GASTROENTEROLOGY

Treatment of functional constipation with the Yun-chang capsule: A double-blind, randomized, placebo-controlled, dose-escalation trial

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Abstract

Background and Aim: Functional constipation is a common functional bowel disorder for which there is no reliable medical treatment. This study was designed to determine the therapeutic efficacy and safety of the Yun-chang capsule, a Chinese herbal formula, in the treatment of patients with functional constipation.

Methods: In our multi-center, prospective, double-blind, randomized, placebo-controlled, dose-escalation trial, patients with functional constipation received 70 mg of Yun-chang capsule plus 35 mg placebo (group A), 105 mg of Yun-chang capsule (group B), or 105 mg placebo (group C), three times daily for 2 weeks. The primary end-points were the changes in main symptom score and cumulative symptom score 2 weeks after the treatment. The secondary end-points were adverse events.

Results: A total of 140 patients were recruited and 132 met the inclusion criteria; 44 patients constituted each of the three treatment groups. Compared with patients in group C, patients in groups A and B had significant improvement in the main symptom score, cumulative symptom score, the change from baseline of the main symptom score, and the change from baseline of the cumulative symptom score at week 1 and week 2. The scores showed slight superiority of group B over group A at week 1 and week 2, although these differences were not statistically significant. There were no differences in adverse events.

Conclusions: The Yun-chang capsule is efficacious and safe for the treatment of patients with functional constipation. Larger and longer-term trials are required to fully assess the benefits and safety of this treatment for functional constipation.

Key words
constipation, randomized controlled trial, traditional Chinese medicine, Yun-chang capsule.

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Introduction

Constipation is a common functional bowel disorder that affects a significant proportion of people, especially women, children, and the elderly. Studies in the USA suggest that 14.7% of the population has this disorder.¹ An epidemiological study conducted in Beijing concluded that 6.1% of the adult population suffers from constipation.² However, the actual occurrence may be higher, as many individuals with constipation suffer without seeking professional care. Patients associate constipation with several symptoms that seriously impact quality of life.

Constipation can be classified into three broad categories: normal-transit constipation (functional constipation [FC]); slow-transit constipation; and disorders of defecatory or rectal evacuation. In patients with FC, the stool traverses the colon at a normal rate and stool frequency is normal, but patients may have hard or lumpy stools, bloating, abdominal discomfort, and psychosocial distress.³ In recent years, various treatments for FC have emerged and include laxatives, tegaserod, lactulose, psyllium, increasing the consumption of dietary fiber, biofeedback training, and, in severe cases, surgery. Unfortunately, evidence for the efficacy of these treatments is limited, and some agents can lead to adverse events.⁴

Dissatisfaction with treatments offered by Western medicine has led many patients to turn to traditional Chinese medicine (TCM) for treating FC in China and other parts of the world. TCM is a 3000-year-old holistic system of medicine that combines medical herbs, acupuncture, food therapy, massage, and therapeutic
exercise for both extensive treatment and prevention of diseases, including FC. For example, the use of electro-acupuncture has been shown to safely improve clinical symptoms and colon transmission time in patients with FC. In a randomized controlled trial comparing electro-acupuncture with cisapride in patients with post-stroke constipation, the use of electro-acupuncture was found to be more beneficial than cisapride based on the cumulative score of clinical symptoms. A review of published herbal trials for treatment of all types of FC concluded that this type of treatment can safely improve symptoms. However, there is insufficient evidence from randomized controlled trials to assess the long-term efficacy and safety of TCM in treating patients with FC.

Here we report the findings of a multi-center, prospective, double-blind, randomized, placebo-controlled trial to determine the therapeutic efficacy and safety of the Yun-chang capsule (YCC) in the treatment of patients with FC.

Methods

Study design

A multi-center, prospective, randomized, double-blind, placebo-controlled, dose-escalation phase II clinical trial was designed to determine the therapeutic efficacy and safety of 70 mg and 105 mg of YCC given three times daily for 2 weeks to patients with FC. The protocol was reviewed and approved by the independent ethics committees at each participating center. The trial was conducted in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki.

