

A Clinical Trial for Traditional Chinese Medicine Following Guidelines of Good Clinical Practice

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Abstract

This paper described the establishment of a Protocol for the clinical trial, using a traditional herbal formula, for the treatment of Menopausal symptoms among women after menopause. Generally, the traditional practitioners would prefer sticking to their classical practice of a dynamic day to day choice of treatment, according to patients' "pattern" of physiological state. However, in the standard hospital setting of limited resources, the traditional way of dynamic treatment, according to patient responses and the subsequent comprehensive analysis of variable data would not be possible. As a result, we decided to design a standard protocol following the requirements of Good Clinical Practice. Our experiences demonstrated that it is feasible to perform a well-designed Traditional Chinese Medicine (TCM) clinical trial although there were many challenges such as placebo preparation, outcome determination and batch-to-batch consistency of TCM medication.

Keywords: *Danggui Buxue Tang* (DBT); Clinical trial; Good clinical practice; Menopausal symptoms

Introduction

Ever since the Helsinki Declaration on Good Clinical Practice (GCP), Randomized Control Trials (RCT's) have been considered the essential steps that need to be taken in order to convince the great majority of people on the efficacy of a clinical treatment [1]. The methodology, rules and regulations related to RCT's are henceforth created, thoroughly endorsed and followed [2].

Traditional Chinese Medicine (TCM) has a long history of over two thousand years during which little is known about basic medical sciences. Clinical treatment is empirical and personal observations on individual cases are indispensable and are carefully recorded. Traditional healers have developed a unique system of problem detection which is followed as guiding principles for diagnosis and subsequent treatment.

While traditional healers might insist that the symptomatic changes could be related to the "internal state" of the individual and hence must be carefully considered in any clinical evaluations. The pharmacological responses to a herbal formula are different between the individual with "cool" internal state and another with "hot" internal state. Other contrasting states (or patterns) like "deep" and superficial "solid" and "vague" were also described [3].

Since RCT's insist on generalization of symptoms and uniformity of evaluations, the standard protocol with the general requirements would not fit the clinical practice of Traditional Chinese Medicine healers.

Those who try to compromise by incorporating the traditional forms of symptoms and "patterns" would be most frustrated because either they find it impossible to include philosophical or conceptual

data into a scientific analysis; or, the number of study clients might have to be blown up to unmanageable levels in order to accommodate many other divergent parameters [4].

In this modern era of scientific beliefs, full emphasis on evidence based practices, has been established. The RCT recommendations provide an easy solution so that generalization overwhelms individual observations leaving the traditional practitioners disappointed.

Menopausal syndrome

Menopause refers to the permanent cessation of menstrual bleeding. Physiologically menopause is associated either with the gradual loss of normal ovarian function, or it may result from the surgical removal or therapeutic suppression of the ovarian activities.

The common menopausal symptoms include hot flushes, sweating and emotional manifestations, which are related to a decline in serum oestrogen levels. Among the Caucasian women, hot flushes and sweating have been reported in 70% and 84% respectively after a surgical menopause and in 60% and 74% following the physiological menopause [5].

Low oestrogen concentrations are also associated with a decline in the quality of life. The use of oestrogen has been shown to be effective as replacement therapy [6].

However, oestrogen replacement may result in unwanted side effects such as breast soreness and nausea [7] and long-term use may increase the risk of breast cancer and thrombosis [8]. In addition, hormonal replacement therapy provides some improvement in the quality of life [9,10].

From a Chinese medicine perspective, menopausal symptoms have been considered as a decline in Kidney *Yin or Yang* or a combination of both, presenting with various degrees of hot flushes, night sweating, depression, and other symptoms.

The herbal formula

The herbal formula to be treated consists of only two herbs viz. *Angelica sinensis* and *Astragalus* (DBT). It was first created by a traditional Chinese clinician SA Chen in the Song Dynasty (1127-1131) [11]. Later, around 1247, a renowned clinician Li Dong-yuan further enhanced and endorsed the formula's indications and clinical value [11,12].

The described indications, apparently, have little to do with the modern description of menopausal syndrome. DBT was described as being good for the anemic, ladies who were weak, thirsty, sometimes flushed and feeling "hot".

Such indications of prescription were diligently followed in the subsequent years. Other symptoms described included oligomenorrhea, drowsiness, sleep and emotional problems. It sounds obvious, therefore, that, although not described as menopausal related, DBT could be identified as a formula that has been used for gynecological symptoms some of which resemble those of menopause. The innovation of this clinical study therefor is involved in the modern use of an ancient formula which would not be expected to give estrogen related adverse effects.

Protocol design

The trial was designed as a single-center, randomized, double blind, and placebo-controlled study. Subjects who met the inclusion/exclusion criteria were randomly assigned to receive *Danggui Buxue Tang* (DBT) or placebo in the 6 months study period.

