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Effect of trimebutine in combined with alprazolam on the gastrointestinal hormones in patients with diarrhea−type IBS

Yong−Li Yang✉, Chun−Qiu Song, Hong−Xia Li, Xiao−Feng Huang, Hong−Mei Zhou

The Seventh People's Hospital, Baoding, Hebei, 073000

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ABSTRACT

Objective: To explore the effect of trimebutine in combined with alprazolam on the gastrointestinal hormones and living quality in patients with diarrhea-type IBS (IBS-D). **Methods:** A total of 117 patients with IBS-D who were admitted in our hospital were included in the study and randomized into the control group (n=58) and the treatment group (n=59). The patients in the control group were given trimebutine, while the patients in the treatment group were given trimebutine in combined with alprazolam. The patients in the two groups were continuously treated for 4 weeks. The levels of gastrointestinal hormones and brain-gut peptide before and after treatment in the two groups were detected and compared. SF-36 was used to analyze the living quality before and after treatment in the two groups. **Results:** MOT, GAS, SP, and 5-HT levels after treatment in the two groups were significantly reduced, while VIP, SS, CCK, and CGRP levels and SF-36 score in each dimension were significantly elevated, and the comparison between the two groups was statistically significant. **Conclusions:** Trimebutine in combined with alprazolam in the treatment of IBS-D can significantly improve the gastrointestinal hormones and brain-gut peptide, and enhance the living quality, with a significant efficacy.

1. Introduction

Irritable bowel syndrome (IBS) is a common disease in the clinic, with main clinical manifestations of repeatedly persistent abdominal pain, abdominal distension, and stool property abnormality. Diarrhea-type (IBS-D) is the overlap of functional dyspepsia (FD) and IBS. In recent years, with the increasement of life pressure, the morbidity of IBS-D is gradually elevated, which can severely affect the patients' living qualities[1−3]. Currently, trimebutine is mainly adopted in the treatment of IBS-D to regulate the gastrointestinal movement in the clinic, but its efficacy is poor. Some researches demonstrate that[4] trimebutine in combined with alprazolam which can regulate the central nerves in the treatment of IBS-D can play a positive role. The study is aimed to explore the effect of trimebutine in combined with alprazolam on the gastrointestinal hormones and living quality in patients with IBS-D.

2. Materials and methods

2.1. General materials

A total of 117 patients with IBS-D who were admitted in the internal medicine department or outpatient clinic from February, 2014 to January, 2016 were included in the study, aged from 18 to 60 years old. Inclusion criteria: (1) those who were in accordance with IBS related diagnostic criteria in Rome III standard[5]; (2) those who had chronic abdominal discomfort; (3) those who were confirmed by ESR, blood biochemistry, thyroid function, stool routine examination, abdominal B ultrasound, X-ray, or digestive endoscopy. Exclusion criteria: (1) those who had inflammatory

✉Corresponding author: Yong-Li Yang, The Seventh People's Hospital, Baoding, Hebei, 073000.
E-mail: senseliyangyong@126.com
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bowel disease, tumor, gastrointestinal tract organic disease, psychiatric history, and severe neurosis; (2) those who had taken mitigation, anti-anxiety, and anti-depression drugs recently.

2.2. Methods

The patients were randomized into the control group (n=58) and the treatment group (n=59). In the control group, 31 were male, and 27 were female; aged from 24 to 57 years old, with an average age of (43±5) years old, course from 1 to 4 years, with an average course of (3.27±1.13) years. In the treatment group, 30 were male, and 29 were female; aged from 25 to 55 years old, with an average age of (43±6) years old, course from 1 to 4 years, with an average course of (3.35±1.32) years. The comparison of gender, age, and course between the two groups was comparable (P>0.05). The patients in the control group were given trimebutine maleate tablets, 0.2 g/time, 3 times/d, while the patients in the treatment group were given trimebutine maleate (0.2 g/time, 3 times/d) in combined with alprazolam, 0.8 mg/time, 3 times/d. The patients in the two groups were continuously treated for 4 weeks. The patients in the two groups were continuously treated for 4 weeks.

2.3. Observation indicators

The morning fasting venous blood before and after treatment in the two groups was collected, centrifuged for the serum, and preserved at -80 ℃ for detection. ELISA was used to detect GAS, MOT, VIP, SP, SS, 6-HT, CCK, and CGRP levels. SF-36 was used to evaluate the living quality in the two groups.

