Effect of electroacupuncture on symptoms of female pelvic organ prolapse (stage II–III) (EAPOP study): protocol of a randomised controlled trial

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ABSTRACT

Introduction Pelvic organ prolapse (POP) is downward descent of pelvic organs, which causes symptoms of the lower genital, urinary and gastrointestinal tracts, and undermines women’s daily activities and quality of life. Although studies indicated that electroacupuncture (EA) may be effective in improving the POP symptoms, evidences were not robust. Therefore, this study aims to conduct a randomised controlled trial (RCT) to evaluate the efficacy and safety of electroacupuncture on relieving symptoms of a POP stage II and III among women.

Methods and analysis A two-arm, multicentre, patient-blind RCT will be conducted to compare EA with sham electroacupuncture (SEA) for treating symptoms of POP stage II and III among women in six tertiary hospitals in China. One hundred and sixty eligible women will be assigned with a 1:1 ratio to have received either EA or SEA for 24 times in 12 weeks and followed-up for 24 weeks. The primary outcome will be the change on the total score of the Pelvic Floor Distress Inventory-short form 20 at week 12 from baseline, and will be analysed by t-test or multiple regression model. Intention-to-treat analysis will be performed for all outcomes, and a p value of less than 0.05 (two-sided testing) will be considered as statistical significance.

Ethics and dissemination The study protocol has been approved by the Medical Ethical Committee of Guang’anmen Hospital (No. 2019-249-KY-01). Patients will be informed about the details of the study and asked to sign consent form before enrolment. The results of this study are expected to be written and published on peer-reviewed journals.

Trial registration number NCT04589715.

BACKGROUND

Pelvic organ prolapse (POP), a disorder exclusive to women, is defined as downward descent of pelvic organs that can affect the anterior and/or posterior vaginal wall, and uterus or apex of the vagina, usually in some combination.1 It causes symptoms of the lower genital, urinary and gastrointestinal tracts that can undermine a woman’s daily activities and quality of life.2 3

It is widely reported that up to 50% of women will develop prolapse in their lifetime, while only 10%–20% of these seek for treatment.4 5 Study reported that about 25% of US women had one or more pelvic floor disorder (2.9% with prolapse), and the prevalence of symptomatic disorder increased significantly with age.6 In 2019 a cross-sectional study in China with 2864 women revealed that the prevalence of symptomatic POP among Chinese women was 9.67% over all age groups, and was up to 26.22% among women aged 70 and above.7

Generally, non-surgical treatment is considered for women with a mild to moderate stage of POP (under stage III, for those who wish to have children, and those unwilling or unable to undergo surgery.8 And commonly applied non-surgical treatments include pessaries, pelvic floor muscle training (PFMT), life style and behaviour interventions, topical oestrogen and so on. Taken PFMT for instance, although previous randomised controlled trials (RCTs) reported that patients in PFMT group reported significantly more improvement on POP symptoms than that in control group, the clinical importance of the differences observed and its long-term effect remain suspicious.9–11 Other factors, such as constrains on indications, incidence of complications and recurrence of POP...
symptoms, often limit the acceptance and application of these non-surgical treatment to a wider population. A series of studies demonstrated that electroacupuncture (EA) or electrical pudendal nerve stimulation at the lumbosacral region could relieve the symptoms of urinary incontinence (UI) by stimulating sacral and pudendal nerve to strengthen pelvic floor muscle contraction. Previous studies demonstrated that a similar pelvic floor weakness, which might be attributable to damaged muscle fibres and neurochemical depletion in the somatic nerves targeting the pelvic floor, has been observed in women with genitourinary prolapse and UI. Two studies in China investigated the effect of acupuncture or EA on symptomatic POP, and showed that both approaches were better in improving the symptoms of POP in comparison with PFMT after 3 months of treatment. However, the two studies adopted acupoints mainly at abdomen (eg, EZ-CA1, EX-CA6) and did not clarify its mechanism of effect with pelvic floor muscle, and were problematic in study design. There were also literature reviews reporting the use of acupoints at lumbosacral region (eg, BL33, BL35), but not clinical trials were identified. In addition, sham control was not applied in these studies to reveal net effect of acupuncture. Therefore, this study aims to conduct a RCT to rigorously evaluate the efficacy and safety of EA on relieving symptoms of POP stage II and III among women, in comparison with sham electroacupuncture (SEA).

