Acupuncture for patients with functional dyspepsia: Study protocol of a randomized controlled trial

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<td>Complete List of Authors:</td>
<td>Zheng, Hui; Chengdu University of Traditional Chinese Medicine, The 3rd Teaching Hospital Xu, Jing; Chengdu University of Traditional Chinese Medicine, The 3rd Teaching Hospital Li, Juan; Chengdu University of Traditional Chinese Medicine, The 3rd Teaching Hospital Li, Xiang; Chengdu University of Traditional Chinese Medicine, The 3rd Teaching Hospital Zhao, Ling; Chengdu University of Traditional Chinese Medicine, The 3rd Teaching Hospital Chang, Xiaorong; Hunan University of Traditional Chinese Medicine, Acupuncture &amp; Tuina Liu, Mi; Hunan University of Traditional Chinese Medicine, Acupuncture &amp; Tuina Gong, Biao; Chongqing Medical University, Traditional Chinese Medicine Li, Xuezhi; Chongqing Medical University, Traditional Chinese Medicine Liang, Fanrong; Chengdu University of Traditional Chinese Medicine, The 3rd Teaching Hospital</td>
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Acupuncture for patients with functional dyspepsia: Study protocol of a randomized controlled trial

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Running Title: Acupuncture to treat functional dyspepsia: study protocol of a RCT

Keywords: Acupuncture, functional dyspepsia, study protocol, randomized controlled trial

Word Count: 3849
Abstract

Objective: Whether acupuncture is efficacious for patients with functional dyspepsia is still controversial. So we designed a randomized controlled trial to settle the problem.

Design: We designed a multicenter, two-arm, sham-controlled clinical trial. 200 participants with functional dyspepsia will be randomly assigned to true acupuncture (TA) group and sham acupuncture (SA) group in a 1:1 ratio. Participants in TA group will receive acupuncture at points selected according to syndrome differentiation. Participants in sham acupuncture group will receive penetrations at sham points. Participants in both groups receive 20 sessions of electro-acupuncture in 4 weeks, 5 times continuously with a 2-days rest in a week. The primary outcome is the proportion of patients reporting absence of dyspeptic symptoms at 16 weeks after inclusion. The secondary outcome includes Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ), Chinese version of 36-Item Short Form Survey (SF-36), Chinese version of Nepean dyspepsia index (NDI), etc.

Discussion: The result of this trial is hopefully to be gained at August, 2014, which would possibly answer whether acupuncture is efficacious for FD patients.

Trials registration: ClinicalTrials.gov NCT01671670

Keywords: Acupuncture; functional dyspepsia; randomized controlled trial; protocol

ARTICLE SUMMARY

Article focus
- Is acupuncture efficacious for patients with functional dyspepsia?
- How will the acupuncture effect change over time?

Key messages
- This study will increase the knowledge about the efficacy of acupuncture for functional dyspepsia.
- The primary outcome is proportion of the proportion of patients reporting absence of dyspeptic symptoms at 16 weeks after inclusion.
- Outcome measurements will be assessed at 0, 4, 8, 12, 16, 20, 24 weeks after inclusion.

Strengths and limitations of this study
- This trial is the first multicenter randomized controlled trial using individualized acupuncture protocol to test the efficacy of acupuncture for functional dyspepsia.
- The first trial focuses on changes of acupuncture effect on functional dyspepsia over time.
- Blinding the care providers is still not applied in this trial, since it is merely impossible to blind acupuncturists.

INTRODUCTION

Functional dyspepsia (FD) is a common gastroduodenal disorder without structural
lesion, which is claimed to affect 20% to 25% of the population in western countries[1]. In Asia, the prevalence of FD is reported to be 5.3% in the adult population of Taiwan [2], while it bothers 24% of the school children in Thailand[3]. Overall, the prevalence of FD range from 8% to 23 in Asia[4]. FD is closely related to low quality of life, psychological disturbances, etc. [5 6], leading to excess healthcare services and costs as well as low work productivity[7 8].

Reasonable treatment approaches based on current evidence are a daily proton pump inhibitor in FD patients with H. pylori-negative, a tricyclic antidepressant, an anti-nociceptive agent, a prokinetic agent, or some form of complementary and alternative medications[9-13]. However, evidence supporting these approaches is still limited [9-13]. Acupuncture, as one of the most popular complementary therapies, is widely used for gastrointestinal diseases in China. Our previous study showed that acupuncture is effective and efficacious for patients with FD[14]. However, in this trial, fixed acupuncture protocols were used, which is not quite the same as conventional acupuncture practice, in which individualized acupuncture protocols are commonly applied. Moreover, we found a trend that effect of acupuncture seems to last for months, but we are not sure how long the effect will last because of short follow-up period. Since FD is a chronic disorder with exacerbations and remissions, it is important to find out the answers[15]. Therefore, we conducted another randomized controlled trial aiming at: first, confirming whether individualized acupuncture treatment is efficacious for FD patients; second, observing and analyzing the change of acupuncture effect over time.

METHODS

Overview of the study design

We designed a multicenter, two-arm, sham-controlled study, in which the interventions will be performed under ideal circumstances. Therefore, this trial will be carried out in academic settings, which were originally planned to be: The first affiliated hospital of Chengdu University of TCM, the first affiliated hospital of hunan university of TCM and Chongqing medical university.

If the participants meet the inclusion criteria, the acupuncturists in each center will send a phone text or an email (including name, age, gender of a participant) to require central randomization, which is managed by a third party (the Brightech Magnsoft Data Services Company). The acupuncturists will receive a text containing the group assignment, randomization sequence and project number, several minutes after sending out the requirement for randomization.

Before baseline, participants will be screened in the above mentioned research centers. After screening process, the FD patients will be asked if they are willing to participate in this trial; if not, they will be given conventional treatment according to guidelines[16], and will be assessed using the same outcome measurements through telephone follow-up.

