Author's response to reviews

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Authors:

Hongli Wu (hlwcapri@yahoo.com.cn)
Zhiwei Jing (drizw@163.com)
Xudong Tang (txdly@sina.com)
Xinyue Wang (wxy6687@sina.com)
Shengsheng Zhang (zss2000@sohu.com)
Hongxin Cao (caohongxin58@yeah.net)
Zhong Wang (zhonw@vip.sina.com)
Luqi Huang (huangluqi@263.net)
Youhua Yu (yuyh@mail.cacms.ac.cn)
Yongyan Wang (yongyanwang@126.com)

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To compare the efficacy of two kinds of Zhizhu pills in the treatment of functional dyspepsia of spleen-deficiency and qi-stagnation syndrome: A randomized group sequential trial

Hong-li Wu¹, Zhi-wei Jing¹, Xu-dong Tang¹, Xin-yue Wang², Sheng-sheng Zhang³, Zhong Wang¹, Hong-xin Cao¹*, Lu-qi Huang¹, You-hua Yu¹, Yong-yan Wang¹

¹China Academy of Chinese Medical Sciences, 16 Nanxiaojie, Dongzhimen nei, Beijing, China
²Dongzhimen Hospital affiliated to Beijing University of Traditional Chinese Medicine, 5 Haiyuncang, Dongcheng District, Beijing, China.
Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, 23 Art Gallery Back Street, Dongcheng District, Beijing, China.

* Corresponding author

Email addresses:
Hong-li Wu: hlwcapri@yahoo.com.cn
Zhi-wei Jing: drjzw@163.com
Xu-dong Tang: txdly@sina.com
Xin-yue Wang: wxy6687@sina.com
Sheng-sheng Zhang: zss2000@sohu.com
Zhong Wang: zhonw@vip.sina.com
Hong-xin Cao*: caohongxin58@yeah.net
Lu-qi Huang: huangluqi@263.net
You-hua Yu: yuyh@mail.cacms.ac.cn
Yong-yan Wang: yongyanwang@126.com
Abstract

Background

In Traditional Chinese Medicine (TCM) theory, functional dyspepsia (FD) is divided into different syndromes according to different clinical symptoms and signs. Spleen-deficiency and qi-stagnation syndrome is the most common one, and can be treated by Chinese traditional patent medicine - two kinds of Zhizhu pills, between which the primary difference in ingredients is that one contains immature orange fruit of Citrus
aurantium L. (IFCA) and the other contains that of Citrus sinensis Osbeck (IFCS). The trial’s objective is to compare the efficacy of the two kinds of Zhizhu pills on the changes in the symptoms in patients with FD of spleen-deficiency and qi-stagnation syndrome.

**Methods**

A randomized, group sequential, double-blinded, multicenter trial was conducted in patients with FD of spleen-deficiency and qi-stagnation syndrome at 3 hospitals in Beijing between June 2003 and May 2005. Participants were randomly allocated into two groups (IFCA group and IFCS group) one of the two kinds of Zhizhu pills orally, 6g each time, 3 times a day, for 4 weeks. A group sequential analysis based on the triangular test (TT) was used to determine
whether the difference in the cure-markedly effective rate of symptoms improvement between the two groups was $\geq 15\%$.

Results

A total of 163 patients were randomized, and 3 patients were excluded from analysis because of early dropouts, leaving 160 patients (IFCA group: $n=82$; IFCS group: $n=78$) for statistical analysis. Three interim analyses were done after 62, 116, and 160 patients had completed their 4-week treatment, respectively. At the third interim analysis, the sample path crossed the upper boundary and the trial was stopped. The cure-markedly effective rate were 67\% and 45\% in the IFCA and IFCS groups, respectively, and the difference was significant ($p=0.005$).
No adverse events were observed in the two groups.

Conclusions

Zhizhu pills containing IFCA might have better efficacy than Zhizhu pills containing IFCS in the treatment of FD of spleen-deficiency and qi-stagnation syndrome. And the application of group sequential analysis in clinical trials of TCM may offer some financial and ethical benefits.