**METHOD**

**Study design**

This will be a two-arm, multicentre, patient-blinded RCT to compare EA for treating symptoms of POP among women with SEA. The study will be performed in six tertiary hospitals across China including Beijing (one centre), Shaanxi (one centre), Hunan (one centre), Guangdong (one centre) and Jiangsu Province (two centres). All procedures and time frames are displayed in figure 1 according to the Standard Protocol Items: Recommendations for Interventions Trials.

The planned start date was 31 October 2020, and end date was 30 June 2022. However, due to the COVID-19 pandemic, the actual enrolment started in early 2021, and progressed slowly.

**Sample size calculation**

In this study change of PFDI-20 score from baseline will be used as the basis for primary sample size estimation. As there is no consensus on the minimal clinically important difference (MCID) of PFDI-20 score, and few RCT on acupuncture was identified, the study decided to use 15 points as MCID based on previous studies on conservative therapies for POP. Assuming a PFDI-20 baseline score of 60 points, it is estimated that 160 patients (80 per group) are needed to provide 80% power for detection of a difference of 15 points between groups at 12 weeks since randomisation, using a SD of 27 points, a two-tailed 5% level of significance and 10% loss of follow-up rate. ASS V.15 software was used for sample size calculation.

**Participants**

Eligible patients with symptoms of POP will be recruited in six tertiary hospitals across China through public advertisement (eg, hospital social media account, poster in hospital and communities and newspaper). Research staff will introduce background and process of the study in detail to potential subjects who contact the research team and express interests of participation. Once the informed consent form is signed, patient will be evaluated for eligibility via medical history, urinalysis and pelvic examination by gynaecologist.

**Diagnosis criteria of POP**

The pelvic organ prolapse quantification (POP-Q) system approved by the International Continence Society, the American Urogynecologic Society and the Society of Gynecologic Surgeons in 1996 will be adopted for diagnosis and quantification of female POP and pelvic floor dysfunction. The POP-Q can assess vaginal support by measuring the location of predetermined points on the vaginal surface in relation to the hymen on maximal strain, and summarise the stage of prolapse (from 0 to IV for diagnosis purpose). Details are shown in table 3.

**Inclusion and exclusion criteria**

Patients should meet all the following inclusion criteria to be eligible: (1) female patients, age ≥35 years old; (2) diagnosed as POP at stage II to III according to performance of a POP-Q examination conducted by a specialised gynaecologist; (3) having a sensation of bulging, protrusion, dragging or heaviness from vaginal area, with or without urinary, bowel and sexual disorders; (4) having a score of PFDI-20 >24; and (5) providing signed informed consent.

Patients are excluded if any of the following criteria are met: (1) having cognitive disorders and cannot understand the content of questionnaires; (2) having severe heart, lung, brain, liver, kidney, haematopoietic system and immune system diseases, or severe malnutrition; (3) having cancer or at terminal stage of severe diseases; (4) requiring finger assistance for defecation, or having severe prolapse of rectum, sigmoid colon or small intestine; (5) received or having on-going treatments for pelvic floor disorders, including POP, stress UI and constipation, in the past 1 month; (6) having any on-going treatment for other gynaecological diseases; (7) having uncontrolled symptomatic urinary tract infection, or residual urine volume ≥100 mL; and (8) having diseases affecting the neurological function of pelvic organ, for example, spinal cord injury, or peripheral nerve injury caused by surgery at lumbosacral area or pelvic floor.

**Randomisation**

Randomisation will be performed by an independent data management agency (Linkermed Technology, Beijing, China) using central computer system. Eligible
patients will be assigned to either experiment or control group according to the random sequence, which will be stratified by research centres with block length of four or six within each centre to reach a 1:1 ratio of patients in EA and SEA group.