All herbs used in this trial were recognized as safe for use by the State Food and Drug Administration (SFDA) of China. This trial was also authorized by the SFDA of China (No. 2006L00233). We reported the outcomes according to the Consolidated Standards of Reporting Trials statement.

Based on our experience with TCM in treating FC and on other similar studies in the literature, we assumed that the cure rates of the cumulative symptom score for patients treated with active TCM were 54.0% in group A, 50.0% in group B, and 20.0% in group C. Forty patients would be required in each study group to achieve a power of 0.8 and a two-sided \( P \)-value of 0.05. We allowed for a dropout rate of approximately 10%. Therefore, 132 FC patients were needed for this study.

Eligibility criteria

A total of 140 eligible patients were recruited from five centers in China between April 2007 and May 2008. All patients were examined by one of the clinical study gastroenterologists and were enrolled in the study according to the inclusion and exclusion criteria described in Table 1. All patients gave written informed consent prior to participation. In light of the study procedure, patients were seen by a gastroenterologist at baseline, at the end of 1 week, and at the end of 2 weeks. During each visit, patients were interviewed by the gastroenterologist to ascertain symptoms, compliance, and occurrence of adverse events. At baseline and at the end of 2 weeks, patients also underwent laboratory evaluation (i.e. routine blood, urine, and stool tests along with hepatic and renal functions and electrocardiogram) and physical examination. A flowchart illustrating the study procedure is provided in Supplementary material 1.

Table 1 Inclusion and exclusion criteria

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<tr>
<th>Inclusion criteria</th>
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<tr>
<td>1. 18 to 65 years of age.</td>
<td>1. Patient has not suffered from functional constipation.</td>
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<td>2. Diagnosis of functional constipation by a gastroenterologist according to Rome III criteria and the syndrome criteria of deficiency of positive Qi and Yin together with invasion by pathogen in TCM.</td>
<td>2. Symptoms of constipation caused by intestinal stenosis as a result of colorectal lesions such as intestinal tumor, intestinal tuberculosis, Crohn’s disease, or intestinal polyps, etc.</td>
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<td>3. Patient has taken any medication for relief of symptoms within 2 weeks prior to study initiation.</td>
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<td>4. Patients who are on analgesic or anti-inflammatory regimen requiring treatment with analgesics, non-steroidal anti-inflammatory drugs, or steroids.</td>
<td>4. Patient is pregnant, nursing, or a woman of childbearing potential not practicing adequate contraception. (Women who were uncertain if they were pregnant could participate in the study if they underwent a pregnancy test that showed a negative result.)</td>
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<td>5. Patient has comorbid condition, uncontrolled metabolic condition or psychiatric condition that might make tolerance or evaluation of the symptoms difficult.</td>
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Randomization

A total of 132 eligible patients met the inclusion criteria and were randomized into group A (35 mg x 2 capsules of YCC plus 35 mg x 1 capsule of placebo), group B (35 mg x 3 capsules of YCC), or group C (35 mg x 3 capsules of placebo). Forty-four patients were required in each treatment group. Randomization was conducted in blocks of five in a 1:1:1 ratio using the PRECO PLAN function of the analysis system of SAS (Version 6.12 for Windows). The randomization lists were placed in two sealed envelopes and the details were unknown to the study investigators and the patients throughout the course of the study. One envelope was kept by Lunan Pharmaceutical Group (Shandong Province, China) and the other was kept at the study centers to be opened in case of medical emergency.

