Efficacy of St. John's wort compound preparation (Shugan Jieyu capsule) combined with mosapride for the treatment of functional dyspepsia: a multicenter real-world clinical study

The clinical research collaboration group of Chinese Digestive Psychosomatic Union

Abstract:

Objective: To observe the clinical efficacy of concomitant use of Shugan Jieyu capsule (a St. John's wort compound preparation) and mosapride citrate dispersible tablets in the treatment of functional dyspepsia (FD).

Methods: 3240 FD patients were recruited from 89 hospitals in China between June 2018 and March 2019. According to the chief complaints, the patients were divided into postprandial distress syndrome (PDS) group and epigastric pain syndrome (EPS) group. Patients in these two groups were given the concomitant treatment with a proton pump inhibitor (PPI; served as a basic treatment regimen), Shugan Jieyu capsules, and mosapride citrate dispersible tablets. Both groups received the combination therapy for 6 weeks. Gastrointestinal (GI) symptom scores and the scores of depression and anxiety were evaluated before treatment and at the end of the 2nd and 6th weeks of treatment.

Results: GI symptom scores and the scores of depression and anxiety of the patients in both groups significantly decreased after 2 or 6-week treatment ($P < 0.0001$ compared to baseline). Moreover, the symptom improvement and the proportion of patients displaying excellent or effective response after treatment in patients with PDS showed no significant difference from those of patients with EPS ($P > 0.05$).

Conclusions: The concomitant use of PPI, Shugan Jieyu capsule, and mosapride can significantly improve the GI and psychological symptoms in FD patients. The treatment regimen was equally effective in patients with EPS and in patients with PDS.

Key words: Functional dyspepsia; Shugan Jieyu; mosapride.

Introduction

Functional dyspepsia (FD) is a gastrointestinal (GI) disorder commonly diagnosed in the outpatient of Gastroenterology with an incidence of 11.0%-29.2%. The GI symptoms include postprandial bloating,[1,2] early satiety, and upper abdominal pain and burning sensation.[3-6]However, no organic, systemic, or metabolic diseases that are likely to explain the symptoms can be found. FD is divided into two subtypes based on the predominant symptoms, i.e. epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS). [7]In the diagnosis and treatment of FD, we often pay attention to physiological factors such as GI motility, flora and inflammation. In fact, genetic factors, environmental factors, and especially psychological and emotional factors may also play important roles in the pathogenesis of functional gastrointestinal diseases (FGIDs).[8,9]The complex etiology of FGIDs

leads to chronic and recurrent symptoms, which could greatly affect life quality of patients. Long-term sustained psychological stress (adverse emotions such asdepression and anxiety) could lead to dysregulation of the neuroendocrine system, which may deteriorate the GI symptoms. On the other hand, chronic and recurrent GI symptoms may exert an adverse effect on the physiological and mental health of patients, leaving the patients in a state of anxiety or depression and thus forming a vicious circle.[10]Therefore, according to Rome IV, the abnormal brain-gut interactions may play a critical role in the pathogenesis of FD and alleviating the psychological symptoms may benefit the treatment of FD patients.

Mosapride citrate dispersible tablet (mosapride) is a commonly used drug to promote GI motility and treat FD.[11]It is a first-line drug recommended for the treatment of both EPS and PDS. Shugan Jieyu capsule (a St. John's wort compound preparation) is suitable for patients with mild to moderate unipolar depression who are suffering from liver stagnation and spleen deficiency.[12]Clinical data shows that combination treatment with gastroprokinetic agents and psychiatric drugs can improve the therapeutic efficacy with a low rate of recurrence.[8]The aim of the present study was to describe the real-world efficacy of a treatment regimen based on the concomitant use of a proton pump inhibitor (PPI), Shugan Jieyu capsule and mosapride citrate dispersible tablets in patients with FD. The clinical efficacy after 6 weeks was evaluated in EPS and PDS subgroups.

