

Xiaoyao pill for treatment of functional dyspepsia in perimenopausal women with depression

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Abstract

AIM: To evaluate the efficacy and safety of the Xiaoyao pill for treatment of functional dyspepsia (FD) associated with perimenopausal depression.

METHODS: This was a double-blind, randomized, controlled trial including 180 patients with FD accompanied by depression that were divided into two groups of 90. Patients in the treatment group received oral administration of the Xiaoyao pill for soothing the liver and activating the spleen, and patients in the control group received a placebo. This trial included an 8-wk therapy period with a follow-up period of 6 mo. The total efficacy and degree of depression, as assessed by the Hamilton Rating Scale for Depression (HRSD), were evaluated. Plasma levels of motilin and gastrin were measured and a gastric emptying test was conducted in each participant.

RESULTS: The Xiaoyao pill had a good therapeutic effect and improved the symptoms in patients with perimenopausal FD as assessed by the HRSD score,

motilin and gastrin levels, and rate of gastric emptying. The total effective rate of the Xiaoyao pill in the treatment group was significantly superior to that of the placebo in the control group. In the control group, the initial HRSD score was 12.12 ± 2.29 and decreased to 7.14 ± 1.67 after therapy ($P < 0.01$). In the treatment group, the initial HRSD score was 11.44 ± 2.15 , which significantly decreased to 6.20 ± 2.08 after therapy ($P < 0.01$). Moreover, the HRSD score in the treatment group was significantly lower than in control group after 8 wk ($P < 0.01$). Motilin and gastrin levels in both groups were significantly increased after the 8-wk therapy ($P < 0.05$). The gastric emptying rate was also improved in both groups after therapy ($P < 0.05$), and the improvement was significantly better in the treatment group compared to the controls ($P < 0.05$). These results confirm the therapeutic effects of the Xiaoyao pill in perimenopausal FD patients and indicate that it is worthy of clinical promotion.

CONCLUSION: The Xiaoyao pill is effective and safe for the treatment of perimenopausal women with FD associated with depression.

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Key words: Chinese herbal medicine; Functional dyspepsia; Perimenopausal women; Xiaoyao pill

Core tip: This study observed the clinical effects of the Xiaoyao pill for treatment of perimenopausal women with functional dyspepsia (FD) and depression. The Xiaoyao pill improved patient symptoms as assessed by the Hamilton rating scale for depression and gastric emptying rate. The mechanism of these effects may be related to the observed increases in plasma motilin and gastrin levels, which can accelerate gastric emptying and improve propulsion through the small intestine.

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INTRODUCTION

The etiology and pathogenesis of functional dyspepsia (FD) are not clear. Many researchers consider that it is caused by several different pathogenic factors. At present, it is thought to be mainly related to gastrointestinal motility disorder, increased visceral sensitivity, and psychological abnormality. However, perimenopausal FD (PMFD) is a manifestation of perimenopausal syndrome in the digestive system. At present, it is thought to be mainly caused by endocrine hypofunction, gastrointestinal motility functional disorder, and psychological factors. Gastrointestinal motility functional disorder is the main pathologic basis of FD, including proximal gastric accommodation abnormality, gastric emptying delay, gastroduodenal motility coordination abnormality, and inter-digestive phase III gastrointestinal motility abnormality. Recent research shows that if abnormalities arise in some parts of the brain-gut axis, digestive tract motility disorder or reduced visceral sense threshold occurs; both of which may become important factors in PMFD pathogenesis^[1]. Other research shows that digestive tract motility is related to estrogen, which has inhibitory effects on two aspects of stomach physiological functions: (1) gastric emptying, motility and rhythm; and (2) gastric secretion^[2].