**Blinding**
The participants will be blinded in this study as the sham EA will be used. However, it will not be possible to blind acupuncturists who will be performing the treatment in either study group as the acupoints, needles used and approach of needle insertion are different in the two study groups. The outcome assessor will be different from treating acupuncturists, and will be blinded for allocation to minimise the bias associated with data collection. Data analyst will also be blinded for allocation. The allocation will only be revealed when it is needed for final comparison between arms.

**Intervention**
Patients in either group will be treated by the same acupuncturist throughout the study period. Patients randomised to EA group will receive EA at 33rd and 35th points of Bladder meridian of foot-taiyang (BL33 and BL35), and 33rd point of Spleen meridian of foot taiyin (SP6). While patients assigned to SEA group will receive EA at the sham BL33 point (1 cun ($\approx$20 mm) laterally parallel with BL 33), the sham BL35 point (1 cun laterally parallel with BL 35) and the sham SP6 (the mid-point of horizontal connecting line from SP6 to the medial margin of Achilles tendon). The first treatment in both groups will start right after randomisation and last for 12 weeks (24 times in total) with a varying frequency. The duration of EA treatment was based on consideration of recommended duration for PFMT and previous study of EA for mixed UI. Details of EA and SEA interventions, including acupoints location, needle, insertion approach,
electric current setting and treatment schedule, are shown in Table 1. Figure 2 demonstrates detailed location of acupoints and needle insertion approach.

To ensure the blinding to the patients, they will be informed that the sense of electric current will be mild due to its intensity setting in this study, and will diminish over time due to body resistance and tolerance. Enrolled patients will be treated separately by interventions group to prevent potential contamination, and will be discouraged for receiving any additional treatments for POP symptom unless emergencies. Any use of additional treatments should be recorded and reported to the researcher in a timely manner.

### Table 1 Description of interventions

<table>
<thead>
<tr>
<th>Group</th>
<th>EA group</th>
<th>SEA group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acupoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Name</strong></td>
<td>BL33</td>
<td>BL35</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>The third posterior sacral foramina</td>
<td>0.5 cun (=10 mm) lateral to the coccyx end</td>
</tr>
</tbody>
</table>

| **Needling** |          |           |
| **Model** * | 0.30×75 mm | 0.30×75 mm | 0.30×40 mm | 0.30×40 mm |
| **Depth**   | 60–70 mm  | 60–70 mm  | 25–30 mm   | 2 to 3 mm  |
| **Insertion approach** | Needle should be inserted into the skin with an angle of 45° in an inferomedial direction towards BL33 | Needle should be inserted into the skin with a slightly superolateral direction towards BL35 | Needle should be inserted into the skin perpendicularly towards SP6 | Needle should be inserted into the skin with a minimum depth to stand still without any other manipulation |

| **Electric current settings** † |          |           |
| **Frequency** | Continuous wave 20 Hz | Continuous wave 20 Hz |
| **Intensity** | 2 to 6.5 mA | 2 to 6.5 mA | 1–3.5 mA | 1–2 mA |
| **Setting** | The current intensity should be gradually adjusted from 0 to the maximum tolerance level of each patient (preferably with the skin around the acupoints shivering mildly without pain) at the beginning of each session | The stimulation will only last for 30 s with a minimum currency intensity that patient can sense |
| **Connection** | Paired electrodes from the electroacupuncture apparatus were attached transversely to the needle handles at bilateral BL33, BL35 and SP6 | Paired electrodes from the electroacupuncture apparatus were attached transversely to the needle handles at bilateral sham BL33, sham BL35 and sham SP6 |

| **Treatment schedule** |          |           |
| **Time per session** | 30 min |
| **Overall duration** | 12 weeks (24 times in total) |
| **Frequency** | 3 times per week in week 1–4 | 2 times per week in week 5–8 | 1 time per week in week 9–12 |

*The Huatuo Brand disposable sterilised needles will be used in this study.
†The Yingdi KWD-808 type I electroacupuncture apparatus will be used in this study.

