of this study showed that compared with those before treatment, the scores of chest pain, epigastric fullness, mental fatigue, emotional depression or irritability, and xitaixi in the two groups decreased ($P < 0.05$), and the efficacy in the observation group was significant ($P < 0.05$). This indicated that the combined treatment of Chinese and Western medicine could significantly improve the clinical manifestations of patients and improve the quality of life of patients, which was related to the enhanced synergistic effect of tenofovir dipyrfurate fumarate tablets and Xuefu Zhuyu decoction.Studies have shown that in addition to hepatic blood flow disorder and venous reflux obstruction, patients with chronic liver diseases are often accompanied by systemic microcirculation disorder, inducing hemodynamic changes. Compared with before treatment, PVV and HV-HA in the two groups increased ($P < 0.05$), and PV-CI decreased ($P < 0.05$). PVV and HV-HA in the observation group were significantly higher than those in the control group after treatment ($P < 0.05$), and PV-CI was significantly lower than that in the control group ($P < 0.05$). It is concluded that conventional chemotherapy combined with traditional Chinese medicine can effectively regulate the state of hepatic microcirculation, reduce portal vein pressure and portal vein diameter.

Hepatic fibrosis is a necessary stage of cirrhosis. Serum fibrosis markers can be used to evaluate the severity of hepatic fibrosis. Studies have shown that when patients with liver cirrhosis attack, the content of serum liver fibrosis index is abnormally increased, and the sensitivity is high. In this study, the fibrosis indexes LV, IV-C, PC III and HA of patients after treatment were significantly decreased ($P < 0.05$), and those of the observation group were significantly lower than those of the control group ($P < 0.05$). This may be related to the synergistic anti-fibrosis effect of Xuefu Zhuyu decoction and tenofovir disoproxil fumarate tablets. It is suggested that Xuefu Zhuyu Decoction in the treatment of hepatitis B cirrhosis can effectively reduce the body ' s inflammatory response and significantly improve liver fibrosis, which has certain guiding significance for clinical treatment.

MMP1 is an important indicator of collagen degradation, TIMP1 is an important indicator of inhibition of collagenase degradation activity. The two were in a balanced state. When cirrhosis occurred, the occurrence of fibrosis made TIMP1 / MMP1 unbalanced. The results of this study showed that MMP1 in both groups increased significantly after treatment ($P < 0.05$), TIMP1 and TIMP1 / MMP1 decreased ($P < 0.05$), and the above indexes in the observation group changed significantly ($P < 0.05$). The results showed that Xuefu Zhuyu Decoction and tenofovir dipyrfurate fumarate tablets could simultaneously improve the activity of collagenase and reduce the inhibitory effect on the activity of collagenase degradation, thereby improving liver cirrhosis and liver fibrosis. Observation group post-treatment HBV-DNA was significantly lower than in the control group ($P< 0.05$), and the group treated liver function index ALT、AST was significantly lower than in the control group ($P< 0.05$). The results showed that Xuefu Zhuyu Decoction and tenofovir dipyrfurate fumarate tablets could effectively improve the clinical efficacy, improve the viral response, promote the recovery of liver function indexes, and help to control the development of diseases. The combined effect of Chinese and Western medicine was more obvious, which might be related to the anti-hepatic fibrosis and improvement of liver microcirculation of Xuefu Zhuyu Decoction, which could help improve the blood supply of liver cells and promote the repair of damaged liver cells. There was no significant difference in the adverse reactions between the two groups ($P > 0.05$). This indicated

that Xuefu Zhuyu Decoction combined with tenofovir dipyrfurate fumarate tablets in the treatment of hepatitis B cirrhosis with liver depression and blood stasis did not increase the incidence of adverse reactions while improving the efficacy, and the safety was good. Considering that this may be related to fewer cases and shorter medication time, it is necessary to increase the number of cases, prolong medication time, and conduct detailed evaluation and genotyping before treatment in future studies.

In the treatment of chronic hepatitis B and hepatitis B cirrhosis, oral nucleoside analogues are the preferred treatment for hepatitis B and cirrhosis, and there are few studies on the treatment of integrated traditional Chinese and Western medicine. Most studies in China are limited to single Chinese patent medicine preparations, and do not carry out dialectical treatment according to the specificity of hepatitis B and cirrhosis.In this study, the subjects were selected as liver cirrhosis, and the curative effects of Xuefu Zhuyu Decoction combined with tenofovir fumarate tablets and oral tenofovir fumarate tablets were compared. The treatment ideas of hepatitis B and liver cirrhosis were broadened, and the best method of combining traditional Chinese and western medicine was sought. However, there are limitations such as small sample size and short follow-up time. In the next study, the number of samples and follow-up time need to be further verified.

To sum up, Xuefu Zhuyu combined with tenofovir disoproxil fumarate tablets in the treatment of liver stagnation and blood stasis type of hepatitis B cirrhosis has significant curative effect, and its mechanism may be related to improving liver hemodynamics, regulating fibrosis and liver function.