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Background

According to the proposition of an international committee meeting in Rome in 1991, the term "dyspepsia" refers to pain or discomfort centered in the upper abdomen\(^1\), while discomfort refers to a subjective negative (or aversive) feeling, such as early satiety, fullness, bloating and nausea (the so-called Rome criteria). In Rome I and Rome II reports\(^2-3\), functional dyspepsia (FD) is defined as a persistent or recurrent dyspepsia for at least 12 weeks in the preceding 12 months, if there is no evidence for organic disease (including upper endoscopy) that could cause the symptoms. An epidemiological survey of western countries showed that the prevalence of FD ranged from 11.5% to 14.7%\(^4\). It is also a common clinical condition
in China, and the report on the incidence of FD in citizens of Tianjin, China, revealed that the proportion of patients with FD reached 23.29% of the total population.5

In western medicine, the treatment of FD remains a major unsolved problem in gastroenterology, and this is a discouraging, unsatisfactory situation for treating physicians.

In traditional Chinese medicine (TCM), FD is considered nearly equivalent to the TCM term “stuffiness and fullness” 6, which is divided into different syndromes according to different clinical symptoms and signs. The basic syndromes include liver-stomach disharmony syndrome (qi-stagnation syndrome), fluid and food retention syndrome, dampness-heat of spleen and stomach syndrome, spleen-stomach weakness
syndrome (spleen-deficiency syndrome), and cold and heat in complexity syndrome. It should be noted that in clinical practice, qi-stagnation syndrome and spleen-deficiency syndrome often come together, which is known as the spleen-deficiency and qi-stagnation syndrome. As the most common syndrome, FD of spleen-deficiency and qi-stagnation syndrome can be treated by Chinese traditional patent medicine - two kinds of Zhizhu pills. Both of them are made from Rhizoma Atractylodis Macrocephalae (stir-baked) and Fructus Aurantii Immaturus (immature orange fruit, stir-baked), while the primary difference in ingredients is that one contains immature orange fruit of Citrus aurantium L.(IFCA) and the other contains that of Citrus sinensis Osbeck (IFCS). In
clinical practice, both Zhizhu pills have been considered to be effective in the treatment of functional dyspepsia (FD) of spleen-deficiency and qi-stagnation syndrome. The trial’s objective is to compare the effect of two kinds of Zhizhu pills on the changes in symptoms in patients with FD of spleen-deficiency and qi-stagnation syndrome.

Methods

Trial design

A randomized, group sequential, double-blinded, multicenter trial was conducted in patients with FD of spleen-deficiency and qi-stagnation syndrome at 3 hospitals in Beijing between June 2003 and May 2005.

Participants
Based on the Rome-II criteria and the Guiding principle for clinical research on new drugs of traditional Chinese medicine (trial implementation) 6, patients with FD of spleen-deficiency and qi-stagnation syndrome were enrolled in the study. The spleen-deficiency and qi-stagnation syndrome is defined as having the main symptoms and at least two of the accompanying symptoms, as well as pale tongue with whitish tongue coating and deep and thready pulse. The main symptoms include epigastric stuffiness and fullness, and asthenia, while the accompanying symptoms include epigastric stuffiness and fullness aggravated after meal, epigastric pain, decreased appetite, belching and acid regurgitation, fullness and discomfort in chest and hypochondrium, nausea and vomiting.
and constipation or loose stool. Other inclusion criteria included TCM syndrome integral $\geq 8$, aged 18 to 65 years old, and able and willing to provide a signed and dated informed consent form.

Patients who had gastric ulcer or duodenal ulcer revealed by upper gastrointestinal endoscopy, gastroesophageal reflux disease with typical symptoms like heartburn or acid regurgitation, or any malignant diseases were excluded from this study. Other exclusion criteria included pregnant or breast feeding women as well as patients with serious hepatic, cardiovascular, renal, or hematological diseases. Patients with a known history of hypersensitivity to Zhizhu pills were also excluded.
Interventions

Both kinds of Zhizhu pills (Approval No. granted by State Food and Drug Administration of China (SFDA): 00406105), with a same instruction on usage and dosage, were provided by the experimental pharmaceutical factory, a subsidiary to China Academy of Chinese Medical Sciences (CACMS). The pills should be taken 6g orally each time, 3 times a day after meals, for 4 weeks.