Estrogen can also affect many neurotransmitters, including promoting the production of 5-hydroxytryptamine (5-HT), and increasing intracephalic 5-HT receptors^[3]. However, insufficiency of 5-HT function gives rise to depressive symptoms. Therefore, a decrease in estrogen may cause depressive symptoms and increase the occurrence of FD. Some Chinese researchers use low doses of conjugated estrogens to treat PMFD, which improves FD and psychiatric symptoms. In particular, nausea, abdominal distension, and epigastric discomfort are obviously improved. However, hormones are not used for replacement therapy in the control groups. Instead, patients are provided with oral gastric motility stimulants, without obvious improvement to FD and psychiatric symptoms. It is inferred from this that estrogen is related to, and can improve, the FD symptoms of perimenopausal women. Due to the obvious decrease in estrogen level, the occurrence of emotional disorders (such as depression, anxiety, and sleep disorders) in perimenopausal women is increased among FD patients^[4]. Moreover, such factors often exist at the same time and affect each other.

At present, there are no effective Western medicines for PMFD. Most researchers have attempted to use psychotherapy for patients with FD, and have found that it has better effects when compared with simple drug

therapy, especially for FD patients with serious symptoms or treatment resistance^[5]. Frequently used drugs include antacids, prokinetic agents, anxiolytics and antidepressants, digestants, and anti-*Helicobacter pylori* treatment^[6,7]. Standardized treatment for FD includes combination, comprehensive and individualized treatment. In China, however, there is considerable experience in treatment of PMFD with traditional Chinese medicine (TCM) and other methods^[8-11]. TCM considers that this disease is related to emotional repression and weak spleen and stomach. The disease is located in the stomach, and is closely related to the liver and spleen, that is, liver depression and spleen deficiency syndrome. It refers to the fact that the syndrome is dominated by epigastric pain due to liver qi stasis, stomach invasion and stomach imbalance.

In this study, we investigated the curative effect of the TCM Xiaoyao pill in women with PMFD and depression, by observation of motilin, gastrin and rate of gastric emptying, as well as the Hamilton Rating Scale for Depression (HRSD). We also investigated the possible pathogenesis of PMFD.

MATERIALS AND METHODS

Patient selection and diagnostic criteria

One hundred eighty patients with FD accompanied by depression were selected from the Department of Internal Medicine, The Second People's Hospital Affiliated with Fujian University of Traditional Chinese Medicine from December 2012 to December 2013. The patients were randomly divided into a treatment or control group by a random number table method.

The diagnostic criteria were based on the Rome III criteria^[12]. All subjects 41-52 years of age, who complained of at least one of the symptoms (early satiety, epigastric pain, epigastric burning, and postprandial fullness), which had lasted > 6 mo and had become more severe in the past 3 mo, were enrolled.

The TCM standard for diagnosing syndromes was worked out with reference to the standard for diagnosing the type of liver depression and spleen deficiency in the guidelines of diagnosing and treating FD. Major symptoms are stomach pain or discomfort and anorexia and loose stools. Minor symptoms include: (1) abdominal distention and pain; (2) impatience; (3) insomnia and dreamful sleep; (4) belching and acid reflux; (5) physical and mental fatigue; and (6) abdominal distention after eating. Patients with all the major symptoms and two or more minor symptoms were diagnosed as suffering from the syndrome of liver depression and spleen deficiency.

Inclusion and exclusion criteria

To be included in the study, patients had to meet the following inclusion criteria: (1) perimenopausal women 41-52 years of age who met the Rome III criteria for FD; (2) had liver depression and spleen deficiency syndrome; (3) ability to cease all medical treatment that could influence gastrointestinal motility at least one week prior to

Table 1 Curative effect of the Xiaoyao pill

Group	<i>n</i>	Cure	Obvious effect	Effectiveness	Ineffectiveness	Effective rate
Control	90	5	18	16	51	43.33%
Treatment	90	20	16	42	12	86.67% ^b

^b*P* < 0.01 *vs* control.

the test; and (4) agree to participate and give signed informed consent. Patients were excluded if they: (1) had structural diseases, such as esophagitis, erosive gastroduodenal lesions or ulcers that could explain symptoms; (2) had systemic diseases; (3) were pregnant or breast-feeding; (4) were receiving hormone replacement therapy; or (5) had a mental disease.

