CLINICAL EFFICACY AND SAFETY OF DIET CONTROL THERAPY COMBINED WITH DIGESTIVE ENZYME PREPARATION IN TREATING FUNCTIONAL GASTROINTESTINAL DISORDERS

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ABSTRACT

Objective: *To explore the clinical efficacy and safety of diet control therapy combined with digestive enzyme preparation in treating functional gastrointestinal disorders (FGIDs).*

Methods: *The clinical data of 90 FGIDs patients treated in our hospital (01, 2019 to 01, 2020) were selected for the retrospective analysis, and the patients were divided into the experimental group (EG, n=45) and control group (CG, n=45) according to the admission order. Patients in CG received routine treatment and those in EG accepted diet control therapy combined with digestive enzyme preparation, and various clinical indicators were compared between the two groups.*

Results: *Compared with CG after treatment, EG obtained obviously lower clinical symptom score, PHQ-9 score, GAD-7 score and total incidence rate of adverse reactions ($p<0.05$), and significantly higher serum biochemical indexes ($p<0.001$).*

Conclusion: *Combining diet control therapy with digestive enzyme preparation has exact efficacy and higher safety, which is a reliable scheme to improve the clinical symptoms in FGIDs patients. This strategy greatly improves patients' quality of life. Further research will be conducive to providing a better solution for such patients.*

Keywords: *Diet control therapy, digestive enzyme preparation, functional gastrointestinal disorders (FGIDs), clinical efficacy, safety.*

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Introduction

FGIDs is short for functional gastrointestinal disorders, which refers to long-standing recurrent gastrointestinal symptoms that are difficult to be explained by the observed physiological abnormalities and anatomy[1 - 2]. The pathogenesis and etiology of FGIDs are still unclear, and most scholars believe that social factors and psychological factors are the main inducing factors[3]. Relevant literature pointed out that FGIDs are relatively common in digestive diseases and account for 45 % of patients visiting the specialist clinic of the digestive department[4 - 5]. Meanwhile, an analysis of global surveys conducted by the Rome Foundation reported that FGIDs have a global prevalence of over 40 % and are more prevalent in women than in men, and a pathological summary revealed that FGIDs are mainly found among five common diseases, i.e., functional dyspepsia, irritable bowel syndrome, functional abdominal distension, functional diarrhea, and functional constipation[6 - 7]. In addition, large variations in prevalence are found among different regions/countries, and relevant data show that the prevalence of functional dyspepsia is 0.7 % in India, 2.2% in Japan, 12.3% in Egypt, and 18% - 45% in China[8]. In addition, clinical findings indicate that FGIDs have a long disease course and

complex condition and are easy to recurrent, which are characterized clinically by nausea, early satiety, palpitation and anorexia, etc., and the presence of overlapped symptoms in some patients will severely affect the quality of life (QOL). Therefore, it is clear that FGIDs have gradually become one of the serious public health problems at present[9].

Traditional drug therapies for FGIDs aim to alleviate patients' visceral pain and improve their bowel habits, whereas in the emerging field of therapeutics, attempts are being made to modify patients' gastrointestinal microbes and improve the clinical symptoms. Routine treatment, although it has certain clinical efficacy, is difficult to meet clinical needs because of its weakness in regulating central and enteric nerves[10]. With the improvement of people's health and care awareness, dietary therapy has become a new idea for treatment. However, few studies have reported the efficacy of dietary therapy combined with digestive enzyme preparations in the treatment of FGIDs so far. Tan Niandi[11] reported that the prevalence of FGIDs was associated with dietary habits, psychological and genetic factors.

There is a lot of evidence proving that the type of food is closely related to digestive system symptoms, for example, milk and banana can trigger flatulence, and fried food can trigger satiety. Related reports have indicated that the affected group of FGIDs mostly had complicated psychosocial disorders, among which depression and anxiety were more common, which could easily trigger poor appetite and then reduce the therapeutic effect of dietary therapy[12]. It is found clinically that the cellulose contained in digestive enzyme preparation can promote digestion and absorption, and alleviate the clinical symptoms of patients, thus effectively improving the negative emotions and benefiting prognosis. Therefore, this article will explore the therapeutic efficacy of diet control therapy combined with digestive enzyme preparation for the treatment of FGIDs, so as to confirm the clinical utility of this therapeutic model.