In addition to the above treatment, patients should not receive any concomitant medications associated with the treatment of this disease, and were also required to stop taking such drugs at least 1 week before their study entry, which include but not limited to anti-cholinergic drugs, antispasmodic agents,
emetic agents, H$_2$ receptor antagonists, and any other gastric motility drugs. Moreover, patients were also asked to stop smoking, drinking alcohol or tea throughout the trial.

Outcomes

Primary outcomes

We assessed each patient’s symptoms before and after treatment by means of a rating scale (See appendix 1), which was completed by the treating physicians when they interviewed their patients before and after treatment (at baseline and Week 4). The rating scale consisted of 11 items (2 for the main symptoms, 7 for the accompanying symptoms and 2 for tongue and pulse) with 2 (yes or no) or 4 options (absent, mild, moderate or severe) for each item. Each option was represented by
a fixed score, the higher the score, the more severe the symptom, and vice versa. The total score of the rating scale was called syndrome integral.

Based on the efficacy standards for patients with FD of spleen-deficiency and qi-stagnation syndrome recommended in the "Guiding principle for clinical research on new drugs of traditional Chinese medicine (trial implementation)\textsuperscript{6}", the overall efficacy was judged as clinical recovery (the main symptoms and signs disappeared or almost disappeared, and therapeutic index $\geq 95\%$, which was defined as $(1 - \text{the syndrome integral after-treatment}/ \text{the syndrome integral before-treatment}) \times 100\%$, significant improvement (the main symptoms and signs improved significantly, and $70\% \leq$ therapeutic
index < 95%), somewhat improvement (the main symptoms and signs somewhat improved, and 30% ≤ therapeutic index < 70%), no change (therapeutic index < 30%), somewhat worsening, or significant worsening. For statistical convenience, the overall efficacy was categorized into 2 groups in this study. Clinical recovery and significant improvement were judged as cured and significantly improved, and can be expressed as the cure-markedly effective rate, which was the primary endpoint of this trial; while somewhat improvement, no change, somewhat worsening and significant worsening were judged as not significantly improved.

Secondary outcome

The secondary outcome, gastric emptying
rate, was affected by the group sequential stopping rules. Therefore, a conventional analysis of secondary endpoints was not planned in this study.

**Randomisation and Allocation**

A central-randomization scheme was performed in the study. The trial organizer generated and conserved the random allocation sequence, and Participants were randomly allocated into two groups (IFCA group and IFCS group) in a 1:1 ratio.

**Blinding**

This study was a double-blind clinical trial, with the patient, the treating physician, the statistician, the monitor and any other site personnel being unaware of group allocation. Efforts to maintain blinding included identical
appearance, packaging and labeling of the two kinds of Zhizhu pills.

Unblinding should be done by the statisticians when the data collection process was completed or treating physicians when serious adverse events occurred.

**Sample size**

Before the trial was initiated, the sample size was calculated according to the following hypotheses: based on the results of our previous study, we anticipated that the cure-markedly effective rate of the two kinds of Zhizhu pills in the treatment of FD of spleen-deficiency and qi-stagnation syndrome was 40% (IFCS) and 55% (IFCA), respectively, and the type I and II error rates were chosen at their usual values of 0.05.
Under these conditions, the required sample size with the use of a single-stage design and a one-sided test would have been 472 in total. In order to save time and money, we designed this study with the triangular test (TT).

**Statistical methods**

Sequential analysis was performed on the primary outcome. Interim analyses were planned approximately after every 50 patients completed their 4-week treatment.