Materials and methods

General information

Consecutive 3240 patients (aged 18–70 years old and with a disease history of 9 months to 8 years) with FD diagnosed according to the Rome IV criteria were recruited from 89 hospitals nationwide between June 2018 and March 2019. Patients with abdominal distension, abdominal pain, nausea and other symptoms caused by organic diseases were excluded. All patients were asked to complete the GI Symptom Evaluation Scale and the Mental & Psychological Screening Scale during the first visit. Only those patients with a score of > 6 were enrolled in this study.

Methods 1084 patients were allocated into the EPS group and 2156 patients into the PDS group. All patients weregiven dietary guidance and psychological counseling. Then they received a basic treatment of a PPI, i.e. omeprazole (AstraZeneca Pharmaceutical), in combination with mosapride citrate dispersible tablets (mosapride, 5mg, tid; Kanghong Pharmaceutical, China) and Shugan Jieyu capsule (3 capsules, tid; Kanghong Pharmaceutical). The course of treatment was 6 weeks. The patients were followed up at the end of the 2nd and 6th week, respectively. During the follow-ups, the patients were asked to complete the GI Symptom Evaluation Scale and the Mental & Psychological Evaluation Scale.

Observational indicators The GI symptom scores and the scores of depression and anxiety of the patients in the two groups were compared. In addition, the adverse reactions were recorded. The GI symptoms included heartburn, upper abdominal pain, early satiety, and abdominal distension. Each symptom scored 0-3 points, with 0 representing asymptomatic and 3 representing the most severe. The mental & psychological symptoms included the lack of interest in work, the lack of hope and depression, inability to stop or control worrying, and easy irritability. Each symptom scored 0-3 points, with 0 representing asymptomatic and 3 representing the most severe. The sum of the scores of all the

symptoms in the two scales was used as the symptom scores. The reduction rate of symptom scores = (post-treatment scores - baseline scores)/baseline score×100%. Total effective rate = (number of cases showing excellent response + number of cases showing effective response)/total number of cases×100% (excellence: the symptom score was decreased by≥50% compared with baseline after treatment; effective: the symptom score was decreased by 30%-50% compared with baseline after treatment; ineffective: the symptom score was decreased by <30% compared with baseline after treatment). Moreover, symptom scores of patients in the two groups were compared at the end of the 2nd and 6th week, respectively. The observed adverse reactions included dry mouth, rash, nausea, vomiting, and diarrhea.

Statistical analysis Results were stratified by FD subtypes (PDS and EPS). Means with SD were calculated for continuous data, and proportions were calculated for categorical depression and anxiety) could lead to dysregulation of the neuroendocrine system, which may deteriorate the GI symptoms. On the other hand, chronic and recurrent GI symptoms may exert an adverse effect on the physiological and mental health of patients, leaving the patients in a state of anxiety or depression and thus forming a vicious circle.[10]Therefore, according to Rome IV, the abnormal brain-gut interactions may play a critical role in the pathogenesis of FD and alleviating the psychological symptoms may benefit the treatment of FD patients. Mosapride citrate dispersible tablet (mosapride) is a commonly used drug to promote GI motility and treat FD.[11]It is a first-line drug recommended for the treatment of both EPS and PDS. Shugan Jieyu capsule (a St. John's wort compound preparation) is suitable for patients with mild to moderate unipolar depression who are suffering from liver stagnation and spleen deficiency.[12]Clinical data shows that combination treatment with gastroprokinetic agents and psychiatric drugs can improve the therapeutic efficacy with a low rate of recurrence.[8]The aim of the present study was to describe the real-world efficacy of a treatment regimen based on the concomitant use of a proton pump inhibitor (PPI), Shugan Jieyu capsule and mosapride citrate dispersible tablets in patients with FD. The clinical efficacy after 6 weeks was evaluated in EPS and PDS subgroups.