After randomization, the participants will be either assigned to acupuncture group or sham acupuncture group. And they will go through a total research period of 25 weeks, including 1 week baseline, 4 weeks of acupuncture treatment, and 20 weeks of
follow-up phase. Included participants will receive 20 sessions of acupuncture treatment in 4 weeks, 5 times continuously with a 2-days rest in a week. Outcome measurements will be assessed at 0, 4, 8, 12, 16, 20, 24 weeks after inclusion, with outcome assessors blinded to the group assignment. The study protocol has been approved by local institutional review boards and ethics committees (From April to August, 2012). It follows the principle of CONSORT and STRICTA statements as well as the Declaration of Helsinki (Sixth revision, 2008).

**Participant eligibility**

We consider to recruit the FD patients diagnosed on the basis of the Rome III criteria[17]. And we choose to include FD patients classified as postprandial distress syndrome (PDS), ruling out those classified as epigastric pain syndrome (EPS). According to our previous research, 70% of the FD patients were classified as PDS, which is a larger suffered population than EPS. Additionally, to ensure an ideal circumstance for this efficacy trial, we will include PDS patients only, although it will partially narrow the generality of the results. Doctors responsible for screening patients will be gathered and trained using the ROME III criteria in each center. Then a pre-trial screening will be performed, with all the doctors screening a group of participants. Finally, a comparison of the screening results among different doctors will be made, and homogeneity should be achieved. Details of the inclusion and exclusion criteria of the participants are listed in table 1.

After a diagnosis of FD was established, gastrointestinal symptoms and the quality of life will be evaluated to determine the patient’s baseline status. Then the participants will go through randomization process.

**Recruitment strategies and Randomization**

We will recruit participants through 3 methods: first, call the participants who join our previous study, if they are interested in coming for this study; second, specific doctors received training will screen and recruit participants in outpatient clinics in each center; third, advertisement and recruitment notice would be put in newspaper, local media, health promotion manual, etc.

If patients are eligible, the doctor will ask if they are interested in participating. If so, the doctor will refer them to a research coordinator, who will introduce the aim and the methods of this study and ask the participants to sign the informed consent.

Participants who completed informed consents will be introduced to the outcome assessor for baseline evaluation, and then be referred to an acupuncturist to apply for randomization.

Central randomization is used in this study. The acupuncturists are trained to apply for randomization through text messages, online website, or telephone application. Qualified acupuncturists will have their cell phone number registered in the randomization center (located in Brightech Magnsoft Data Services Company), with the permission to send application for randomization of participants. Randomization is automatically performed in a real time mode by the central computer. Subjects are randomized in blocks of varying size within each site, stratified by age and duration.
of FD.

**Blinding**
Participants will be blinded to group assignment in this trial. We will inform them that there are two types of acupuncture treatment provided for FD in this trial, both of which are used in clinical practice. And we will also notify that one of the acupuncture treatment is a traditional style, while the other is a style designed according to rationale of western medicine. Acupuncturists (care providers) will not be blinded in this trial, because it is merely impossible. Acupuncturists could easily guess the group assignment, through recognizing the function of the acupuncture points, which we should clearly tell them. So in this trial, we ask the acupuncturists give the same stimulation method to acupuncture points and sham acupuncture points, to control the risk of performance bias.

**Study groups**

**Acupuncture arm**

In the planning phase, we formulated the acupuncture protocol in 3 steps: First, through a systematic review of published studies, text books and ancient literatures, we decided the syndrome differentiation protocol for acupuncture treatment of FD (excess syndrome and deficiency syndrome), as well as a range of acupuncture points to manage the condition. Second, we held a face-to-face meeting to discuss the protocol and turn it into a standardized approach. Third, we send out questionnaires to acupuncturists across the country, asking whether this standardized protocol is commonly used in their clinical practice and suggestions for improvement. Fourth, a final version of the protocol was used in Phase I study, with 10 healthy subjects and 10 FD participants included, to test the safety, effect size and tolerance of the acupuncture treatment for the condition.

We choose Zusanli(ST36) and Neiguan(PC6) as basic acupuncture points, which will be needled in every participants. ST36 belongs to stomach meridian according to traditional acupuncture theories, which is believed to be one of the best acupuncture points specifically selected for gastrointestinal diseases. PC6 is frequently used for upper gastrointestinal conditions, such as nausea and vomiting associated with acute myocardial infarction[18], chemotherapy[19], hyperemesis gravidarum[20], etc. Regarding the FD patients manifest mainly as upper gastrointestinal discomfort, ST36 and PC6 were chosen as basic points.

Additionally, there are two groups of optional points, which would alternatively selected according to syndrome differentiation. First group, if the participants are differentiated as excess syndrome, Taichong (TR3) and Neiting (ST2) will be selected. Second group, if differentiated as difficiency syndrome, Gongsun (SP4) and Yinlingquan (SP9) will be selected. The excess and deficiency syndromes are defined according to dyspepsia session in *Guidance of clinical research of traditional Chinese medicine* published by State Food and Drug Administration (SFDA) in China[21]. The excess syndrome mainly refers to excess of liver Qi and stomach fire , while the deficiency syndrome mainly refer to deficiency of spleen and stomach Qi. So the TR3
(belongs to liver meridian) and ST2 (belongs to stomach meridian) fit for the excess syndrome, whereas SP4 and SP9 (both belong to spleen meridian) are selected for the deficiency syndrome. Therefore, selection of acupuncture points consists of two basic points and two optional points, which is similar to conventional acupuncture practice. Each point is puncture using a filiform needle (25-40 mm in length and 0.25 mm in diameter), and achieving Deqi sensation (refers to a sensation of numbness, distension, or electrical tingling at the needle site which might radiate along the corresponding meridian) is needed. Then an auxiliary needle (13 mm in length and 0.18 mm in diameter) will be puncture 2 mm lateral to the first needle, to a depth of 2 mm without arrival of Deqi. Electro-acupuncture will be used at every point with one electrode connected to the filiform needle and the other to the auxiliary needle. This method limits electrical stimulation on points, rather than going across human body surface to cause performance bias. Electrical stimulation will last for 30 minutes in each acupuncture session. A total of 20 acupuncture session will be given during 4 weeks, once daily for 5 days with 2-days rest in a week.