### Outcome measurements

Outcome data will be collected at baseline (week 0), at completion of treatment (week 12 since randomisation, primary end point) and at two follow-up points (week 24 and week 36 since randomisation), respectively. A summarised schedule of outcomes measurement is presented in Table 2. At baseline, the study will also collect data on patients’ general characteristics and medical history, including age, body mass index (BMI), education and occupation, history of gravidity and parity, POP diagnosis and treatment, history of constipation, chronic cough and heavy lifting and postvoiding residual volume.
Primary outcome
The primary outcome of the study will be the change on the total score of the Pelvic Floor Distress Inventory-short form 20 (PFDI-20) at week 12 (completion of treatment) since randomisation. The PFDI-20 questionnaire has been tested in Chinese population and evaluates the severity of POP symptoms in the past 3 months, including POP, colorectal–anal and urinary symptoms. The total score of the questionnaire is between 0 and 300, and the higher the score is, the more severe the symptoms are.27 32

Secondary outcomes
Severity of POP will be assessed by the POP-Q system examination conducted by a gynaecologist. The higher the stage of POP-Q is, the more severe the prolapse is.30 Details are shown in table 3.

Impact of bladder, colorectal and vaginal symptoms on daily life, personal relationship and emotion will be assessed by the total score of the Pelvic Floor Impact Questionnaire Short Form-7 (PFIQ-7). The PFIQ-7 questionnaire has been tested in Chinese population and evaluates the quality of life affected by POP in the past

Table 2  Schedule of outcome measurements

<table>
<thead>
<tr>
<th>Time of data collection</th>
<th>Baseline</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurements</td>
<td></td>
<td>Week 0</td>
<td>Week 12</td>
</tr>
<tr>
<td>PFDI-20 questionnaire</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>POP-Q examination</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFIQ-7 questionnaire</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ICIQ UI-SF questionnaire</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PISQ-12 questionnaire</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PGI-I questionnaire</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients' expectation to the treatment effect</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding effect assessment</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td>Throughout the whole study</td>
</tr>
<tr>
<td>Additional medication intake</td>
<td></td>
<td></td>
<td>Throughout the whole study</td>
</tr>
<tr>
<td>Adherence to treatment assignment and schedule</td>
<td></td>
<td></td>
<td>Throughout the whole study</td>
</tr>
</tbody>
</table>

Table 3  Five stages of pelvic organ support as defined by the POP quantitation system31

<table>
<thead>
<tr>
<th>POP stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No prolapse</td>
</tr>
<tr>
<td>I</td>
<td>The most distal portion of the prolapse is &gt;1 cm above the level of the hymen</td>
</tr>
<tr>
<td>II</td>
<td>The most distal portion of the prolapse is ≤1 cm proximal or distal to the hymen</td>
</tr>
<tr>
<td>III</td>
<td>The most distal portion of the prolapse is &gt;1 cm below the hymen but protrudes no further than 2 cm less than the total vaginal length</td>
</tr>
<tr>
<td>IV</td>
<td>Complete eversion of the total length of the vagina</td>
</tr>
<tr>
<td></td>
<td>The distal portion protrudes at least the total vaginal length minus 2 cm beyond the hymen</td>
</tr>
</tbody>
</table>

POP, pelvic organ prolapse.
3 months. For each question, the scale ranges from 0 to 3 (no bother=0, mild bother=1, moderate bother=2 and severe bother=3). The higher the total score is, the more severe the quality of life is impacted.32 33

Severity of incontinence and its impact on quality of life in the past 1 month will be assessed by the total score of the validated Chinese version of International Consultation on Incontinence Questionnaire-Incontinence Short Form (ICIQ UI-SF). The ICIQ UI-SF is a 4-item questionnaire with a total score between 0 and 21. The higher the total score is, the more severe the incontinence is.34

Impact of POP on sexual life will be assessed by the score of Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-12 (PISQ-12). For each question, the scale ranges from 0 to 4 (never=0, sometimes=2, often=3, rarely=1 and always=4). The higher the total score is, the more severe the impact of POP/incontinence to sexual life is.35

Overall treatment effect from patient’s perspective will be assessed by the Patient Global Index of Improvement (PGI-I). The questionnaire measures patient’s feelings on change of symptoms after treatment with seven levels (major improvement, moderate improvement, mild improvement, no improvement, mild worsening, moderate worsening and major worsening).36 Although the questionnaire has not been used in patients with POP, it has been proved to be valid in patients with stress UI.37

Patients’ expectation to the treatment effect will be assessed at the baseline by the question ‘in your expectation how is your symptoms like in 3 months’ with five choices of answers (much better, slightly better, I don’t know, no change and worse).