Treatment schedule

All randomized patients in group A were required to take 70 mg of YCC plus 35 mg placebo three times daily for 2 weeks; those in group B took 105 mg of YCC three times daily for 2 weeks; and those in group C took 105 mg of placebo three times daily for 2 weeks. Because patients with FC were diagnosed with
An initial group of 140 patients was recruited over a 13-month period, with 132 eventually meeting the inclusion criteria and being placed into one of three treatment groups. The trial was conducted from April 2007 to May 2008. All patients provided written informed consent prior to inclusion. The primary outcome was the change in main symptom score 2 weeks after treatment completion. The secondary outcomes included a cumulative symptom score among the three groups, and adverse events were recorded for each group. All patients received study medication and attended at least one study visit after the start of treatment. The primary analysis of efficacy was performed in the intent-to-treat (ITT) population, which included all randomized patients who received study medication and attended at least one study visit after the start of treatment. The primary endpoint analysis was performed on the ITT population; all quantitative data were expressed as means ± standard deviation (SD), and one-way ANOVA was used to compare the data. A \( \chi^2 \)-test was performed to calculate differences in qualitative data between the three groups. A P-value of < 0.05 was considered to indicate statistical significance. Data were analyzed using the statistical software Intercooled Stata version 8.2 for Windows (Stata Corporation, College Station, TX, USA).

**Results**

**Demographic data and baseline characteristics**

A total of 140 patients were recruited during a period of 13 months from April 2007 to May 2008; 132 of these patients met the inclusion criteria and 44 patients were placed into each treatment group. A total of 11 patients (8.33%) withdrew during the 2-week course of the trial: three (6.82%) in group A, four (9.09%) in group B, and four (9.09%) in group C (P = 1.00). Nine patients were withdrawn from the trial because the intervention was ineffective during the treatment period, and two patients were withdrawn from the trial because they were lost to follow up (Fig. 1). There were no significant differences in baseline characteristics in terms of sex ratio, age, weight, height, duration of constipation, main symptom score, or cumulative symptom score among the three groups.
Compliance with the study medication was high as measured by capsule count and showed no statistical difference among the groups (95% for group A, 94% for group B, and 95% for group C).

**Main symptom score**

An improvement in main symptom score was observed from baseline to week 2 in all three groups (Fig. 2A). However, compared with patients in group C, the ITT analysis showed that patients in groups A and B had significant improvement in their main symptom score ($P < 0.0001$) and the change from baseline of main symptom score ($P < 0.0001$) at weeks 1 and 2. In addition, these scores showed a slight superiority of group B over group A at week 1 and week 2, although these differences were not statistically significant (Fig. 2B, Table 4).

**Cumulative symptom score**

An improvement in the cumulative symptom score was observed from baseline to week 2 in all three groups (Fig. 2C). However, compared with patients in group C, the ITT analysis showed that patients in groups A and B had significant improvement in cumulative symptom score ($P < 0.0001$) and change from baseline of cumulative symptom score ($P < 0.0001$) at weeks 1 and 2. In addition, these scores showed a slight superiority of group B over group A at week 1 and week 2, although these differences were not statistically significant (Fig. 2D, Table 4).

**Follow-up assessment**

The patients in each treatment group were followed up for 4 weeks after finishing the treatment. Of the 16 patients in group A with an improved status after treatment, 24.38% suffered from...
recurrence, and of the 19 patients in group B with an improved status after treatment, 21.05% suffered from recurrence. In group C, three patients had an improved status after treatment, but all three suffered from recurrence. The recurrence rate of the treated group was obviously lower than that of the placebo group ($P < 0.05$), but the difference in recurrence rate was not statistically significant between group A and group B ($P = 0.72$).
Safety
There were no deaths during the study. The two patients with adverse effects were both in group A (2/44, 4.55%). One patient developed diarrhea (3–4 times/day) accompanied by mild abdominal pain after taking the 70 mg of YCC for 3 days. In this patient, we reduced the dose of the experimental drugs and the symptoms were prevented by routine treatment. Another patient developed abdominal pain after eating popsicles, but this pain gradually eased in the absence of any treatment. No adverse events were reported in groups B and C. In addition, no clinically significant changes were noted in laboratory evaluations or physical examinations. We concluded that there was no significant correlation between the use of YCC and adverse events.