Sham acupuncture arm
The same sham points as used in our previous study will be adopted in this trial, and details of the location the points are described elsewhere [22]. Participants in sham control group will also receive the same electrical stimulation, and the same duration of treatments as the participants received in the acupuncture group. The intervention of this trial is rigorous acupuncture schedule, to ensure the compliance of acupuncturists to the schedule, we ask them to take a pre-trial training and a entrance exam for this trial. Only the qualified acupuncturists will be admitted to this trial, and we will monitor the compliance of the staff to the protocol every month.

Outcome measurements
The primary outcome
The primary outcome of this study was first targeted through a review of previous studies, then was selected based on consensus from researchers in the territory of functional gastrointestinal disorders, dyspepsia patients and physicians. The proportion of patients reporting complete absence of dyspeptic symptoms is considered to be the most important outcome measurement [23]. So, the participants in this trial will undergo a self-assessment of global relief of the dyspepsia symptoms, with a five grade scale: absence of dyspeptic symptoms, significantly improved, moderately improved, not changed and deteriorated. The primary outcome is the proportion of patients reporting absence of dyspeptic symptoms at 16 weeks after inclusion, at which the participants are supposed to achieve maximum relief of the dyspeptic symptoms according to our previous study [14].

Secondary outcomes
Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ) [24] is a five question instrument for assessing the dyspeptic symptoms. Five symptoms epigastric pain,
postprandial distention, indigestion, heartburn and nausea will be graded the severity on a 5-point Likert scale from very mild to very severe: no symptoms (0 point), mild symptoms without influence of regular work (1 point), mild symptoms with influence of regular work (2 points), moderate symptoms (3 points), sever symptoms (4 points) and extremely sever symptoms (5 points). The SF-LDQ is a validated and reliable tool to assess the dyspeptic symptoms of FD patients [24 25], with higher scores indicating worse dyspeptic outcomes.

A Chinese version of Nepean dyspepsia index (NDI) will be used in this trial to assess the disease-specific quality of life. This scale was validated and confirmed to be a reliable tool for the Chinese population in our previous study[26]. The NDI scale consists of 25 items, with a total score ranging from 0 to 99. Higher scores indicate poorer quality of life. Each of the items is a 5-point likert scale that scores the severity of symptoms from “not at all” to “extremely sever”. Moreover, the 25-item NDI measure the quality of life in four domains: interference (13 items), know/control (7 items), eat/drink (3 items) and sleep/disturb (2 items). Finally, a Chinese version of 36-Item Short Form Survey (SF-36) will be used to assess the overall health status of the included participants.

Time points of outcome measurement

We choose the time points of assessments under the consideration of the following aims: first, to capture the key milestones in the management of FD patients with acupuncture; second, to see how the acupuncture effect changes over time. According to our previous study[14], a duration of 4 weeks is reasonable and reliable to assess the change of dyspeptic symptoms of FD patients. Therefore, we follow up the participants at the time points of 4, 8, 12, 16, 20 and 24 weeks after inclusion. At baseline, the participants will be given the physical examination, outcome assessments and regular tests. The regular tests include routine blood, urine and stool tests, liver and kidney function test, gastroscopy, ultrasonic examination in the upper abdomen and pregnancy test. The pregnancy test is to exclude the risk of acupuncture may bring to the pregnant women, who don’t know the information. An overview of measurements at different time points is presented in table 2.

Assessment of adverse events

According to our previous study, acupuncture may cause several adverse events[27]. So we will record adverse events caused by acupuncture and the reasons for these events during treatment and follow-up phases. These adverse events include bleeding, hematoma, fainting, serious pain, and local infection, etc. Number of adverse events will be calculated for each group.

Sample size calculation

Based on our previous study[14], after receiving 20 sessions of acupuncture treatments, 46.1% of the FD patients with PDS responded to true acupuncture, whereas 14.1% of the patients responded to sham acupuncture, so a difference of 32% was observed. In this trial, different acupuncture protocol were used, so
conservatively we expected a responder rate of 50% in the acupuncture group, and 25% in the sham acupuncture group, to detect a difference of 25% between true and sham acupuncture. Considering a two sided significant level of 5% and power of 90%, 85 participants per group will be needed, calculated by Fisher’s exact test in G*Power(version 3.1.5). To minimized attrition bias, a dropout rate of 15% was considered, making it necessary to include at least 100 participants per group.

**Statistical analysis**

The primary analysis will be a comparison of the proportion of patients reporting absence of dyspeptic symptoms between acupuncture and sham acupuncture at 16 weeks after inclusion (comparison of the primary endpoint). We will use chi-square test to detect the difference between groups, with a significant level of 0.05. To analyze how the primary outcome changes overtime after acupuncture treatment, we will use the model of generalized estimating equations (GEE) with adjustments for clinical centers, baseline assessments of dyspeptic symptoms, duration of the FD symptoms (continuous value calculated by months) and age (continuous value calculated by years). The secondary analysis will be performed to assess the changes of SF-LDQ, NDI scores and SF-36 from baseline to 24 weeks after inclusion, we use linear mixed models adjusted for clinical sites and baseline scores. The rates of adverse events will be compared between groups. We perform the above analysis using the intention to treat method. Missing values will be handled using multiple-imputation method, on the assumption that values at each time point follow a specific distribution calculated by computer software R project (version 2.15.3, http://www.R-project.org/). We will also perform a complete-case analysis without imputation of missing values, to find out if the results are consistent with the above analysis. The data will be analyzed using SPSS 20.0 (IBM SPSS Statistics, IBM Corp, Somers, NY).

**Data management**

All data are managed by the data coordinating center in a third party, the Brightech Magnsoft Data Services Company. This company developed a password-protected website for this trial, which is designed with the function of randomization, data entry of the research data (including information of screening and eligibility, outcome assessments, adverse events and quality control) and overview of the process of this trial. All data will be backed up in different network drives located both in Chengdu and Beijing.

**DISCUSSION**

We describe the rationale, design and analytic methods of a randomized controlled trial comparing acupuncture and sham acupuncture for FD patients, at different time points. Hopefully, convincing evidence will be found to clarify whether acupuncture is efficacious for this condition.