Assessment of blinding will be evaluated within 5 min after any treatment in week 12. By informing that there is a 50% chance of receiving either traditional EA with deeper insertion or mild EA with shallower insertion, patients will be asked ‘whether do they think they have received traditional EA’ and answer with either yes or no.

Adherence to treatment assignment and schedule will be assessed by recording number and dates of treatment sessions the patients attended. Patients attending more than 80% of treatments will be regarded as having good adherence.

Adverse events, either associated with acupuncture or not, will be monitored and recorded during the whole study period. Numbers and types of any adverse event will be documented as soon as it is reported in any centres. During every visit, each participant will be asked by outcome assessor if the following types of adverse events happened: (1) acupuncture, regardless of EA or SEA, associated adverse event, including but not limited to broken needles, haematoma, infection and abscess around the location where the needle was inserted, fainting, unbearable pain (VAS ≥8), vomiting, nausea, palpitations, dizziness, anorexia and insomnia presented during or after acupuncture; and (2) any other unexpected adverse event that happened after the initiation of the study without clear evidence of association to acupuncture.

Both types of adverse events, their severity and possible relationship with interventions will be recorded in detail on Case Report Form (CRF) and followed-up throughout the study period. Standardised procedure for adverse event management, especially for severe adverse events, has been prepared and trained for all research staff and doctors.

Data management and quality control

Intervention of both experimental and control group will be performed by licensed acupuncturists with at least 2 years of experience in acupuncture. All acupuncturists and outcome assessor will be trained for 2 days by the senior staff of the research team on details of diagnosis, inclusion and exclusion criteria, intervention (including location of acupoints, approach of needle insertion and treatment regimen for both groups), timing and tools of data collection, informed consent, and management rules. Clinical trial inspector will be assigned to each centre and monitor the progress of patient recruitment, treatment and data quality on a regular basis.

Data collected in the study will first be recorded on a standardised paper-based case report form, then input by outcome assessor at each centre to the predesigned electric data collection (EDC) system developed by independent data management agency (Linkermed Technology, Beijing, China). The EDC can check for logical errors automatically, and clinical trial inspector will check the data reliability and validity on a regular basis. Both paper version and electronic version of case report forms, consent forms and lab results from all centres will be kept safely in designated place for inspection at any time during and 10 years after the study. Patients will be coded by numbers in the study, and all identifiable information of patients will be kept by each centre and separately from the data for analysis. All data collected in the study will only be used for the purpose of the designated scientific study.

Statistical analysis

Preliminary statistical analysis plan has been developed for data analysis. Baseline patient characteristics in both groups will be presented using descriptive statistics (mean (SD) for continuous variables, and number (proportions) for categorical variables) to check similarity between groups.

In primary analysis, t-test (two-tailed) will be performed first to observe the significance of difference on change of the total score of PFDI-20 at week 12 from baseline between the EA and SEA groups. Then general linear regression model will be used to further analyse the primary outcome with control of important potential confounders to the treatment effect. Factors, such as education and occupation, will be fixed effect in the model. And factors, such as age, BMI, number of parities, history of constipation, chronic cough and heavy lifting, centre and number of treatment sessions, will be treated as random effect.
For secondary outcomes, χ² test or Fisher’s exact test will be used for categorical variables, for example, POP-Q stage, PGI-I rank and incidence of adverse events. And t-test or Wilcoxon rank-sum test will be used to analyse continuous variables, for example, change of total score of PFQI-Q from baseline, change of total score of ICQ UI-SF from baseline, change of total score of PISQ-12 from baseline, and so on. Generalised linear model will be used for secondary outcomes where appropriate.

Intention-to-treat analysis will be performed for all outcomes. Missing data will be imputed using the multiple imputation method under the missing-at-random assumption. R software V.4.0.2 will be used to perform the analysis, and a p value of <0.05 (two-sided testing) will be considered as statistical significance.