Therapy

Randomization was performed by opening a sealed envelope that contained a preassigned randomized treatment generated by computer on entry to the study. Both the investigators and patients were blinded to the assigned treatment throughout the study. The Xiaoyao and placebo pills were identical in appearance. In the treatment group, the patients were treated with the Xiaoyao pill, consisting of *chai hu* (*radix bupleuri*), *dang gui* (*Angelica sinensis*), *bai shao* (*radix paeoniae alba*), *chao bai zhu* (roasted *rhizoma atracylodes macrocephalae*), *fu ling* (*Wolfiporia extensa*), *zhi gan cao* (*radix glycyrrhizae*), *bo he* (mint), and *sheng jiang* (*rhizoma zingiberis recens*). In the control group, the patients were given a placebo, *chaoguya* (*fructus setariae germinatus*). Drugs were produced by Fuzhou Jinxiang Co. Ltd. They were administered at 3 g each time, 30 min before breakfast and supper, for 8 wk. During treatment, patients stopped taking other drugs.

Standard for evaluating curative effect

According to the TCM Diagnosis and Treatment Norms on Functional Dyspepsia Approved by the China Association of Chinese Medicine, Professional Committee of Spleen and Stomach Diseases, all symptoms are divided into three grades, mild, medium and severe, with a score of 1, 2 and 3, respectively, or 0 for no symptoms. The grading of symptoms is as follows: mild, symptoms do not affect work and life, and are bearable; medium, symptoms affect work and life, but are bearable; severe, symptoms hinder work and life, and are unbearable.

With reference to the Guideline for Directing Clinical Research into Treatment of Distention and Fullness with New Chinese Drugs, clinical control means that clinical symptoms and signs disappear and the accumulated score of syndromes is reduced by $\geq 95\%$. Obvious effect means that clinical symptoms and signs are obviously improved and the accumulated score of syndromes is reduced by $\geq 70\%$. Effectiveness means that clinical symptoms and signs are improved and the accumulated score of syndromes is reduced by $\geq 30\%$. Ineffectiveness means that clinical symptoms and signs are not improved

or aggravated, and the accumulated score of syndromes reduces by < 30%.

The formula for assessing the curative effect was: (accumulated score before treatment - accumulated score after treatment)/accumulated score before treatment $\times 100$. The HRSD was categorized according to Davis *et al.*^[13]: > 24 points, the patient may be suffering from severe depression; 17-24 points, the patient may be suffering from medium depression; 8-16 points, the patient may be suffering from mild depression; ≤ 7 points, the patient is without depressive symptoms.

Testing index and method

Before and after the therapy period, the two groups were tested for plasma levels of motilin and gastrin, evaluated with the HRSD, and gastric emptying rate (total number of barium $\times 100\%$ ^[14]) was determined. Tests were repeated 6 mo later to determine the recurrence.

Statistical analysis

All data are presented as mean \pm standard deviation and tested using SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA). A Student's *t*-test was used to compare the differences between the two sample means, χ^2 tests were used for numerical data, and the Ridit test was used to compare the clinical efficacy between the groups. *P* < 0.05 was considered to represent statistical significance.

RESULTS

The 90 patients in the treatment group were 41-49 years of age (average: 45.30 ± 2.81 years) and their disease course was 1-8 years (average: 4.20 ± 2.30 years). The 90 patients in the control group were 42-52 years of age (average: 46.09 ± 2.45 years) and their disease course was 1-9 years (average: 3.96 ± 2.43 years). There were no statistical differences between the two groups regarding age, illness course, or symptom distribution.

Comparison of curative effect of treatment

The curative effect was significantly higher in the treatment group compared to the control group (86.67 *vs* 43.33%, *P* < 0.01) (Table 1).

Comparison of HRSD scores

HRSD scores in the two groups were significantly lower after 8 wk (*P* < 0.01). HRSD scores in the treatment group were significantly lower than in the control group (*P* < 0.01) (Table 2).

Table 2 Hamilton rating scale for depression

Group	n	Before	After 8 wk
Control	90	12.12 ± 2.29	9.14 ± 1.67 ^a
Treatment	90	11.44 ± 2.15	6.20 ± 2.08 ^{b,d}

^a*P* < 0.01 *vs* the control group; ^d*P* < 0.01 *vs* before.