Before this trial, we have conducted a multicenter randomized trial to assess the effect of acupuncture for FD patients[14]. In the trial, 712 FD patients were randomly
assigned to 6 groups, 4 acupuncture groups versus one sham acupuncture group and a drug (Itopride) control group. The results showed that acupuncture at specific points of stomach meridian is superior over acupuncture at points of other meridians and sham points, as well as oral administration of Itopride. Results of this trial, for the first time, confirmed that acupuncture is superior to Itopride, which was reported to be an efficacious treatment for FD patients in the year 2006, couple of months before planning and carrying out of the trial [28]. However, Itopride was then reported to be a treatment no better than placebo in a larger sample phase III trial [23], which makes our conclusion that acupuncture is effective for FD still inconclusive. Moreover, although the results showed that acupuncture is superior over sham, it is not conclusive either. A design of 4 acupuncture arms versus 1 sham acupuncture arm was used, indicating that there may be a chance that the results are false positive, because of multiple comparisons among groups. In outcome assessments, we used scores of symptom index of dyspepsia as primary outcome, which is a scale without going through validation and reliability test, but is commonly used in China. Thus the results are not as reliable as we expected, because of a weak primary outcome assessment.

An interesting result of that trial showed that acupuncture effect seems to last at least 3 months after 20 sessions of acupuncture treatment. However, we are not sure for how long this effect last, since we followed up the participants for only 16 weeks. This long lasting effect may be an advantage of acupuncture treatment, which therefore justify a new trial with a much longer follow-up period.

Combining the above facts, we found that the existing evidence is not enough to draw a firm conclusion on the effectiveness and efficacy of acupuncture for FD. So we hypothesized that: Acupuncture is superior over sham acupuncture (acupuncture is efficacious) in relieving dyspeptic symptoms of FD patients. To test these hypotheses, we design this trial, with a control group of sham acupuncture, to reduce the likelihood of reaching a false positive outcome caused by multiple comparisons. And we used proportion of patients reporting absence of dyspeptic symptoms as primary outcome, to reach a more reliable conclusion compared to our previous trial.

Moreover, we planned a follow-up period of 24 weeks, to fully understand this long lasting effect of acupuncture for relieving dyspeptic symptoms. In our previous trial, we included FD patients classified as postprandial distress syndrome (PDS) or epigastric pain syndrome (EPS). In this trial, we planned to recruit participants with PDS only, because a narrow and specific population will be more appropriate in a trial using efficacy design.

A major issue in designing this trial is how to distinguish the treatment effect of acupuncture from effect brought by other factors, like improvement to a more healthy living style, administration of drugs to improve gastrointestinal function, etc. To minimize the bias contributed by these factors, we considered the following solutions: first, we give the participants an education of healthy living style in both groups. The participants will receive a handbook of preventing FD, including health style of diet, appropriate exercise to improve gastrointestinal function, etc.; second, we ask the participants not to take drugs unless there is a urgent need, e.g., dyspeptic symptoms
are not relieved after 10 session of acupuncture treatment, or dyspeptic symptoms significantly lower the quality of life; third, we revise our acupuncture protocols several times according to the literature review and expert experience, to ensure the effectiveness of the experimental arm.

Another major issue is how to collect data in different time points correctly. 5 follow up time points across 20 weeks are defined in this trial. So we may get inaccurate parameters during outcome assessments in such a long follow up period. To avoid bias from outcome assessment, we firstly train the outcome assessors to use telephone interview, email contact to collect follow-up data; secondly we ask the assessors to help the participants to fully understand the follow-up questions, which we try our best to minimize the number of questions, to avoid frustration of participants in responding; thirdly, we promise the participants with 5 more acupuncture treatments if they respond to the whole follow-up interview.

CONCLUSION
This article presents a design and protocol of acupuncture for patients with FD, to clarify the efficacy of acupuncture for this condition. The results are expected to give answers to the following questions: first, whether acupuncture is superior to sham acupuncture; second, whether acupuncture effect last longer than the sham.

Contributors
HZ, JX, JL, XL, LZ, XrC, BG and FrL participated in the design of the trial, in writing the data analysis plan, and in drafting the manuscript. JL, ML and XzL collect the information needed for the performance of this trial in each center. All the authors discussed, read, revised the manuscript, and finally approved for publication of this protocol.

Funding
This trial was financially supported by the National Basic Research Program of China “973 Program” (No. 2012CB518501).

Ethics approval
The study protocol has been approved by institutional review boards and ethics committees of the first affiliated hospital of Chengdu University of TCM, the first affiliated hospital of hunan university of TCM and Chongqing medical university, respectively (From April to August, 2012).

Competing interests
None.

Acknowledgements
We appreciate the help from the staff of Brighttech Magnsoft Data Services Company, who contribute a lot in the design and statistical analysis plan of this trial. And we acknowledge the help and contributions from acupuncturists, experts, investigators in each center. We also acknowledge the contributions from FD patients participating in this trial.

References


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Table 1 Inclusion and exclusion criteria for this trial

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<th>Rationale</th>
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<td>Age 18 to 65</td>
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<td>Without intake of any prokinetic agents in 15 days, and not involved in any clinical trials</td>
<td>To avoid bias from the treatment effect of medication.</td>
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<td>Sign the inform consent</td>
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Exclusion criteria

| Psychological, unconscious, unable to cooperate in outcome assessment | To ensure the results of outcome measurements are accurate.                                    |
| Accompanying aggressive tumor, cachexia, infectious, bleeding diseases, etc. | Aggressive and serious diseases require additional drug treatment, thus bringing additional confounding factors. |
| Accompanying serious diseases of cardiovascular, liver, nephritic, digestive, hematopoietic system, etc. | Whether acupuncture is safe for pregnant women or women who plan to be is still controversial, so it is better to rule out this population. |
| Women in pregnant, or intent to, or in breast feeding period during 6 months |                                                                                                 |

Table 2 Measurements at different time points

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Abstract

Objective: Whether acupuncture is efficacious for patients with functional dyspepsia is still controversial. So we designed a randomized controlled trial to settle the problem.