**Patient and public involvement**

The design of the study was inspired by the knowledge we gained from our previous studies on UI. By convenience sampling, we interviewed some of the patients with UI with POP symptoms in the conception period of the study, and acquired knowledge on major symptoms of bother and its impact to quality of life, changes to symptoms after EA and acceptance of and opinions on EA. These knowledge informed later study design, especially regarding target population, disease severity of concern, outcome measures and treatment regimen. The study protocol has given full consideration to patients’ best interest during the whole study period, and was approved by the Medical Ethical Committee of Guang’ammen Hospital. The results of the study will be described in plain language and disseminated to public, including study participants, through public and social media.

**ETHICS AND DISSEMINATION**

This study has been approved by the Medical Ethical Committee of Guang’ammen Hospital (No. 2019-249-KY-01) on 1s April 2020, and will be performed in agreement with the Declaration of Helsinki. The progress of the study will be reviewed by the Medical Ethical Committee on yearly basis, and any amendments made to the original protocol will be communicated and approved by Medical Ethical Committee of Guang’ammen Hospital.

All participants will be given complete written and oral information on aim, process of study, possible benefits, harms and the alternative treatments for POP that participants could consider before signing the consent form. All participants will be informed that their participation in this trial is voluntary and can be ceased at any time without any consequence. Contacts of the focal points of the research team and Medical Ethical Committee will be provided to all participants in case further consultations or complaints are needed. The results of this study are expected to be written and published on peer-reviewed journals.

**DISCUSSION**

According to previous study, EA is effective and safe in comparison to SEA or active control in the treatment of UI, which may share similar neurophysiological mechanism and often present in conjunction with POP. However, acupuncture’s role and effect in managing POP has not been well established and proved due to absence of well-designed RCT. To mitigate such gap, this RCT is the first one of this kind designed to investigate the efficacy of EA on symptoms of mild to moderate POP, using SEA as control.

Pelvic floor muscles play a critical role in giving structural support to the pelvic organs. A weaker pelvic floor muscle may lead to genitourinary prolapse and stress UI. One plausible mechanism of EA’s effect on symptoms of POP could be to improve nerve conduction of a denervated pelvic floor muscle and consequently to strengthen pelvic floor muscle by stimulating the sacral and pudendal nerve. Studies have demonstrated that EA or electrical pudendal nerve stimulation at the lumbosacral region could relieve the symptoms of UI by stimulating sacral and/or pudendal nerve to strengthen pelvic floor muscle contraction. Such mechanism is similar to that of PFMT for POP as found in many previous studies. However, study also showed that the effect of EA tended to continue for 24 weeks when the treatment stopped.

This study has some strengths. First, the study is based on previous studies on UI conducted by the same team, and will be implemented in multiple centres across China, which will lend more power to the study result. Second, different from other trials of this kind using PFMT or no treatment as control group, the study is adopting SEA as control group to reveal the net effect of EA on symptoms of POP. SEA at non-acupoint has been proved as a successful approach for blinding of patients and minimising the interference of placebo effect in acupuncture trials.

In terms of limitations, the parameters used in the sample size of this study was based on data from studies using PFMT for mild POP among other population, thus this may lead to underestimation or overestimation of sample size. To deal with such situation, the study will make necessary adjustments when data on PFMT-20 come in. The study does not target the anatomical change of POP as primary outcome, as it is still debatable that asymptomatic patients with POP diagnosis defined by examination should be treated, and the measurement of the severity of POP using POP-Q system can be subject to bias caused by variations from procedure and tools adopted by examining gynaecologists. In addition, the treating doctors who apply EA or SEA to patients cannot be blinded, but will be separated from outcome assessors who will be blinded to group allocation together with patients.

**Acknowledgements** Sincere appreciation to all the patients, researchers and doctors from each center, especially patient advisers who have generally provided their insights to make the study design a better one.

**Contributors** ZL led the development and implementation of the study and revised the manuscript. HC contributed to the study design and drafted the manuscript. XL, HS and YY contributed the background research and manuscript development. All authors have read and approved the final manuscript.
REFERENCES