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Results

Changes in GI symptom scores of patients with PDS or EPS after treatment

As Table 1 shows, GI symptom scores in both PDS and EPS groups decreased significantly after 2 weeks of treatment ($P < 0.0001$ compared to baseline scores). The reduction rate of GI symptoms was 41.84% ± 35.69% and 50.73% ± 30.58% for PDS group and EPS group, respectively. After 6 weeks of treatment, GI symptom scores in these two groups showed more pronounced decrease ($P < 0.0001$ compared to baseline scores), with reduction rates of 75.61% ± 24.55% and 79.75% ± 27.39% for PDS group and EPS group, respectively. The baseline GI symptom scores and scores after 2 or 6-week treatment in PDS group and EPS group showed no difference ($P > 0.05$). In addition, similar symptom improvement was observed in these two groups (0.05).

Table 1. Changes in gastrointestinal (GI) symptom scores of patients with PDS or EPS after treatment

	PDS group	EPS group	Total
Baseline GI symptom scores			
n (missing)	2156 (0)	1084 (0)	3240 (0)
Mean (SD)	13.23 (6.49)	10.85 (6.50)	12.43 (6.59)
Reduction in symptom scores at the end of 2nd week (relative to baseline scores)			
Mean(SD)	-5.94 (4.37)	-5.55 (4.57)	-5.81 (4.44)
P value (Paired t test)	<.0001	<.0001	<.0001
Reduction rate of symptom scores at the end of 2nd week (relative to baseline scores)			
Mean (SD)	41.84 (35.69)	50.73 (30.58)	44.82 (34.32)
Reduction in symptom scores at the end of 6th week (relative to baseline scores)			
Mean (SD)	-10.07 (5.62)	-8.76 (5.81)	-9.63 (5.72)
P value (Paired t test)	<.0001	<.0001	<.0001
Reduction rate of symptom scores at the end of 6th week (relative to baseline scores)			
Mean (SD)	75.61 (24.55)	79.75 (27.39)	77.00 (25.61)

Efficacy evaluation of GI symptoms in patients with PDS or EPS after treatment

After 2 weeks of treatment, the proportion of patients showing excellence response was 45.18% and 57.56% and that of patients showing effective response was 32.70% and 23.15% in PDS group and the EPS group, respectively. The total effective rate in these two groups was 77.88% and 80.72%, respectively. After 6 weeks of treatment, the proportion of patients with excellence response was 89.10% and 92.99% and that of patients with effective response was 6.45% and 3.51% in PDS group and the EPS group, respectively. The total effective rate in these two groups was 95.55% and 96.49%, respectively. The proportion of patients with excellence or effective response and the total effective rate showed no significant difference in these two groups ($P > 0.05$) (Table 2).

Table 2. Efficacy evaluation of GI symptoms in patients with PDS or EPS after treatment.

	PDS group	EPS group	Total	*P* Value (PDS vs EPS)
After 2-week treatment				
Efficacy Evaluation				0.11
Excellent response, n (%)	974 (45.18)	624 (57.56)	1598 (49.32)	
Effective response, n (%)	705 (32.70)	251 (23.15)	956 (29.51)	
Patient number (missing)	2156 (0)	1084 (0)	3240 (0)	
Total effective rate				0.26
Effective response, n (%)	1679 (77.88)	875 (80.72)	2554 (78.83)	
Patient number (missing)	2156 (0)	1084 (0)	3240 (0)	
After 6-week treatment				
Efficacy Evaluation				0.21
Excellent response, n (%)	1921 (89.10)	1008 (92.99)	2929 (90.40)	
Effective response, n (%)	139 (6.45)	38 (3.51)	177 (5.46)	
Patient number (missing)	2156 (0)	1084 (0)	3240 (0)	
Total effective rate				0.41
Effective response, n (%)	2060 (95.55)	1046 (96.49)	3106 (95.86)	
Patient number (missing)	2156 (0)	1084 (0)	3240 (0)	