2.4. Statistical analysis

SPSS 12.0 software was used for the statistical analysis. The measurement data were expressed as mean ± SD, and the independent t test and paired t test were used. P<0.05 was regarded as statistically significant.

3. Results

3.1. Comparison of the levels of gastrointestinal hormones before and after treatment between the two groups

The comparison of MOT and GAS levels before treatment between the two groups was not statistically significant (P>0.05). MOT and GAS levels after treatment were significantly reduced when compared with before treatment (P<0.05 or P<0.01). MOT and GAS levels after treatment in the treatment group were significantly lower than those in the control group (P<0.05) (Table 1).

Table 1.

Comparison of the levels of gastrointestinal hormones before and after treatment between the two groups (pg/mL).

Group	Control group (n=58)		Treatment group (n=59)	
	Before treatment	After treatment	Before treatment	After treatment
MOT	97.81±47.49	69.73±51.39**	97.76±49.68	50.82±49.24$^{**\#}$
GAS	74.35±5.31	72.06±6.06*	73.21±5.29	69.67±6.18$^{**\#}$

$^{\#}P$<0.05, when compared with the control group; $^{*}P$<0.05, $^{**}P$<0.01, when compared with before treatment.

3.2. Comparison of various indicators of brain-gut peptide before and after treatment between the two groups

The comparison of various indicators of brain-gut peptide before treatment between the two groups was not statistically significant (P>0.05). SP and 5-HT levels after treatment were significantly reduced when compared with before treatment (P<0.05 or P<0.01), while VIP, SS, CCK, and CGRP levels were significantly elevated (P<0.05 or P<0.01). The improvement of above indicators after treatment in the treatment group was significantly superior to that in the control group (P<0.05 or P<0.01) (Table 2).

3.3. Comparison of the living quality evaluation before and after treatment

The comparison of SF-36 scores before treatment between the two groups was not statistically significant (P>0.05). SF-36 scores after treatment were significantly elevated when compared with before

Table 2.

Comparison of various indicators of brain-gut peptide before and after treatment between the two groups.

Indicators	Control group (n=58)		Treatment group (n=59)	
	Before treatment	After treatment	Before treatment	After treatment
SP (pg/mL)	106.74±19.63	93.73±16.49**	106.81±20.01	67.86±11.19$^{**\#\#}$
VIP (pg/mL)	0.33±0.09	0.36±0.06*	0.32±0.08	0.39±0.07$^{**\#}$
5-HT (pg/mL)	382.69±46.88	365.75±21.09*	382.76±44.84	357.86±20.91$^{*\#}$
SS (μg/L)	6.16±1.37	7.22±1.06**	6.21±1.24	8.34±1.02$^{**\#\#}$
CCK (ng/L)	46.49±6.75	49.02±4.83*	45.92±6.71	50.89±4.92$^{**\#}$
CGRP (pg/mL)	62.79±9.41	67.47±10.62*	62.83±9.32	72.18±10.75$^{**\#}$

$^{\#}P$<0.05, $^{\#\#}P$<0.01, when compared with the control group; $^{*}P$<0.05, $^{**}P$<0.01, when compared with before treatment.

Table 3.

Comparison f SF-36 scores before and after treatment.

Dimensions	Control group (n=58)		Treatment group (n=59)	
	Before treatment	After treatment	Before treatment	After treatment
PF	73.02±14.51	82.93±12.96**	72.96±16.02	91.11±13.03$^{**\#\#}$
RP	47.53±13.62	57.69±12.39**	48.08±19.34	79.31±15.91$^{**\#\#}$
BP	65.03±15.22	77.22±11.72**	64.98±14.45	88.98±19.37$^{**\#\#}$
GH	43.34±16.21	57.12±15.58**	42.35±18.33	71.41±20.24$^{**\#\#}$
VT	56.87±15.45	67.14±14.25**	57.42±13.28	77.45±15.38$^{**\#\#}$
SF	63.03±15.28	74.37±19.51*	62.95±17.37	88.43±18.54$^{**\#\#}$
RE	59.31±16.81	71.56±17.58*	58.97±20.01	80.18±22.42$^{**\#\#}$
MH	56.95±14.22	67.59±15.04**	57.32±14.17	78.33±20.26$^{**\#\#}$

$^{**}P$<0.01，$^{*}P$<0.05, when compared with before treatment; $^{\#\#}P$<0.01, when compared with the control group.

treatment (P<0.01 or P<0.05). The various scores after treatment in the treatment group were significantly higher than those in the control group (P<0.01) (Table 3).