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TABLES

Table 1
Comparison of curative effect between the two groups

Group	Number of cases	Remarkable effect	Effective	Invalid	Total effective
Control group	75	22（29.33）	38（50.67）	15（20.00）	60（80.00）
Observation group	75	31（41.33）	38（50.67）	6（8.00）	69（92.00）
χ^2					4.485
P					0.034

Table 2
Comparison of liver hemodynamic indexes between the two groups（ $\bar{\chi}$±s）

Group	Number of cases	PVD（cm）		PVV（cm/s）		PV-CI（cm/s）		HV-HA（s）	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	75	1.42±0.26	1.37±0.21	16.56±3.02	17.85±2.59*	0.12±0.04	0.10±0.03*	7.32±1.85	7.88±1.56*
Observation group	75	1.40±0.31	1.35±0.18	16.47±3.18	19.96±2.84*	0.13±0.05	0.07±0.03*	7.28±1.93	8.39±1.47*
t		0.428	0.626	0.178	4.754	1.353	6.124	0.130	2.061
P		0.669	0.532	0.859	0.000	0.178	0.000	0.897	0.041

Note: Compared to this group before treatment, * P< 0.05.

Table 3
Comparison of TCM syndrome scores between the two groups（ $\bar{\chi}$±s，Minute）

Symptom	Time	Control group（n=75）	Observation group（n=75）	t	P
Chest and hypochondriac pain	Before treatment	4.63±1.02	4.57±1.10	0.346	0.730
	After treatment	2.36±0.64*	1.54±0.45*	9.077	0.000
Abdominal distension	Before treatment	4.57±1.09	4.48±1.14	0.494	0.622
	After treatment	2.13±0.48*	1.29±0.34*	12.367	0.000
Tired	Before treatment	4.41±0.96	4.46±1.04	0.306	0.760
	After treatment	2.35±0.81*	1.67±0.67*	5.602	0.000
Depression or irritability	Before treatment	2.31±0.56	2.41±0.51	1.143	0.255
	After treatment	1.62±0.42*	1.02±0.29*	10.181	0.000
Xi Taixi	Before treatment	2.56±0.32	2.49±0.28	1.426	0.156
	After treatment	1.14±0.38*	0.85±0.21*	5.785	0.000
Note: Compared to this group before treatment, * P< 0.05.					

Table 4
Comparison of fibrosis indexes between the two groups ($\bar{\chi}$±s，ng/mL)

Group	Number of cases	LV		IV-C		PCIII		HA	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	75	185.96±22.85	92.05±19.63*	148.63±25.15	79.56±15.02*	153.69±21.85	84.01±14.15*	185.63±25.26	109.65±24.12*
Observation group	75	191.02±29.73	74.02±12.05*	152.12±22.33	57.52±11.09*	147.52±17.38	63.52±18.14*	179.51±22.08	75.89±15.33*
t		1.169	6.779	0.899	10.223	1.914	7.713	1.580	10.230
P		0.244	0.000	0.370	0.000	0.058	0.000	0.116	0.000
Note: Compared to this group before treatment, * P< 0.05.									

Table 5
Comparison of liver function indexes between the two groups ($\bar{\chi}$±s，U/L)

Group	Number of cases	ALT		AST	
		Before treatment	After treatment	Before treatment	After treatment
Control group	75	412.36±61.85	115.86±24.56*	329.56±46.25	113.63±18.96*
Observation group	75	406.36±57.41	95.36±17.41*	335.12±41.08	82.54±10.14*
t		0.616	5.897	0.778	12.522
P		0.539	0.000	0.438	0.000
Note: Compared to this group before treatment, * P< 0.05.					

Table 6
Comparison of MMP1, TIMP1 and TIMP1 / MMP1 between the two groups ($\bar{\chi}$±s)

Group	Number of cases	MMP1（μg/L）		TIMP1（μg/L）		TIMP1/MMP1	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	75	9.25±1.96	11.14±2.14*	182.03±42.36	145.22±34.01*	19.12±5.88	13.52±2.84*
Observation group	75	9.31±2.05	12.96±2.27*	178.12±45.62	125.85±26.75*	19.04±4.97	10.12±2.05*
t		0.183	5.052	0.544	3.877	0.090	8.407
P		0.855	0.000	0.587	0.000	0.928	0.000
Note: Compared to this group before treatment, * P< 0.05.							

Table 7
Comparison of HBV-DNA between the two groups ($\bar{\chi}$±s)

Group	Number of cases	HBV-DNA，log[copies/mL]	
		Before treatment	After treatment
Control group	75	6.58±1.05	4.16±1.24*
Observation group	75	6.61±1.21	3.53±1.04*
t		0.162	3.371
P		0.871	0.001
Note: Compared to this group before treatment, * P< 0.05.			

Group	Number of cases	Indigestion	Abdominal pain	Rash	Headache	Total
Control group	75	3（4.00）	1（1.33）	1（1.33）	2（2.67）	7（9.33）
Observation group	75	2（2.67）	2（2.67）	1（1.33）	1（1.33）	6（8.00）
χ^2						0.084
P						0.772