As Table 3 shows, depression scores in both PDS and EPS groups decreased significantly after 2 weeks of treatment, with a mean reduction of 2.52 and 2.36 for PDS group and EPS group, respectively ($P < 0.0001$ compared to baseline scores). After 6 weeks of treatment, depression scores in these two groups showed more pronounced decrease, with a mean reduction of 4.49 and 4.27 for PDS group and EPS group, respectively ($P < 0.0001$ compared to baseline scores). The baseline depression scores in PDS group and EPS group showed no difference ($P > 0.05$). In addition, similar symptom improvement after 2 or 6-week treatment was observed in these two groups ($P > 0.05$).

Table 3. Changes in depression scores of patients with PDS or EPS after treatment.

	PDS group	EPS group	Total
Baseline depression scores			
n (missing)	2156 (0)	1084 (0)	3240 (0)
Mean (SD)	6.33 (3.23)	5.96 (3.08)	6.21 (3.18)
Reduction in depression scores at the end of 2nd week (relative to baseline scores)			
Mean (SD)	-2.52 (2.02)	-2.36 (1.98)	-2.47(2.01)
P value (Paired t test)	<.0001	<.0001	<.0001
Reduction in depression scores at the end of 6th week (relative to baseline scores)			
Mean (SD)	-4.49 (2.80)	-4.27 (2.71)	-4.42 (2.77)
P value (Paired t test)	<.0001	<.0001	<.0001

Anxiety scores in both PDS and EPS groups decreased significantly after 2 weeks of treatment, with a mean reduction of 1.68 and 1.58 for PDS group and EPS group, respectively ($P < 0.0001$ compared to baseline scores). After 6 weeks of treatment, anxiety scores in these two groups showed more pronounced decrease, with a mean reduction of 2.75 and 2.59 for PDS group and EPS group, respectively ($P < 0.0001$ compared to baseline scores). The baseline anxiety scores in PDS group and EPS group showed no difference ($P > 0.05$). In addition, similar symptom improvement after 2 or 6-week treatment was observed

in these two groups ($P > 0.05$) (Table 4).

Table 4. Changes in anxiety scores of patients with PDS or EPS after treatment.

	PDS group	EPS group	Total
Baseline anxiety scores			
n (missing)	2156 (0)	1084 (0)	3240 (0)
Mean (SD)	3.53 (2.49)	3.29 (2.37)	3.45 (2.45)
Reduction in anxiety scores at the end of 2nd week (relative to baseline scores)			
Mean (SD)	-1.68 (1.70)	-1.58 (1.65)	-1.65 (1.69)
P value (Paired t test)	<.0001	<.0001	<.0001
Reduction in anxiety scores at the end of 6th week (relative to baseline scores)			
Mean (SD)	-2.75 (2.24)	-2.59 (2.17)	-2.70 (2.22)
P value (Paired t test)	<.0001	<.0001	<.0001

Adverse reactions occurring during the treatment

During the treatment period, 4 patients in PDS group and 2 patients in EPS group had nausea, and 1 patient in EPS group had insomnia. The incidence of adverse reactions was 0.22%. The difference between the two groups was not significant in terms of the incidence of adverse reactions ($P > 0.05$).

Discussion

FD belongs to FGIDs with symptoms of dyspepsia lasting for 6 months without the evidence of organic lesions that can be used to explain the symptoms. [13,14]At present, the mechanisms underlying the pathogenesis of FD remains unclear, but it is thought to be related to GI motility disorders, helicobacter pylori (HP) infection, GI inflammation, mental or psychological factors, social and environment factors, and immune factors.[15] FD can be divided into two subtypes. The patients with PDS display symptoms of postprandial stomach bloating, discomfort and early satiety after a meal. The accompanying symptoms may include upper abdominal pain or burning, flatulence, and nausea. EPS, the other subtype, is characterized by upper abdominal pain or burning sensation, which can be accompanied by upper abdominal flatulence, belching, and nausea. The symptoms of the two subtypes can overlap.[16]