4. Discussion

The pathogenesis of IBS-D is not yet completely clarified, with delayed and refractory condition, which can severely affect the patients' living qualities. Some researches demonstrate that[6-8] the pathogenesis of IBS-D is probably associated with the gastrointestinal dysfunction, immunological dysfunction, and visceral hypersensitivity. Trimebutine which can regulate the gastrointestinal movement is usually adopted by the modern western medicine in the treatment of IBS-D, but single medication often fail to achieve the expected therapeutic effect. Alprazolam is a kind of benzodiazepines central nervous suppressant which can alleviate the anxiety, and keep calm. Some scholars argue that[9] the combination of trimebutine and aprazolam can significantly improve the mental state and gastrointestinal function in patients with IBS-D, and enhance the living quality. The results in the study showed that SF-36 scores in each dimension in the treatment group were significantly higher than those in the control group, indicating that the combination of trimebutine and aprazolam can inhibit the anxiety and depression, protect the gastric mucosa from damage, and alleviate the clinical symptoms, which is similar to the results reported by Wang et al[10].

MOT can accelerate the strong gastric contraction, and promote the small intestine segmentation and colon movement through motivating the myoelectricity activity during the digestion period III phase. This kind of physiological effect can not only regulate the esophagus, gastrointestine, colon, and gall bladder movement, but also maintain and balance the gastrointestinal water-electrolyte content. When MOT level is abnormally elevated, the gastrointestinal peristalsis function is strengthened, which can significantly shorten the passing time of food, and water-electrolyte from the gastrointestinal tract, resulting in diarrhea and abdominal pain. GAS can promote the large secretion of gastric acid and pepsinogen, stimulate the growth of gastrointestinal mucosa membrane, shrink the gastrointestinal smooth muscle, and loose the pyloric sphincter[11]. The results in the study showed that MOT and GAS levels after treatment in the two groups were significantly reduced, and those in the treatment group were significantly lower than those in the control group, indicating that trimebutine and aprazolam play a vital role in regulating the gastrointestinal movement. It can be expected that trimebutine has a double efficacy in stimulating and inhibiting the gastrointestinal motor function, and maintain the gastrointestinal smooth muscle contraction and relaxation balance through acting on the calcium and potassium channel of gastrointestinal smooth muscle cell membrane. Meanwhile, timebutine can act on the adrenergic nerve L_2 receptor or cholinergic nerve J receptor to promote the body to selectively release the neurotransmitter. Meanwhile, aprazolam can act on the benzodiazepine receptor of central nervous system to promote the opening of chlorine channel, reduce the excitability of neurons, and regulate the spirit and emotion to recover the gastrointestinal function[12-15].

The brain-gut peptides obtained from the secretion of gastrointestinal endocrine cells, can effectively regulate the gastrointestinal physiological function, and plays a vital role in the visceral sensation, whose abnormal change of various indicators will cause the gastrointestinal dysfunction[16], among which 5-HT is a brain-gut medium involved in the gastrointestinal function, can combine with the different intestinal receptors, stimulate the gastrointestinal peristalsis, and is closely associated with the visceral hypersensitivity; CCK can promote the pancreatic acini to secrete different kinds of digestive enzymes, whose elevation can inhibit the gastrointestinal motility, and slow down the gastric emptying; SP is a kind of tachykinin which can increase the gastrointestinal peristalsis, aggravate the strong contraction of gastrointestinal smooth muscle, and expand the gastrointestinal vessels; VIP can inhibit the gastrointestinal motility, promote the relaxation of intestinal smooth muscle, reduce the visceral resistance, and maintain the water-electrolyte balance; CGRP belongs to the pro-inflammatory sensory neuropeptide, promote the rapid relaxation of colic artery, and

accelerate the gastrointestinal peristalsis, resulting in diarrhea[17-20]. The results in the study showed that SP and 5-HT levels after treatment in the two groups were significantly reduced, while VIP, SS, CCK, and CGRP levels were significantly elevated, indicating that the combination of trimebutine and aprazolam can inhbit the gastrointestinal peristalsis, relax the intestinal smooth muscle, reduce the visceral sensitivity, and alleviate the condition.

In conclusion, trimebutine in combined with alprazolam in the treatment of IBS-D can significantly improve the gastrointestinal hormones and brain-gut peptide, and enhance the living quality, with a significant efficacy; therefore, it deserves to be widely recommended in the clinic.

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