Discussion
To our knowledge, this is the first randomized, prospective, double-blind, placebo-controlled, dose-escalation trial designated to evaluate the efficacy and safety of TCM in an adult population from China. Our study demonstrated that YCC was efficacious and safe for the management of FC. Patients receiving 70 mg and 105 mg of YCC treatment three times daily demonstrated significant improvement in the main symptom score and cumulative symptom score compared to patients receiving the placebo at weeks 1 and 2. Patients receiving 105 mg of YCC three times daily showed a slight benefit in their main symptom score and cumulative symptom score over patients receiving 70 mg of YCC three times daily during treatment, although this difference was not statistically significant.

In this study, FC patients with a deficiency of positive Qi and Yin together with invasion by a pathogen were selected for treatment, and the herbal recipe of the YCC was designed for these patients according to the fundamental principles of TCM. According to these principles, FC belongs to the scope of constipation, abdominal pain, etc. TCM theory holds that Qi is the driving power and that Qi deficiency will result in insufficient Qi in driving, irregular defecation, and ultimately constipation. The treatment of tonifying Qi is to improve transportation and promote defecation. Pharmacological studies have shown that ginseng and aurantii fructus immaturus, which are included in the YCC, have a significant effect on improving intestinal motility. In addition, dryness in the intestine due to invasion by pathogens attacking body fluids can lead to Yin deficiency. When Yin deficiency occurs, the intestine fails to lubricate and the accumulated stool becomes dry, which makes it difficult to pass. The treatment of nourishing Yin and promoting the generation of body fluid to moisten the intestine and promote defecation could be applied to soften the stool. The commonly used medicines to tonify Yin and lubricate the intestine are fleeceflower root and aloe, which are included in the YCC. In addition, deficiency of hsueh (blood) will definitely result in Yin deficiency. For constipation of the combined hsueh and Yin deficiency type, gelatina nigra is used to tonify hsueh and generate Yin.

Laxatives are currently considered to be a primary and complementary measure for the treatment of all types of FC. They may improve the frequency of stools, but they have no proven effect on the multiple symptoms, such as straining, abdominal bloating, or weakness. Therefore, patients often rely on multiple treatments, which are often ineffective, to control their symptoms. This has led to high patient dissatisfaction and frustration with current treatments for FC. Thus, there is a need for simple, safe, and effective first-line therapies to treat the multiple symptoms of patients with this disorder. TCM stresses differentiation of symptoms and signs; it considers the human being to be an organic entirety and treatment should be emphasized on the entirety. Besides, TCM counts on the synergistic effects of the herbs, which have a general specter of action. Therefore, TCM practitioners usually use a substantial number of herbs to treat various conditions. This will overcome the shortcomings of Western medicine.

Studies have reported that a conventional dose of Western agents can significantly induce drug resistance, drug addiction, or severe adverse events in patients with FC. Popular opinion confirms that the general public believes TCM to be safe, to cause fewer side-effects, and to be less likely to cause dependency. In our study, only two patients who were receiving 70 mg of YCC three times daily reported transient diarrhea and abdominal pain after eating popsicles, respectively. Therefore, we concluded that there was no significant correlation between the use of the YCC and adverse events. Nevertheless, many herbs can be toxic, especially in high quantities and with frequent use. Furthermore, herb-synthetic drug interactions can be problematic. Hence, the analysis of adverse effects of TCM for treating FC is indeed very important.

This study had some potential weaknesses. The trial was conducted only for a 2-week treatment period. However, after only 1 week of treatment, the efficacy of the YCC appeared when compared with the placebo, and this finding supports the premise that the study was of sufficient duration to assess the long-term benefit and safety of the YCC. Also, we were unable to assess the efficacy of the YCC as compared with other treatments for FC.

In conclusion, during a treatment period of 2 weeks, the YCC significantly improved the main symptom score and cumulative symptom score in patients with FC. Patients receiving 105 mg of YCC three times daily showed a slight benefit in their main symptom score and cumulative symptom score over patients receiving 70 mg of YCC three times daily during treatment, although this difference was not statistically significant. Larger and longer-term trials are required to fully assess the benefits and safety of the use of the two dosages of the YCC for treating FC.

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