The purpose of FD treatment is to control or alleviate upper GI symptoms, so as to improve the quality of life of patients and improve their bad mood.[17] The use of PPIs can be part of anti-HP treatment, and it can also quickly and effectively relieve symptoms such as upper abdominal pain, burning sensation, and bloating. Due to delayed gastric emptying and reduced gastric relaxation in FD patients, the key to treat FD is to use drugs to enhance GI motility.[18] Mosapride is a third-generation drug to enhance gastric motility via selectively acting on 5-HT4 receptors on cholinergic interneurons and myenteric plexuses of GI smooth muscles. It can promote acetylcholine release from cholinergic nerve endings, thus promoting gastric emptying without affecting gastric acid secretion[19,20] to alleviate the clinical symptoms of FD patients.

However, many patients in the clinic setting cannot recover from FD by using the classic treatment regimen of PPI plus prokinetic drugs. In these patients, the symptoms are not significantly improved after 3 months of treatment by antacids, prokinetic drugs, digestive enzymes, antibiotics, and microecological preparations. Moreover, the clinical symptoms of these patients tend to recur frequently.[21]In recent years, great progress has been made in

understanding the etiology and pathogenesis of FGIDs. It is generally believed that the emotional responses of depression and anxiety coexist with the GI symptoms of digestive disorders, causing the interactions between each other. Therefore, FGIDs are regarded as disorders of "gut brain interactions".[22-24]For patients with "refractory" FD, the treatment regimen should be optimized.[26] For patients with "identifiable psychosocial factors", psychotropic drugs should be used.[27]

In this study, the drug used to intervene psychosocial factors, i.e., Shugan Jieyu capsules, contains two ingredients of traditional Chinese medicine: hypericum perforatum and acanthopanax senticosus. Hypericum perforatum, also known as St. John's Wort in Western society, is the most widely used anti depressant botanical drug in the world. Its main active ingredients are benzodioxin derivatives hypericin and pseudohypericin, which can pass through the blood brain barrier and enter into the brain. Hypericum perforatum also contains ingredients with inhibitory activity against monoamine oxidase (MAO) to improve the level of neurotransmitters that are useful to maintain the normal mood and emotional stability in the brain, thus relieving stress and stabilizing mood. The other ingredient, acanthopanax senticosus, was initially described as a top grade drug in the "Shen Nong's Herbal Classic". The top grade indicates that the drug is non-toxic and its long-term use can promote health and longevity with no harm. It is a more basic adjuvant component in the formula and plays a complementary and consolidation effect. The formula of Shugan Jieyu capsules is simple, scientific and safe. For non-psychiatric specialists, it is easy to grasp the method of using Shugan Jieyu capsules.

The FD patients enrolled in this study were all accompanied by mild to moderate psychosocial problems. Therefore, in the use of the regimen of a PPI plus a prokinetic drug, the addition of Shugan Jieyu capsules could significantly improve the symptoms by improving the GI symptom scores and depression/ anxiety scores. At the same time, it was also found that this treatment regimen was effective in the treatment of both PDS or EPS, and there was no significant difference in the total effective rate between the two groups of patients.

This clinical practice included the assessment of diverse patient groups located in different areas and at different medical levels of current medical conditions. Compared with randomized controlled trials, the inclusion criteria of this clinical practice were broader and its patient population was more representative of the actual medical environment. However, its disadvantage was that a large number of collected cases were biased, and hence many cases of the clinical study were lost after these biased cases were removed.

In summary, the combined therapy with PPI, Shugan Jieyu capsules and mosapride can significantly improve the GI symptoms and the mental state of FD patients without increasing adverse reactions. There is no significant difference in the treatment efficacy of PDS and EPS patients. Our results suggest that this combination therapy is beneficial to treatment of FD.

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