Design: We designed a multicenter, two-arm, sham-controlled clinical trial. 200 participants with functional dyspepsia will be randomly assigned to true acupuncture (TA) group and sham acupuncture (SA) group in a 1:1 ratio. Participants in TA group will receive acupuncture at points selected according to syndrome differentiation. Participants in sham acupuncture group will receive penetrations at sham points. Participants in both groups receive 20 sessions of electro-acupuncture in 4 weeks, 5 times continuously with a 2-days rest in a week. The primary outcome is the proportion of patients reporting absence of dyspeptic symptoms at 16 weeks after inclusion. The secondary outcome includes Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ), Chinese version of 36-Item Short Form Survey (SF-36), Chinese version of Nepean dyspepsia index (NDI), etc.

Ethics and dissemination: The study protocol has been approved by institutional review boards and ethics committees of the first affiliated hospital of Chengdu University of TCM, the first affiliated hospital of hunan university of TCM and Chongqing medical university, respectively (From April to August, 2012). The results of this trial will be disseminated in a peer-reviewed journal and presented at international congresses.

Discussion: The result of this trial is hopefully to be gained at August, 2014, which would possibly answer whether acupuncture is efficacious for FD patients.

Trials registration: ClinicalTrials.gov NCT01671670

Keywords: Acupuncture; functional dyspepsia; randomized controlled trial; protocol

ARTICLE SUMMARY

Article focus

- Is acupuncture efficacious for patients with functional dyspepsia?
- How will the acupuncture effect change over time?

Key messages

- This study will increase the knowledge about the efficacy of acupuncture for functional dyspepsia.
- The primary outcome is proportion of the proportion of patients reporting absence of dyspeptic symptoms at 16 weeks after inclusion.
- Outcome measurements will be assessed at 0, 4, 8, 12, 16, 20, 24 weeks after inclusion.

Strengths and limitations of this study

- This trial is the first multicenter randomized controlled trial using individualized acupuncture protocol to test the efficacy of acupuncture for functional dyspepsia.
- The first trial focuses on changes of acupuncture effect on functional dyspepsia over time.
Blinding the care providers is still not applied in this trial, since it is merely impossible to blind acupuncturists.

INTRODUCTION

Functional dyspepsia (FD) is a common gastroduodenal disorder without structural lesion, which is claimed to affect 20% to 25% of the population in western countries[1]. In Asia, the prevalence of FD is reported to be 5.3% in the adult population of Taiwan [2], while it bothers 24% of the school children in Thailand[3]. Overall, the prevalence of FD range from 8% to 23 in Asia[4]. FD is closely related to low quality of life, psychological disturbances, etc. [5 6], leading to excess healthcare services and costs as well as low work productivity[7 8].

Reasonable treatment approaches based on current evidence are a daily proton pump inhibitor in FD patients with H. pylori-negative, a tricyclic antidepressant, an anti-nociceptive agent, a prokinetic agent, or some form of complementary and alternative medications[9-13]. However, evidence supporting these approaches is still limited [9-13]. Acupuncture, as one of the most popular complementary therapies, is widely used for gastrointestinal diseases in China[14]. Our previous study showed acupuncture is effective and efficacious for patients with FD[15]. However, in this fixed acupuncture protocols were used, which is not quite the same as conventional acupuncture practice, in which individualized acupuncture protocols are commonly applied. Moreover, we found a trend that effect of acupuncture seems to last for but we are not sure how long the effect will last because of short follow-up period. Since FD is a chronic disorder with exacerbations and remissions, it is important to out the answers[16].

Therefore, we will conduct another randomized controlled trial aiming at: first, confirming whether individualized acupuncture treatment is efficacious for FD patients; second, observing and analyzing the change of acupuncture effect over time.

METHODS

Overview of the study design

We designed a multicenter, two-arm, sham-controlled study, in which the will be performed under ideal circumstances. Therefore, this trial will be carried out in academic settings, which were originally planned to be: The first affiliated hospital of Chengdu University of TCM, the first affiliated hospital of Hunan university of TCM and Chongqing medical university.

If the participants meet the inclusion criteria, the acupuncturists in each center will send a phone text or an email (including name, age, gender of a participant) to require central randomization, which is managed by a third party (the Brightech Magnsoft Data Services Company). The acupuncturists will receive a text containing the group assignment, randomization sequence and project number, several minutes after sending out the requirement for randomization.

Before baseline, participants will be screened in the above mentioned research centers. After screening process, the FD patients will be asked if they are willing to participate
in this trial; if not, they will be given conventional treatment according to guidelines[17], and will be assessed using the same outcome measurements through telephone follow-up.

After randomization, the participants will be either assigned to acupuncture group or sham acupuncture group. And they will go through a total research period of 25 weeks, including 1 week baseline, 4 weeks of acupuncture treatment, and 20 weeks of follow-up phase. Included participants will receive 20 sessions of acupuncture treatment in 4 weeks, 5 times continuously with a 2-days rest in a week. Outcome measurements will be assessed at 0, 4, 8, 12, 16, 20, 24 weeks after inclusion, with outcome assessors blinded to the group assignment.

The study protocol has been approved by local institutional review boards and ethics committees (From April to August, 2012). It follows the principle of CONSORT and STRICTA statements as well as the Declaration of Helsinki (Sixth revision, 2008).

**Participant eligibility**

We consider to recruit the FD patients diagnosed on the basis of the Rome III criteria[18]. And we choose to include FD patients classified as postprandial distress syndrome (PDS), ruling out those classified as epigastric pain syndrome (EPS). According to our previous research, 70% of the FD patients were classified as PDS, which is a larger suffered population than EPS. Additionally, to ensure an ideal circumstance for this efficacy trial, we will include PDS patients only, although it will partially narrow the generality of the results. Doctors responsible for screening patients will be gathered and trained using the ROME III criteria in each center. Then a pre-trial screening will be performed, with all the doctors screening a group of participants. Finally, a comparison of the screening results among different doctors will be made, and homogeneity should be achieved. Details of the inclusion and exclusion criteria of the participants are listed in table 1.

After a diagnosis of FD was established, gastrointestinal symptoms and the quality of life will be evaluated to determine the patient’s baseline status. Then the participants will go through randomization process.