Materials and methods

General data

The clinical data of 90 FGIDs patients treated in our hospital (01, 2019 - 01, 2020) were selected for the retrospective analysis, and the patients were divided into the experimental group (EG, n=45) and control group (CG, n=45) according to the admission order.

Enrollment of study objects

Inclusion criteria were as follows:

• The patients met the Rome IV new classification and diagnosis criteria, and were diagnosed with FGIDs after analyzing the medical history and imaging examinations;

• The patients were 18-60 years old; their Insight and Treatment Attitudes Questionnaire (ITAQ)[13] score was ≥10 points;

• The patients did not have heart, liver, kidney dysfunction;

• The patients did not have organic lesion in the digestive system;

• The study met the World Medical Association Declaration of Helsinki[14].

Exclusion criteria for the patients:

• Pregnant or lactating women;

• Allergy to the drugs involved in the trial;

• Chronic enteric diseases, such as Crohn disease, ulcerative colitis;

• Systemic tumors, or history of hereditary insanity;

• Severe systemic disease and epilepsy.

Methods

Routine treatment

Routine treatment was performed to patients in CG. Patients orally took 1 domperidone tablet (manufactured: Shanghai Sine Tianping Pharmaceutical Co., Ltd.; NMPA approval no. H20031280; specification: 10 mg) 15 min - 30 min before meal.

Diet control therapy combined with digestive enzyme preparation

Diet control therapy

• Clinicians performed health education to patients, explained the significance and precautions of controlling dietary habits in detail, and made reasonable diet plans for patients;

• Total daily intake was reasonably distributed according to patients' body mass, height, age and physical activities, the calorie proportion of three meals was 1:2:2, and the nutrient proportion was 55 % of carbohydrate, 15 % of protein, and 30 % of fat;

• Patients with severe condition could have many timed meals but little food at each, the frequency of having meals should be 5 times a day, the optional food included protein food, vegetables, fatty food, carbohydrate, and vitamins, stimulating food such as

onion and garlic was prohibited, and the intake of high fibre foodstuffs was limited;

• The intake of protein should be mainly aquatic products, dairy foods, and poultry and eggs, vegetables should be mainly stem and leafy plants less than 300 g/d, the salt intake was 5 g/d, smoking and drinking were prohibited, and regular diet and scientific, reasonable, and balanced meals were ensured;

• Reasonable diet system was established, the patients were advised repeatedly to chew carefully and swallow slowly, talk less, keep a relaxed mind and good mood, and not to read books or watch TV;

• The patients took a walk to promote food absorption and digestion 15 min after meal, drank 1 cup of aloe juice every morning and before going to sleep at night, and in daily time, drank hot ginger tea instead of plain boiled water.

Digestive enzyme preparation

Patients were treated with digestive enzyme preparation. The drug used was DAGES capsule (manufactured: Hanlim Pharmaceutical Co., Ltd.; registration no. H20181242; specification: 20 capsules), and patients took 1-2 capsules each time and 3 times a day after meal.

Patients in the two groups were treated for 2 months.

Observation indicators

Patients' recovery of clinical symptoms after treatment was compared between the two groups by the 4-grade scoring method, and the total score was 21 points, with 0 points indicating no obvious symptoms, 1 point indicating that patients complained of mild malaise, 2 points indicating that patients complained of serious but tolerable symptoms, and 3 points indicating that patients complained of obvious symptoms that greatly affected their daily life and work, and such symptoms included poor appetite, vomiting, belch, nausea and epigastric pain.

After treatment, 3 mL of fasting venous blood was drawn from patients in the two groups, and the serum was centrifuged and placed under -20°C for standby application.

The changes in patients' calcitonin generelated peptide (CGRP), neuropeptide S receptor-1 (NPSR-1) and motilin (MTL) indicators were measured by ELISA in strict accordance with the instructions and operational process in the kits that were purchased from Immuno-biological Laboratories Co., Ltd. After treatment, patients' degree of depression was evaluated by PHQ-9 for depression[15], which was a self-rating instrument for depression based on Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).

The scale was consisted of 9 items, and the answers for each item included not at all, several days, over 1 week and almost everyday, which were corresponding to 0 point, 1 point, 2 points and 3 points. The total score was 27 points, with higher scores indicating more serious depression.