Comparison of motilin and gastrin levels and gastric emptying rate

Motilin and gastrin levels in the two groups were significantly increased after therapy (*P* < 0.05), and the levels in the treatment group were significantly higher than in the control group (*P* < 0.05). The gastric emptying rate was significantly improved after 8 wk (*P* < 0.05), and the improvement in the treatment group was significantly greater than in the control group (*P* < 0.05) (Table 3).

Safety assessment

There were no abnormalities in routine blood and urine examinations, or in renal or hepatic functions. None of patients in the two groups had any adverse drug reactions. According to the follow-up visit 6 mo after therapy, there were five relapses in the control group and none in the treatment group.

Comparison of symptoms in the follow-up period

The patients were subject to drug withdrawal 8 wk after treatment as well as a follow-up visit at 6 mo, after which, their symptoms were recorded. There was no significant difference between symptoms in PMFD patients before and after drug withdrawal, which indicates that there was no symptom relapse after 6 mo.

DISCUSSION

The prevalence of FD in Western countries is 20%-25%, compared with 8%-23% in Asia^[15,16]. In China, dyspepsia patients account for approximately 10% of the general medicine outpatient service, and 50% of the cases at digestive internal medicine clinics^[9]. Although there are numerous FD patients, rigorous clinical research rarely shows that therapeutic methods are more effective than placebo^[17]. As a result, treatment efficacy is not ideal, and FD can easily recur, which has a serious effect on quality of life.

TCM proposes liver controlling dispersion and spleen governing transportation and transformation. Liver controlling dispersion refers to comprehensive physiologic functions of unchoking, smoothing, ascending, dredging, and discharging, which mainly reflects regulation of spiritual emotion, and promotion of digestion and absorption. Liver qi refers to a manifestation of the physiologic function of the liver, mainly reflected in adjustment of spirit and emotion and promotion of digestion and absorption^[18-20]. If the discharging function of the liver is normal, the body is better able to coordinate its spiritual and emotional activities. Besides, it is

conducive to the order of the spleen, stomach and bile secretion, for maintaining normal digestion and absorption. Liver dysfunction may affect this order, resulting in abnormal digestive function, such as appetite disorder, dyspepsia, belching pantothenic acid, abdominal distension, and diarrhea. Spleen governing transportation and transformation means that the spleen is able to transform water and cereal into refined nutritious substances, and transport these into various organs and tissues throughout the body. Dysfunction of spleen transportation may cause abnormal digestion and absorption, resulting in pathologic changes in abdominal distension, loose stools, appetite disorder, and lassitude.

The Xiaoyao pill is made from eight types of TCM: *radix bupleuri*, Chinese angelica, *radix paeoniae alba*, parched white *atractylodes rhizome*, *poria cocos*, honey-fried licorice root, mint, and fresh ginger. The monarch drug, *radix bupleuri* is used to smooth the liver, dispel melancholy, and soothe liver-qi stagnation. Chinese angelica is bitter and is used to nourish and activate the blood, and *radix paeoniae alba* is used to nourish the blood and liver; the drugs are adjuvant drugs. Liver dysfunction may cause spleen deficiency, so we use white *atractylodes rhizome*, licorice root, and *poria cocos* to invigorate the spleen and supplement qi. Modern pharmacologic research shows that saikoside has anti-inflammatory, immunoregulatory and liver protective functions, but can also inhibit cholinesterase, act as a quasi-choline sample and adjust the digestive and nervous systems^[21,22]. This consequently cures liver stagnation and soothes liver-qi stagnation. White *atractylodes rhizome* can activate the muscarinic receptors of the gastrointestinal tract and acetylcholine receptors, and accelerate gastrointestinal motility and evacuation^[23]. *Poria cocos* can increase 5-HT levels^[24], indicating that the Xiaoyao pill can alter central monoamine neurotransmitter and hormone levels, thereby improving the clinical symptoms of stagnation of liver qi and spleen deficiency.

Motilin is mainly expressed in the gastrointestinal tract and strongly stimulates mechanical and electrical activity of the upper gastrointestinal tract. It can give rise to intense shrinkage of the stomach and obvious segmentation movement of the small intestine. Gastrin is a gastrointestinal hormone that is secreted by the ventricular sinuses and duodenum. It mainly promotes shrinkage of the gastroesophageal sphincter and smooth muscle of the digestive tract, and stimulates secretion of gastric acid, pancreatic enzymes, bile and small intestinal juice. Hyposecretion can relax smooth muscle in the stomach and intestine, relieving stomach tension and peristalsis, extending gastric emptying time and weakening movement of the small intestine^[25-27].