**Recruitment strategies and Randomization**

We will recruit participants through 3 methods: first, call the participants who join our previous study, if they are interested in coming for this study; second, specific doctors received training will screen and recruit participants in outpatient clinics in each center; third, advertisement and recruitment notice would be put in newspaper, local media, health promotion manual, etc.

If patients are eligible, the doctor will ask if they are interested in participating. If so, the doctor will refer them to a research coordinator, who will introduce the aim and methods of this study and ask the participants to sign the consent form. Participants who provide consent will be introduced to the outcome assessor for baseline evaluation, and then be referred to an acupuncturist to apply for randomization.

Central randomization is used in this study. The acupuncturists are trained to apply for
randomization through text messages, online website, or telephone application. Qualified acupuncturists will have their cell phone number registered in the randomization center (located in Brightech Magnsoft Data Services Company), with the permission to send application for randomization of participants. Randomization automatically performed in a real time mode by the central computer. Subjects are randomized in blocks of varying size within each site, stratified by age and duration FD.

Blinding
Participants will be blinded to group assignment in this trial. We will inform them that there are two types of acupuncture treatment provided for FD in this trial, both of are used in clinical practice. And we will also notify that one of the acupuncture treatment is a traditional style, while the other is a style designed according to of western medicine. Acupuncturists (care providers) will not be blinded in this trial, because it is merely impossible. Acupuncturists could easily guess the group assignment, through recognizing the function of the acupuncture points, which we should clearly tell them. So in this trial, we ask the acupuncturists give the same stimulation method to acupuncture points and sham acupuncture points, to control the risk of performance bias.

Study groups
Acupuncture arm
In the planning phase, we formulated the acupuncture protocol in 3 steps: First, through a systematic review of published studies, text books and ancient literatures, we decided the syndrome differentiation protocol for acupuncture treatment of FD (excess syndrome and deficiency syndrome), as well as a range of acupuncture points to manage the condition. Second, we held a face-to-face meeting to discuss the protocol and turn it into a standardized approach. Third, we send out questionnaires to acupuncturists across the country, asking whether this standardized protocol is commonly used in their clinical practice and suggestions for improvement. Fourth, a final version of the protocol was used in Phase I study, with 10 healthy subjects and 10 FD participants included, to test the safety, effect size and tolerance of the acupuncture treatment for the condition.

We choose Zusanli(ST36) and Neiguan(PC6) as basic acupuncture points, which will be needled in every participants. ST36 belongs to stomach meridian according to traditional acupuncture theories, which is believed to be one of the best acupuncture points specifically selected for gastrointestinal diseases. PC6 is frequently used for upper gastrointestinal conditions, such as nausea and vomiting associated with acute myocardial infarction[19], chemotherapy[20], hyperemesis gravidarum[21], etc. Regarding the FD patients manifest mainly as upper gastrointestinal discomfort, ST36 and PC6 were chosen as basic points.

Additionally, there are two groups of optional points, which would alternatively selected according to syndrome differentiation. First group, if the participants are differentiated as excess syndrome, Taichong (TR3) and Neiting (ST2) will be selected.
Second group, if differentiated as deficiency syndrome, Gongsun (SP4) and Yinlingquan (SP9) will be selected. The excess and deficiency syndromes are defined according to dyspepsia session in *Guidance of clinical research of traditional Chinese medicine* published by State Food and Drug Administration (SFDA) in China[22].

Excess syndrome mainly refers to excess of liver Qi and stomach fire, while the deficiency syndrome mainly refer to deficiency of spleen and stomach Qi. So the TR3 (belongs to liver meridian) and ST2 (belongs to stomach meridian) fit for the excess syndrome, whereas SP4 and SP9 (both belong to spleen meridian) are selected for the deficiency syndrome. Therefore, selection of acupuncture points consists of two basic points and two optional points, which is similar to conventional acupuncture practice. Each point is puncture using a filiform needle (25-40 mm in length and 0.25 mm in diameter), and achieving Deqi sensation (refers to a sensation of numbness, distension, or electrical tingling at the needling site which might radiate along the corresponding meridian) is needed. Then an auxiliary needle (13 mm in length and 0.18 mm in diameter) will be puncture 2 mm lateral to the first needle, to a depth of 2 mm without arrival of Deqi. Electro-acupuncture will be used at every point with one electrode connected to the filiform needle and the other to the auxiliary needle. This method limits electrical stimulation on points, rather than going across human body surface to cause performance bias. Electrical stimulation will last for 30 minutes in each acupuncture session. A total of 20 acupuncture session will be given during 4 weeks, once daily for 5 days with 2-days rest in a week.

Sham acupuncture arm

The same sham points as used in our previous study will be adopted in this trial, and details of the location the points are described elsewhere[23]. Participants in sham control group will also receive the same electrical stimulation, and the same duration of treatments as the participants received in the acupuncture group.

The intervention of this trial is rigorous acupuncture schedule, to ensure the compliance of acupuncturists to the schedule, we ask them to take a pre-trial training and a entrance exam for this trial. Only the qualified acupuncturists will be admitted to this trial, and we will monitor the compliance of the staff to the protocol every month. The principle investigator (Fanrong Liang) will assign a specific researcher in every center to check if the acupuncturists follow the treatment protocol, and to report the compliance every month to the Brightech Magnsoft Data Services Company.

Outcome measurements

The primary outcome

The primary outcome of this study was first targeted through a review of previous studies, then was selected based on consensus from researchers in the territory of functional gastrointestinal disorders, dyspepsia patients and physicians. The proportion of patients reporting complete absence of dyspeptic symptoms is considered to be the most important outcome measurement[24]. So, the participants in this trial will undergo a self-assessment of global relief of the dyspepsia symptoms, with a five grade scale: absence of dyspeptic symptoms, significantly improved,
moderately improved, not changed and deteriorated. The primary outcome is the proportion of patients reporting absence of dyspeptic symptoms at 16 weeks after inclusion, at which the participants are supposed to achieve maximum relief of the dyspeptic symptoms according to our previous study[15].