In brief, in the triangular test\(^8-10\), two straight lines, called the boundaries of the test, delineate a continuation region (between these two lines), and the equations of the boundaries are \( U: Z=6.569+0.1515V \) for the upper boundary and \( L: Z=-6.569+0.4546V \) for the lower boundary.
The consecutive points \((V, Z)\), obtained from the data collected at each analysis, define a sample path from the left to the right of the continuation region. When the sample path crosses one of the boundaries, the study is stopped and the conclusion is obtained: crossing the lower boundary causes the inefficacy hypothesis not to be rejected, whereas crossing the upper boundary causes the inefficacy hypothesis to be rejected.

A conventional statistical analysis was also performed to compare the baseline data between the two groups. The student t test or Mann-Whitney and Wilcoxon signed-rank tests was applied according to different conditions. A p-value less than 0.05 (two-tailed) was considered significant.
Results

Study population
A total of 163 participants were included in the study, of whom 3 (1 in the IFCA group and 2 in the IFCS group) dropped out prematurely for personal reasons [微软用户1]. The remaining 160 participants were evaluable in the statistical analysis. All the results presented refer to this population.

Participant flow
The flow of the participants in the study is summarized in Figure I.

Baseline data
Table I shows the general characteristics of evaluable population. No significant differences were identified between the two
primary outcome (sequential analysis)

Table II shows the cumulated numbers of evaluable population at each step and the corresponding values of the two statistics V and Z computed for each sequential analysis. Fig II represents the triangular test and the corresponding sample path.

Three interim analyses were done after 62, 116, and 160 patients had completed their 4-week treatment, respectively. At the third interim analysis, the sample path crossed the upper boundary and the trial was stopped. In
the evaluable population, the cure-markedly effective rates were 67% and 45% for Zhizhu pills (containing IFCA) and Zhizhu pills (containing IFCS), respectively, and the difference was statistically significant (p=0.005).

Adverse events and tolerance

Throughout the trial, the two kinds of Zhizhu pills were generally safe and well-tolerated by all patients. No major adverse events were observed in the two groups.

Discussion

The pathophysiology of FD has been under investigation during the past two decades. Multiple mechanisms such as abnormal gastric emptying, visceral hypersensitivity, impaired
gastric accommodation, and central nervous system factors are likely involved. So the possibilities of pharmacological therapy for FD are still limited, however, experience of using prokinetics, tricyclic antidepressants, selective serotonin-reuptake inhibitors (SSRIs), proton-pump inhibitors (PPIs), and several alternative techniques (such as Acupuncture, Multicomponent herbal preparations and hypnotherapy) has been accumulated\textsuperscript{11}. Although the efficacy of some established treatments (e.g., antisecretory agents or prokinetics) has been proven in placebo-controlled trials, the majority of controlled clinical trials have shown only minor advantages of these drugs compared with placebo\textsuperscript{12,13}. It is likely that patients with FD often present to general practitioners when
their symptoms have become worse. Therefore, spontaneous improvement may partially explain at least part of the placebo response\textsuperscript{14}.

Various herbal medications are used in many countries for the treatment of FD. While some clinicians believe that clinical experience appears to support the use of these remedies, randomized controlled studies supporting the efficacy of these treatments have been lacking in the past decades. Recently, several well-designed placebo-controlled clinical trials have provided evidence for the efficacy of herbal preparations used in the treatment of dyspepsia\textsuperscript{15}.

Based on the concept of TCM, two kinds of Zhizhu pills can be used to treat FD of spleen-deficiency and qi-stagnation syndrome.
But the effect of most Chinese traditional patent medicine is influenced by many factors, which may lead to unstable efficacy in clinical practice. These factors include the differences in the variety of Chinese medicinal herbs, growing areas, harvesting seasons and the processing and preparing of these herbs, of which the variety is a most influential factor. Thus, it is of great importance to make a comparison of a same prescription made from different varieties of medicinal herbs as so to further improve its clinical efficacy.

The purpose of this study is to compare the effect of the two kinds of Zhizhu pills on the changes in symptoms in patients with FD of spleen-deficiency and qi-stagnation syndrome. Pharmacological experiments have indicated that the bioavailability of Zhizhu pills
containing IFCA is superior to those containing IFCS, because flavonoid compounds such as naringin and hesperidin, which can be converted to naringenin and hesperitin in the body and affect the gastrointestinal motility, are part of the substance basis for the efficacy of Zhizhu pills in treating abdominal distension, and the pharmacokinetic parameters after the administration of Zhizhu pills have shown that the sum AUC of naringenin and hesperitin of the former is much bigger than that of the latter. The efficacy of the former is superior to the latter, which is consistent with the findings of our study.