The goal of the clinical trial was to test the hypothesis that DBT, at a daily dose of 3 g, could reduce the severity and frequency of hot flashes and sweating in women with menopausal symptoms. The study took place according to the scheme shown in Figure 1.

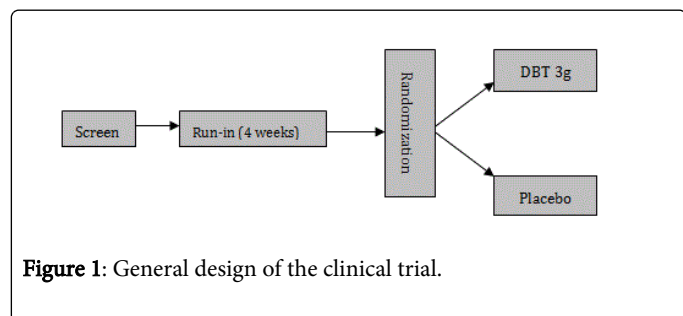


Figure 1: General design of the clinical trial.

A total of 100 patients (mean age 52.8+4.9 years in the treatment group and 51.2+4.6 years in the placebo group) were recruited to the trial.

All women with an intact uterus had been amenorrhic for at least 12 months.

The conduction of the trial is given in the following chart. The numbers shown are the real number of patients in a trial already completed (Figure 2).

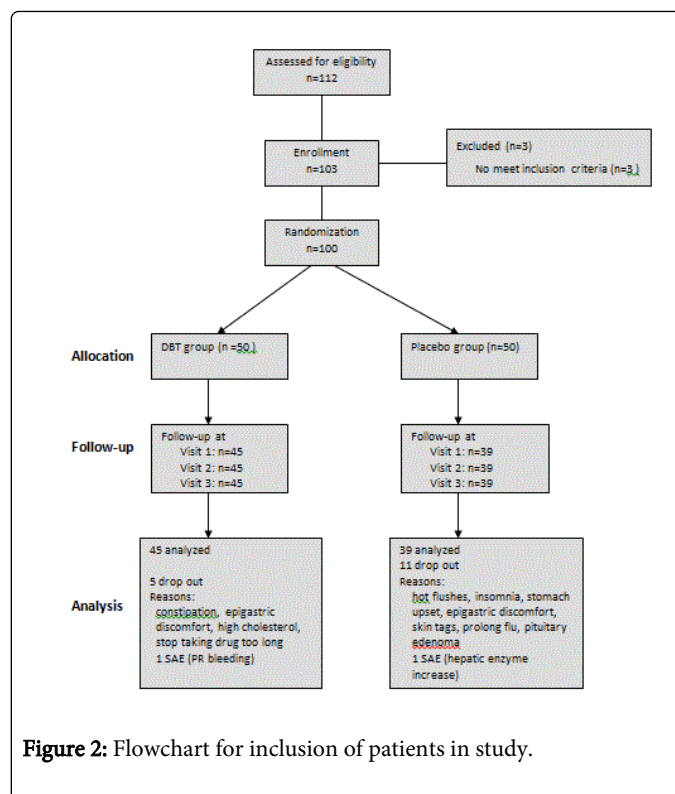


Figure 2: Flowchart for inclusion of patients in study.

The sample size was calculated assuming a similar efficacy to that of estradiol in eliminating hot flashes (expected reduction in prevalence from 0.67 to 0.32), with alpha=0.05 and power 0.90 need 41 patients/group. Allowing for an approximately 20% dropouts, 100 women were recruited.

Inclusion and exclusion criteria

The inclusion criteria were:-

Patients with amenorrhoea for more than 12 months.

Follicle stimulating hormone (FSH), luteinizing hormone (LH), oestradiol (E2) in the menopausal range (FSH>18 IU/L, LH>12.6 IU/L, and E2<361 pmol/l)

Exclusion criteria were:-

- Patients with a history of using any form of hormonal replacement therapy within 8 weeks.
- Patients with a history of using Chinese medicine or other therapies which may affect the outcome within 8 weeks.
- Patients who in the judgment of the investigator will be unable to comply with protocol requirements.
- Patients with significant** gastrointestinal, renal, hepatic, bronchopulmonary, neurological, carcinoma, cardiovascular, or allergic diseases.
- Patients with undiagnosed vaginal bleeding.
- Patients with a history of significant drug hypersensitivity.

**Significant is defined as a disease or condition that required hospitalization within the preceding 2 years.

Efficacy and safety assessment

The primary efficacy endpoint was changes in the severity and frequency of hot flushes and sweating. The secondary efficacy endpoints were changes in the score for the domains measured in the Menopause Specific Quality of Life Questionnaire (MENQOL) and changes in values of various markers for cardiovascular disease risks.

The primary safety endpoint was tolerability. Tolerability failure was defined as a permanent discontinuation of DBT as the result of an adverse event.