Secondary outcomes

Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ) [25] is a five question instrument for assessing the dyspeptic symptoms. Five symptoms epigastric pain, postprandial distention, indigestion, heartburn and nausea will be graded the severity on a 5-point Likert scale from very mild to very severe: no symptoms (0 point), mild symptoms without influence of regular work (1 point), mild symptoms with influence of regular work (2 points), moderate symptoms (3 points), severe symptoms (4 points) and extremely severe symptoms (5 points). The SF-LDQ is a validated and reliable tool to assess the dyspeptic symptoms of FD patients [25 26], with higher scores indicating worse dyspeptic outcomes.

A Chinese version of Nepean dyspepsia index (NDI) will be used in this trial to assess the disease-specific quality of life. This scale was validated and confirmed to be a reliable tool for the Chinese population in our previous study[27]. The NDI scale consists of 25 items, with a total score ranging from 0 to 99. Higher scores indicate poorer quality of life. Each of the items is a 5-point likert scale that scores the severity of symptoms from “not at all” to “extremely sever”. Moreover, the 25-item NDI measure the quality of life in four domains: interference (13 items), know/control (7 items), eat/drink (3 items) and sleep/disturb (2 items). Finally, a Chinese version of 36-Item Short Form Survey (SF-36) will be used to assess the overall health status of the included participants.

Time points of outcome measurement

We choose the time points of assessments under the consideration of the following aims: first, to capture the key milestones in the management of FD patients with acupuncture; second, to see how the acupuncture effect changes over time. According to our previous study[15], a duration of 4 weeks is reasonable and reliable to assess the change of dyspeptic symptoms of FD patients. Therefore, we follow up the participants at the time points of 4, 8, 12, 16, 20 and 24 weeks after inclusion. At baseline, the participants will be given the physical examination, outcome assessments and regular tests. The regular tests include routine blood, urine and stool tests, liver and kidney function test, gastroscopy, ultrasonic examination in the upper abdomen and pregnancy test. The pregnancy test is to exclude the risk of acupuncture may bring to the pregnant women, who don’t know the information. An overview of measurements at different time points is presented in table 2.

Assessment of adverse events

According to our previous study, acupuncture may cause several adverse events[28]. So we will record adverse events caused by acupuncture and the reasons for these events during treatment and follow-up phases. These adverse events include bleeding,
hematoma, fainting, serious pain, and local infection, etc. Number of adverse events will be calculated for each group.

Sample size calculation
Based on our previous study[15], after receiving 20 sessions of acupuncture treatments, 46.1% of the FD patients with PDS responded to true acupuncture, whereas 14.1% of the patients responded to sham acupuncture, so a difference of 32% was observed. In this trial, different acupuncture protocol were used, so conservatively we expected a responder rate of 50% in the acupuncture group, and 25% in the sham acupuncture group, to detect a difference of 25% between true and sham acupuncture. Considering a two sided significant level of 5% and power of 90%, 85 participants per group will be needed, calculated by Fisher’s exact test in G*Power(version 3.1.5). To minimized attrition bias, a dropout rate of 15% was considered, making it necessary to include at least 100 participants per group.

Statistical analysis
The primary analysis will be a comparison of the proportion of patients reporting absence of dyspeptic symptoms between acupuncture and sham acupuncture at 16 weeks after inclusion (comparison of the primary endpoint). We will use chi-square test to detect the difference between groups, with a significant level of 0.05. To analyze how the primary outcome changes overtime after acupuncture treatment, we will use the model of generalized estimating equations (GEE) with adjustments for clinical centers, baseline assessments of dyspeptic symptoms, duration of the FD symptoms (continuous value calculated by months) and age (continuous value calculated by years). The secondary analysis will be performed to assess the changes of SF-LDQ, NDI scores and SF-36 from baseline to 24 weeks after inclusion, we use linear mixed models adjusted for clinical sites and baseline scores. The rates of adverse events will be compared between groups. We perform the above analysis using the intention to treat method. Missing values will be handled using multiple-imputation method, on the assumption that values at each time point follow a specific distribution calculated by computer software R project (version 2.15.3, http://www.R-project.org/). We will also perform a complete-case analysis without imputation of missing values, to find out if the results are consistent with the above analysis. The data will be analyzed using SPSS 20.0 (IBM SPSS Statistics, IBM Corp, Somers, NY).

Data management
All data are managed by the data coordinating center in a third party, the Brightech Magnsoft Data Services Company. This company developed a password-protected website for this trial, which is designed with the function of randomization, data entry of the research data (including information of screening and eligibility, outcome assessments, adverse events and quality control) and overview of the process of this trial. All data will be backed up in different network drives located both in Chengdu and Beijing.
DISCUSSION

We describe the rationale, design and analytic methods of a randomized controlled trial comparing acupuncture and sham acupuncture for FD patients, at different time points. Hopefully, convincing evidence will be found to clarify whether acupuncture is efficacious for this condition.

Before this trial, we have conducted a multicenter randomized trial to assess the effect of acupuncture for FD patients[15]. In the trial, 712 FD patients were randomly assigned to 6 groups, 4 acupuncture groups versus one sham acupuncture group and a drug (Itopride) control group. The results showed that acupuncture at specific points of stomach meridian is superior over acupuncture at points of other meridians and sham points, as well as oral administration of Itopride. Results of this trial, for the first time, confirmed that acupuncture is superior to Itopride, which was reported to be an efficacious treatment for FD patients in the year 2006, couple of months before planning and carrying out of the trial [29]. However, Itopride was then reported to be a treatment no better than placebo in a larger sample phase III trial [24], which makes our conclusion that acupuncture is effective for FD still inconclusive. Moreover, although the results showed that acupuncture is superior over sham, it is not conclusive either. A design of 4 acupuncture arms versus 1 sham acupuncture arm was used, indicating that there may be a chance that the results are false positive, because of multiple comparisons among groups. In outcome assessments, we used scores of symptom index of dyspepsia as primary outcome, which is a scale without going through validation and reliability test, but is commonly used in China. Thus the results are not as reliable as we expected, because of a weak primary outcome assessment.

An interesting result of that trial showed that acupuncture effect seems to last at least 3 months after 20 sessions of acupuncture treatment. However, we are not sure for how long this effect last, since we followed up the participants for only 16 weeks. This long lasting effect may be an advantage of acupuncture treatment, which therefore justify a new trial with a much longer follow-up period.