After treatment, patients' degree of anxiety was evaluated by Generalized Anxiety Disorder 7 (GAD-7)[16], which was consisted of 7 items, and the answers for each item included not at all, several days, over 1 week and almost everyday, which were corresponding to 0 point, 1 point, 2 points and 3 points. The total score was 21 points, with higher scores indicating more serious anxiety.

The safety of the two treatment modalities was compared by observing the adverse reactions (lethargy, diarrhea, dizziness and vomiting) after treatment of patients in the two groups.

Statistical analysis

The experimental data were statistically analyzed by SPSS21.0, the picture drawing software was GraphPad Prism 7 (GraphPad Software, San Diego, USA), the enumeration data were examined by X^2 test and expressed by [n (%)], the measurement data were examined by t-test and expressed by ($\bar{x}\pm s$), and differences were considered statistically significant at $p<0.05$.

Results

Baseline data

No significant between-group differences were presented in gender, mean age, BMI value, mean course of disease, educational degree, occupation, family economic status, and place of residence ($p>0.05$). See Table 1.

Clinical symptom scores after treatment

The clinical symptom score after treatment was obviously lower in EG than in CG ($p<0.001$). See Figure 1.

Serum biochemical indexes after treatment

Various serum biochemical indexes after treatment were obviously higher in EG than in CG ($p<0.001$). See Table 2.

Item	EG (n=45)	CG (45)	x^2/t	p
Gender			0.047	0.829
Male	17 (37.78%)	18 (40.00%)		
Female	28 (62.22%)	27 (60.00%)		
Mean age (± s, years)	41.16±11.59	40.38±13.04	0.299	0.765
BMI (kg / m^2)	21.10±0.60	21.00±0.57	0.811	0.419
Mean course of disease (years)	4.13±1.98	4.27±2.24	0.314	0.754
Educational degree				
Primary school and junior high school	7 (15.56%)	8 (17.78%)	0.080	0.777
Senior high school and junior college	20 (44.44%)	19 (42.22%)	0.045	0.832
Junior college and above	18 (40.00%)	18 (40.00%)	0.000	1.000
Occupation				
Jobless	5 (1.11%)	6 (13.33%)	0.104	0.748
Worker	6 (13.33%)	7 (15.56%)	0.089	0.764
Farmer	5 (11.11%)	4 (8.89%)	0.123	0.725
Teacher and civil servant	25 (55.56%)	22 (48.89%)	0.401	0.527
Others	4 (8.89%)	6 (13.33%)	0.450	0.502
Family economic status			0.049	0.824
≥ 3000 yuan / (month·person)	30 (66.67%)	29 (64.44%)		
< 3000 yuan / (month·person)	15 (33.33%)	16 (35.56%)		
Place of residence			0.182	0.670
Urban area	25 (55.56%)	27 (60.00%)		
Rural area	20 (44.44%)	18 (40.00%)		

Table 1: Baseline data.

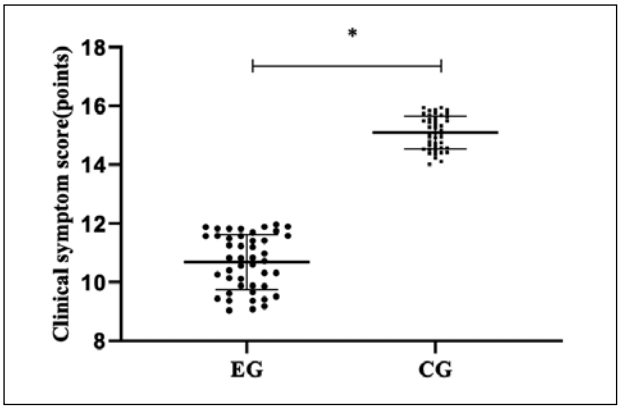

Figure 1: Clinical symptom scores after treatment ($\bar{x}$±s).
*Note: The horizontal axis indicated EG and CG, and the vertical axis indicated the clinical symptom score (points); After treatment, the mean clinical symptom score of EG and CG was respectively (10.69±0.94) and (15.09±0.56); and *indicated significant between-group difference in mean clinical symptom score after treatment (t=26.976, p<0.001).*

Group	n	CGRP (pg/mL)	NPSR-1 (pg/mL)	MTL (pg/mL)
EG	45	126.65±5.83	219.36±9.04	478.10±11.08
CG	45	108.91±5.26	197.26±7.20	443.38±11.14
t		15.156	12.828	14.824
P		<0.001	<0.001	<0.001

Table 2: Serum biochemical indexes after treatment ($\bar{x}$±s).