In conclusion, the results of this study show that the Xiaoyao pill is effective for improving symptoms in patients with PMFD. Its mechanism of action may be related to boosting plasma gastrin and motilin levels, accelerating gastric emptying, and improving propulsion in the small intestine. The relationship among improvement in depression, serum estrogen level, and 5-HT content

Table 3 Levels of motilin, gastrin and gastric emptying rate

Group	Time	MOT (ng/L)	GAS (ng/L)	Gastric emptying rate (%)
Control (n = 90)	Before	86.32 ± 21.89	62.18 ± 13.52	39.23 ± 9.42
	After	100.56 ± 23.34 ^c	76.33 ± 15.27 ^c	46.77 ± 8.52 ^c
Treatment (n = 90)	Before	87.67 ± 23.50	60.25 ± 12.59	41.26 ± 8.38
	After	197.46 ± 26.37 ^{a,c}	110.43 ± 17.47 ^{a,c}	73.35 ± 9.89 ^{a,c}

^aP < 0.05 *vs* control; ^cP < 0.05 *vs* before. MOT: Motilin; GAS: Gastrin.

requires further study. Whether serum estrogen levels in perimenopausal women and 5-HT content influence FD occurrence also requires further study.

COMMENTS

Background

Functional dyspepsia (FD) is a common gastrointestinal disease with high morbidity. Due to the drop in estrogen level, perimenopausal women with FD (PMFD) have an increase in emotional disorders such as depression, anxiety and sleep disorder. As there are no effective treatments currently available, the aim of the present study was to evaluate the clinical effects of the Xiaoyao pill for treatment of PMFD with depression. The authors discuss possible pathogenesis of PMFD through observing overall effects of traditional Chinese medicine, motilin and gastrin levels, gastric emptying rate, and Hamilton Rating Scale for Depression (HRSD). The results provide a basis for clinical application.

Research frontiers

FD etiology and pathogenesis are still not clear and may be related to multiple factors. It is generally acknowledged that gastrointestinal obstruction is the main pathophysiologic basis of FD. Meanwhile, mood, stress and *Helicobacter pylori* infection are thought to be closely related to FD morbidity. There is still no drug treatment with specific effects. Most researchers have attempted psychotherapy for patients with FD. In China, much experience has been gained with traditional Chinese medicine for treating FD. However, research on PMFD is rare.

Innovations and breakthroughs

This was a randomized, double-blind, placebo-controlled study. The authors observed the clinical effects of the Xiaoyao pill in perimenopausal women with FD and depression. This research provides a basis for further clinical applications. It can be inferred that PMFD pathogenesis is related to liver qi stagnation, according to PMFD symptom improvement, gastric emptying and changes in gastrointestinal hormones. The mechanism of action of the Xiaoyao pill may be related to boosting plasma gastrin and motilin levels, accelerating gastric emptying, and improving small intestinal propulsion.

Applications

The Xiaoyao pill was effective in improving symptoms in patients with PMFD, as assessed by HRSD scores, motilin and gastrin levels, and gastric emptying rate. Therefore, Xiaoyao merits consideration for clinical application.

Terminology

PMFD refers to the condition after entering the perimenopausal period, when ovarian functions weaken, estrogen levels drop, gastrointestinal mucosal barrier function reduces, neurologic function of the stomach and intestine is disordered, and is described by symptoms such as epigastric pain, gasteremphraxis, abdominal discomfort, belching, nausea, vomiting, and stomach discomfort.

Peer review

The authors studied the effect of the Xiaoyao pill on PMFD symptoms in a randomized, double-blind, placebo-controlled trial. The study was unique and well organized. The Xiaoyao pill was effective in improving symptoms of patients with PMFD, as assessed by HRSD scores, motilin and gastrin levels, and gastric emptying rate, which may help to describe the mechanism for improving propulsion in the small intestine.

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