As for the methodological aspects of our study, if the classic single-stage design (SSD) was applied, the sample size needed would
have been 472 patients. But given the difficulties encountered in recruitment of eligible patients, it is most likely that it would not have been possible, in only three centers, to bring this study to its end within three years. Moreover, since the primary outcome could be obtained relatively quickly when compared with the recruitment rate, this trial was planned with a group sequential design.

For this trial, triangular test (TT) was considered to be appropriate, is a special case of a class of sequential designs by Anderson this particular test has been advocated by Whitehead and is based on two test statistics. Veronique et. al indicated that the TT, of the sequential tests, seems to be the most appealing with regard to statistical properties: type I and II errors are correctly
maintained to their desired values, and it offers a substantial decrease in sample size compared not only with SSD but also with most of the other tests, whatever the frequency of the analyses.

In group sequential designs, the sample size is a random variable whose distribution depends on the true treatment difference and on the stopping rule used. Stimulation studies indicated that the use of a TT-based sequential analysis design brought about a 50% reduction of the average sample needed, when compared to the fixed-sample design. In this study, using the TT-based sequential analysis, we saved 66% of the patient sample size. Moreover, inclusion in the study could be stopped shortly after 20 months from the inclusion of the first patient. This constituted a substantial gain in
time. This makes the test not only economical but also in line with ethical requirements and could make a case for wider use of group sequential designs in TCM clinical trials.

The major advantage of group sequential designs lies in the early stopping. However, the decision to stop a study early involves ethical, administrative, economic and not just statistical consideration. Statistics should be considered as a tool, which could trigger the procedure to stop a trial but statistics cannot supplant a trial safety committee.

The statistical hypotheses made in the planning phase were drawn from our previous experience. At the third analysis, the upper boundary was crossed, allowing the trial to be stopped. Actually, the cure-markedly effective rate of Zhizhu pills containing IFCA was 67%
(higher than the 55% expected during the planning phase), and that of Zhizhu pills containing IFCS was 45% (about equal to that observed in our pre-clinical study). The variability of the criterion was 22%, which was higher than that expected during the planning phase. There are some discrepancies in the literature about the cure-markedly effective rate of Zhizhu pills in treatment of FD. In our opinion, differences in the diagnosis of the syndrome and the definition of the cure-markedly effective rate may be possible explanations.

Our study inevitably has its limitations. The trial, ended in May 2005, adopted the Rome II criteria, which was modified in 2006 (the Rome III criteria). The Rome I and II criteria did not account for meal-related
symptoms and this was the fundamental change in Rome III criteria\textsuperscript{21}. The other limitation of the present study is the lack of a treatment arm using placebo. In order to further investigate the efficacy of Zhizhu pills containing IFCA in the treatment of FD, a randomized placebo-controlled clinical trial is required.

**Conclusions**

Zhizhu pills containing IFCA might have better efficacy than Zhizhu pills containing IFCS in the treatment of FD of spleen-deficiency and qi-stagnation syndrome. And the triangular test has been successfully applied to this study, and offered some financial and ethical benefits. Thus, for future TCM clinical trials, a group sequential design
should remain a strong consideration.

Competing interests

None declared.

Authors' contributions

Hong-xin Cao, Zhong Wang, Zhi-wei Jing, Xu-dong Tang, Xin-yue Wang, Sheng-sheng Zhang and Hongli Wu contributed to the conception and design of the study. Zhong Wang and Hongli Wu drafted the manuscript. All authors contributed to the further writing of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 - the general characteristics of evaluable population

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<th>IFCS (n=78)</th>
<th>IFCA (n=82)</th>
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<td>Age (years)</td>
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<td>Course of disease (months) before-treatment</td>
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Table 2 - A summary of three group data in a group sequential trial

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