PHQ-9 scores after treatment

The PHQ-9 score after treatment was obviously lower in EG than in CG (p<0.001). See Figure 2.

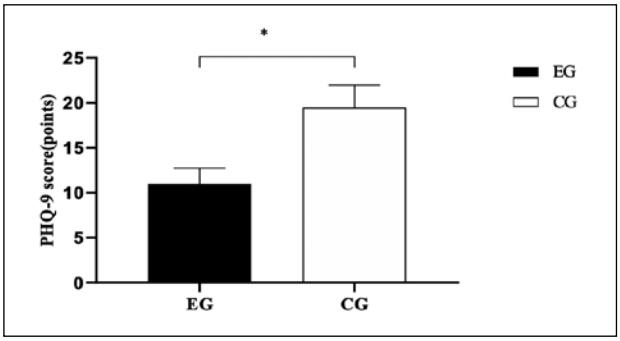

Figure 2: PHQ-9 scores after treatment ($\bar{x}$±s).
*Note: The horizontal axis indicated EG and CG, and the vertical axis indicated the PHQ-9 score (points); The PHQ-9 score after treatment of EG and CG was respectively (10.96±1.76) and (19.47±2.50); and *indicated significant between-group difference in PHQ-9 score after treatment (t=18.672, p<0.001).*

GAD-7 score after treatment

The GAD-7 score after treatment was obviously lower in EG than in CG (p<0.001). See Figure 3.

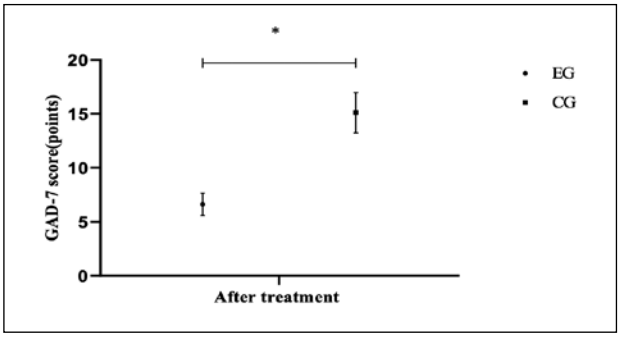

Figure 3: GAD-7 score after treatment ($\bar{x}$±s).
*Note: The horizontal axis indicated after treatment, and the vertical axis indicated the GAD-7 score (point); The GAD-7 score after treatment of EG and CG was respectively (6.62±1.03) and (15.11 ± 1.87); and *indicated significant between-group comparison of GAD-7 score after treatment (t=26.677, p<0.001).*

Adverse reaction rate

The total incidence rate of adverse reactions was obviously lower in EG than in CG (p<0.05). See Table 3.

Group	n	Lethargy	Diarrhea	Dizziness	Vomiting	Total incidence rate
EG	45	1 (2.22%)	0 (0.00%)	1 (2.22%)	1 (2.22%)	3 (6.67%)
CG	45	2 (4.44%)	3 (6.67%)	3 (6.67%)	3 (6.67%)	11 (24.44%)
x^2						5.414
P						<0.05

Table 3: Adverse reaction rate [n (%)].

Discussion

FGIDs are a group of gastrointestinal syndromes with recurrent or chronic manifestations, with organic changes that cannot be detected by various current testing modalities. It has been reported in relevant literature that the increasing prevalence of FGIDs with the changing of modern lifestyles and faster pace of life will not affect the life expectancy of patients or increase the risk of organic diseases, but the symptoms are persistent and recurrent, which not only reduce the quality of life of FGIDs patients but also increase the socioeconomic burden accordingly. Therefore, how to treat FGIDs diseases has become one of the most active fields of research at home and abroad in recent years[17].