Combining the above facts, we found that the existing evidence is not enough to draw a firm conclusion on the effectiveness and efficacy of acupuncture for FD. So we hypothesized that: Acupuncture is superior over sham acupuncture (acupuncture is efficacious) in relieving dyspeptic symptoms of FD patients. To test these hypotheses, we design this trial, with a control group of sham acupuncture, to reduce the likelihood of reaching a false positive outcome caused by multiple comparisons. And we used proportion of patients reporting absence of dyspeptic symptoms as primary outcome, to reach a more reliable conclusion compared to our previous trial.

Moreover, we planned a follow-up period of 24 weeks, to fully understand this long lasting effect of acupuncture for reliving dyspeptic symptoms. In our previous trial, we included FD patients classified as postprandial distress syndrome (PDS) or epigastric pain syndrome (EPS). In this trial, we planned to recruit participants with PDS only, because a narrow and specific population will be more appropriate in a trial using efficacy design. To make the recruitment of the participants easier, we will call...
the participants who join our previous study, if they are interested in coming for this study. We will inform them that new types of acupuncture will be used, which is conducted according to traditional and modern theories, and is different from the previous acupuncture they received. Also, we will exclude the participants who received sham acupuncture in the last trial, to reduce the risk of unblinding, since we will use the same sham points in this trial.

A major issue in designing this trial is how to distinguish the treatment effect of acupuncture from effect brought by other factors, like improvement to a more healthy living style, administration of drugs to improve gastrointestinal function, etc. To minimize the bias contributed by these factors, we considered the following solutions: first, we give the participants an education of healthy living style in both groups. The participants will receive a handbook of preventing FD, including health style of diet, appropriate exercise to improve gastrointestinal function, etc.; second, we ask the participants not to take drugs unless there is a urgent need, e.g., dyspeptic symptoms are not relieved after 10 session of acupuncture treatment, or dyspeptic symptoms significantly lower the quality of life; third, we revise our acupuncture protocols several times according to the literature review and expert experience, to ensure the effectiveness of the experimental arm.

Another major issue is how to collect data in different time points correctly. 5 follow up time points across 20 weeks are defined in this trial. So we may get inaccurate parameters during outcome assessments in such a long follow up period. To avoid bias from outcome assessment, we firstly train the outcome assessors to use telephone interview, email contact to collect follow-up data; secondly we ask the assessors to help the participants to fully understand the follow-up questions, which we try our best to minimize the number of questions, to avoid frustration of participants in responding; thirdly, we promise the participants with 5 more acupuncture treatments if they respond to the whole follow-up interview.

CONCLUSION

This article presents a design and protocol of acupuncture for patients with FD, to clarify the efficacy of acupuncture for this condition. The results are expected to give answers to the following questions: first, whether acupuncture is superior to sham acupuncture; second, whether acupuncture effect last longer than the sham.

Contributors

HZ, JX, JL, XL, LZ, XrC, BG and FrL participated in the design of the trial, in writing the data analysis plan, and in drafting the manuscript. JL, ML and XzL collect the information needed for the performance of this trial in each center. All the authors discussed, read, revised the manuscript, and finally approved for publication of this protocol.

Funding

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Ethics approval
The study protocol has been approved by institutional review boards and ethics committees of the first affiliated hospital of Chengdu University of TCM, the first affiliated hospital of Hunan University of TCM and Chongqing Medical University, respectively (From April to August, 2012).

**Competing interests**

None.

**Acknowledgements**

We appreciate the help from the staff of Brightech Magnsoft Data Services Company, who contribute a lot in the design and statistical analysis plan of this trial. And we acknowledge the help and contributions from acupuncturists, experts, investigators in each center. We also acknowledge the contributions from FD patients participating in this trial.

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   measuring the presence and severity of dyspepsia. Alimentary Pharmacology and
   Therapeutics 1998;12(12):1257-62


### Table 1 Inclusion and exclusion criteria for this trial

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>Diagnosed as FD, also classified as PDS</td>
<td>To ensure an ideal circumstance for this trial of efficacy design</td>
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<td>Age 18 to 65</td>
<td>Aim at including adult population, and ensure higher likelihood of coexisting FD</td>
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<tr>
<td>Without intake of any prokinetic agents in 15 days, and not involved in any clinical trials</td>
<td>To avoid bias from the treatment effect of medication.</td>
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<td>Sign the informed consent</td>
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</table>

**Exclusion criteria**

<table>
<thead>
<tr>
<th>Psychological, unconscious, unable to cooperate in outcome assessment</th>
<th>To ensure the results of outcome measurements are accurate.</th>
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<tr>
<td>Accompanying aggressive tumor, cachexia, infectious, bleeding diseases, etc.</td>
<td>Aggressive and serious diseases require additional drug treatment, thus bringing additional confounding factors.</td>
</tr>
<tr>
<td>Accompanying serious diseases of cardiovascular, liver, nephritic, digestive, hematopoietic system, etc.</td>
<td></td>
</tr>
<tr>
<td>Women in pregnant, or intent to, or in breast feeding period during 6 months</td>
<td>Whether acupuncture is safe for pregnant women or women who plan to be is still controversial, so it is better to rule out this population.</td>
</tr>
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</table>

### Table 2 Measurements at different time points

<table>
<thead>
<tr>
<th>Measurements</th>
<th>0 week</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
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<td>SF-36</td>
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</table>
Screen functional anosmia patients for eligibility.

Obtain informed consent and benefits. Enrolment from participants, and randomize them to two groups:

- Venous acupuncture group
- Sham acupuncture group

30 sessions of acupuncture at true points over 4 weeks.

Weeks 0-4:
Subjects will finish a 4-weeks headache diaries and receive face-to-face assessment by outcome assessors.

Weeks 5-9:
- Weeks 5-7: Weeks 10-12
- Weeks 21-24: Weeks 13-16

Subjects will finish 3 sessions of 4-weeks headache diaries, which will be sent back to research centers by mail or email, and receive telephone assessment by outcome assessors.

Follow-up