Parameters of assessment include:-

- General information
- Hot Flushes per month at baseline and during study treatment
- Changes in MENQOL (four domains)
- Vasomotor symptoms analysis
- Hot Flushes
- Night Sweats
- Sweating
 - Psychosocial
 - Physical
 - Sexual
- Vaginal Maturation Index (VMI), superficial, intermediate, and parabasal cells analysis
- Hormone levels analysis
- Blood chemistry
- Adverse events

Treatment

Study medication and dosage

DBT was manufactured by a GMP (Good Manufacturing Practice) manufacturer in Hong Kong in the form of uniform dose capsules.

The dosage of DBT was 3 g (6 capsules) per day.

Same color and size placebo was also given as 6 capsules/day.

The patients were randomized to receive either DBT or Placebo according to a computerized randomization table. The schedule of assessments was shown in Table 1.

Period	Screening	Baseline	Treatment	
Week		0	12	24
Visit	0	1	2	3
Day	-30 to -1	0	91	182
Medical history	X	X	X	X
Menopausal symptoms	X	X	X	X
Vital Signs	X	X	X	X
Physical Examination	X			
Review of Incl./Excl. Criteria Study	X			
Informed Consent	X			

Urinalysis	X		X	X
Concomitant medications	X	X	X	X
Randomization		X		
Hormone assay	X		X	X
Hematology	X		X	X
Biochemistry	X		X	X
Pelvic Endometrial Ultrasound Sampling/Hysteroscopy	X			
Vaginal maturation	X			X
Body Mass Index (kg/m ²)		X	X	X
Cardiovascular markers		X	X	X
MENQOLc		X	X	X
Arterial reactivity		X	X	X
Dispense medication study		X	X	
Medication accountability			X	X
Record adverse event			X	X

Table 1: Schedule of Assessments.

Data analysis

Data were processed to give group mean values and standard deviations where appropriate. The statistical analysis was made with SPSS 11.5 for windows. For continuous variables, means were compared using analysis of variance. Categorical variables were compared using the χ^2 test.

Changes from baseline in the number and severity of hot flashes were assessed within treatment groups by using paired t-test. Comparisons to placebo were conducted using an ANCOVA with baseline as a covariate. The mean daily number and severity of hot flashes were compared among treatment groups for each month using an ANCOVA, with treatment as a factor in the model and baseline as the covariate. Differences in categorical data between groups were explored by Mann-Whitney Test, Wilcoxon Signed Ranks Test or χ^2 test.

A linear regression analysis was used to analyze the relationship between duration of menopause and the decrease in hot flashes during treatment.

Changes in MENQOL scores from baseline to month 3 and month 6 were analyzed with analysis of variance and analysis (ANOVA) of covariance (ANCOVA).

Vaginal maturation index (VMI) was analyzed by using a two-way of variance or Student's t-test or χ^2 test.

Student's t-test and ANOVA were used to compare the differences of the Hormone levels. χ^2 test was used to compare the incidence of adverse events between the two treatment groups.

Data entry and quality control

The clinical data were entered into the computer by means of Single Data Entry, through a specialist keyboard operator, to ensure completeness, accuracy and consistency. The quality control checks included identifying any missing critical data, checking for consistency of responses and the completeness of dates and logical order.

Discussion

We chose a very simple herbal formula as a herbal agent for the control of menopausal syndrome. We believed that the two herbs, although not classically described as anti-menopausal, might have good chance of being so, since one of the herbs, viz. *Angelica sinensis*, is well known to be supportive of gynecological symptoms; and the other herb *astragali*, is one of the most favored supporting partner to maintain physiological well-being. In our therapeutic design, we followed closely the GCP regulations. The twin herb formula was manufactured and dosed like any pharmaceutical. The evaluation of the efficacy was based on standard symptomatic improvement analyzed with bio statistical tools.

If we, instead of following the requirements of GCP and RCT, chose to adopt the traditional Chinese Medicine experts' practice, we need to subdivide our patient groups firstly according to their clinical symptom patterns, and then selected the appropriate symptom sufferers from each pattern group separately for variable treatment using flexible herbal formulations. DBT might remain as major therapeutic agent, which however, can be freely modified by the attending physician according to the changes in clinical presentation.

A number of queries immediately arise. As the symptom pattern of any patient change with time, how often should their treatment is altered? Once treatment is altered, it becomes an individual case (losing the required uniformity). Altering treatment might mean frequency or dosages. Traditional practitioners might need to add or subtract herbal items. Can this be allowed? The protocol insists that the duration of treatment last for 24 weeks, if the unscheduled modifications occur rather frequently, how could efficacy results be assessed.

We avoid all these difficulties by designing a protocol strictly according to the recommendations of good clinical practice with strict requirements of patient inclusion, standard treatment program and assessment methodology.

As a matter of fact, a clinical trial on post-menopausal women utilizing the protocol had been completed and a full manuscript has been published [13]. After the trial we are able to conclude that DBT was effective controlling some of the symptoms related to menopause. With this experience, we could conclude that a protocol designed according to GCP would serve well in the study of Traditional Medicine.

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