Vasant Dipesh H[18] pointed out that the pathogenesis of FGIDs is complex, and it is mostly related to pathological and physiological changes in patients, for example, FGIDs can be triggered by gastrointestinal dysfunction and abnormal gastrointestinal motility. Domperidone tablets can directly act on the gastrointestinal wall, improve the lower esophageal sphincter tone, enhance gastric motility, and effectively prevent bile reflux. However, it has been found clinically that long-term administration of this drug leads to an increase in prolactin levels, causing amenorrhea, gynecomastia and other phenomenon in patients, and drug toxicities such as burnout, headache and nervosity in some cases, which, combined with the undesirable treatment effect, makes the drug difficult to achieve the clinical needs. The related literature pointed out that FGIDs are mostly inherited gastrointestinal dysmotility disorders, which are sensitive to changes in the outside world and more susceptible in sentimental people. Doctors suggest applying diet control combined with drugs to help such patients and break this vicious circle.

At present, studies have confirmed that eating more fiber rich food can effectively improve the discomfort symptoms of patients after eating, which is of positive significance to improve their clinical symptoms[19]. On this basis, the introduction of digestive enzyme preparation (DAGES capsule) can effectively improve the digestion speed of gastrointestinal cavity, reduce the content of undigested food and alleviate the symptoms such as abdominal flatulence. In this study, the clinical symptom score after treatment was significantly lower in EG than in CG ($p<0.05$), indicating that combining diet control therapy with digestive enzyme preparation had a significant effect on improving patients' clinical symptoms. CGRP, NPSR-1 and MTL are common indicators of gastrointestinal hormones, which can regulate the movement, absorption, and secretion of the digestive system through endocrine and other ways. Therefore, monitoring the level changes of the above indicators is conducive to evaluating the condition of FGIDs. Among them, CGRP can promote blood reflux, regulate visceral sensation and enhance gastrointestinal activity; NPSR-1 is involved in regulating gastrointestinal motility, and its low level will cause symptoms such as postprandial fullness[20-21]; and MTL can stimulate the electrical activity of upper gastrointestinal tract, so as to improve the excitability of gastrointestinal propulsion function. The study results showed that various serum biochemical indexes were obviously higher in EG than in CG ($p<0.05$), demonstrating that combining diet control therapy with digestive enzyme preparation could regulate the indicators of gastrointestinal hormones in FGIDs patients, effectively improve the rate of gastrointestinal emptying, and promote the elimination of clinical symptoms, which was consistent with the findings of Szymaszkiewicz Agata[22] et al.

Chouliaras Giorgos[23] pointed out that the development of FGIDs patients' condition is greatly related to their psychological factors, and failure to improve their mood timely will lead to repeated attacks, making it difficult to achieve the ideal treatment effect. DAGES capsules contain a variety of digestive enzymes, which can be decomposed in human gastric antrum and duodenum, and can promote digestive enzymes to play their role in a variety of environments[24].

Among them, amylase can rapidly decompose maltose; pepsin can accelerate the decomposition of protein; papain can improve the utilization rate of protein; and cellulase can improve the degeneration speed of plant cell wall. A variety of enzymes can enhance the digestion and absorption capacity of the gastrointestinal tract, and dietary therapy can strictly control the number of meals and energy intake, which not only avoids the burden of gastrointestinal tract, but also further corrects gastrointestinal disorders, promoting rapid recovery. Choi Jae Ho[25] stated that when patients' condition is improved or relieved, their psychological stress will also be gradually reduced, and their anxiety and depression are obviously controlled, significantly improving the treatment effect at the same time. The study results presented that the PHQ-9 and GAD-7

scores after treatment were obviously lower in EG than in CG ($p<0.001$), proving that combining diet control therapy with digestive enzyme preparation could greatly improve patients' negative emotions. Moreover, the results showed that the total incidence rate of adverse reactions was obviously lower in EG than in CG ($p<0.05$), demonstrating that compared with the routine treatment, the combination of the two was safer.

Limitation of the study

There are certain limitations in this study. First, the included sample size was small due to relevant conditions, and the sample source was rather limited and lacked representativeness; second, long-term follow-up observation of the intervention effect of patients was lacked, so the study design should be improved in the future and the follow-up time should be extended; finally, the treatment effect was judged by the subjective feelings of most patients, with greater subjectivity.

Conclusion

In conclusion, in the future study, the sample size should be further expanded, the investigation period should be extended, more comprehensive quantification criteria and observation indexes should be selected, and the mechanism of drug action should be studied more deeply, so as to make a more accurate rating for the clinical efficacy of combining diet control therapy with digestive enzyme preparation.

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