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The effect of Chinese herbal medicines (CHM) on menopausal symptoms compared to hormone replacement therapy (HRT) and placebo

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Abstract

Objective: To evaluate within the Traditional Chinese Medicine (TCM) setting, the effect of CHM—formulae on menopausal symptoms.

Design: A double-blind and double-dummy randomised placebo-controlled trial.

Method: Between February and June 2002 and June and October 2004, 31 peri- and postmenopausal Dutch women were recruited to complete 12 weeks of treatment with either CHM formulae ($n = 10$), HRT ($n = 11$) or placebo ($n = 10$) medications plus 4 weeks of non-treatment follow-up observation.

Hereby a double-dummy setting is applied, i.e. the medications and placebo's taken were both capsules and liquid extracts.

Appropriate to the TCM setting, the CHM-prescriptions could be adjusted according to the symptoms and signs of the individuals for that moment.

Main outcome measures: The primary end-point was the reduction in frequency of vasomotor symptoms (hot flushes and night sweats).

Secondary end-point were the improvements measured in quality of life questionnaire SF-36 and other symptoms and signs related to the peri- and postmenopausal period.

Results: Placebo had a score of 30%. Compared to Placebo, on average CHM is 29% significantly ($p < 0.05$) more effective in reducing the amount of hot flushes, while HRT is almost 50%. Although quantitatively there was a significant difference in the reduction of hot flushes between groups, qualitatively there was no overall improvement.

Conclusions: This pilot study proved clearly that CHM could help women with their menopausal problems. The chosen trial methodology with its TCM differential diagnosis after orthodox medicine diagnosis is fully compatible with TCM practice and hence acceptable for western and Chinese medical practitioners. For a place in the western health care system, we need to conduct a larger trial with a more menopause specific questionnaire.

Keywords: Menopause; Randomised controlled trial; Chinese herbal medicines; Comparative methodology

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1. Introduction

For most women, aged between 40 and 55 years, the body slowly produces less of the hormones oestrogen and progesterone and the frequency of their period starts to alter. At onset it is called 'peri-menopause' then when the period has stopped for 12 months it is known as 'menopause'. Besides alteration in periods, other symptoms can occur; hot flushes and night sweats, insomnia, depressed feelings, urogenital complaints, etc.

Across cultures, there is great diversity in symptom intensity. European and American women score highest in vasomotoric symptoms and Asians lowest. It is speculated that the difference might be due to the high consumption of soy products by Asians. Soy has a high content of isoflavones, a kind of phytoestrogen, but trials to confirm this conclusion are still controversial [1].

Until quite recently, the standard treatment for menopausal symptoms was oestrogen-plus-progesterone combination therapy. Due to the negative findings of a sizeable Women's Health Initiative (WHI) long-term trial [2], which had to be stopped promptly in October 2002, menopausal women nowadays are advised to take Hormone Replacement Therapy (HRT) medications at the lowest dose and for the shortest duration needed.

The negative findings were increased risk of heart attack, stroke, blood clot formation and breast cancer while the positive ones were reduced risk of colorectal cancer and fewer fractures.

Although current research shows that the potential absolute risks of oestrogen only (ET)/combined oestrogen–progestogen (EPT) therapies are small (except stroke for EPT for which the figure is above the rare category), particularly for the ET arm [3], many women find the risks are still unacceptable and look for non-hormonal therapies to manage their hot flush problems [4].

Traditional Chinese Medicine (TCM) could offer such an option since TCM has a long history of successful treatment for gynaecological disorders. The medical classic Neijing Suwen (~100 BC) described the changes of women's bodies more in terms of aging process and loss of fertility [5]. While western doctors define menopause as stemming from oestrogen deficiency, in TCM oestrogen along with other hormones is subsumed within the larger category of the substance Essence (Jing) [6]. Stored in 'Kidney' (both as substance and as function) entity in TCM, Jing is the origin of all Yin and Yang. Menopausal problems result from the diminution of Jing and it could easily lead to a balance derangement between Yin and Yang with its manifold of symptoms. Hot flushes are signals of Yin's inability to restrain Yang activities.

2. Methods

2.1. Study design

The working group designed a double-blind and double-dummy randomised controlled trial to evaluate the efficacy of CHM prescriptions on reduction of menopausal symptoms compared to HRT and Placebo. In contrast to most performed trials on the subject matter, all participants had to be diagnosed twice. Firstly, conforming to western medicine menopause criteria and then in accordance with TCM differential diagnosis.

Following the TCM principles, treatment should be tailored to the individual symptoms and signs, although they all have the same western medical diagnosis (i.e. menopause). Also in time-course, the TCM diagnosis had to be re-evaluated and the herbal formulae be modified accordingly.

The Dutch medical ethical committee, Metopp approved the protocol and participants had to give their informed consent before the trial start. They were instructed to record their menopausal symptoms in a diary continuously for 16 weeks (12 weeks intervention + 4 weeks follow-up). A numeric score of hot flushes including night sweats were to be noted four times each day. At the start, a minimum of 20 hot flushes in a week was a requirement and intervention is considered effective if frequency is reduced by at least 50%. In addition to the diary, participants had to fill-in the SF-36 ('quality of life') questionnaire at the start and again at week 12 (end of intervention).

2.2. Participants

Participants were recruited by local Dutch newspapers in two cities and there were two trial settings in

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2002 and 2004. Immediately after trial 1 the WHI negative publication on HRT appeared and it was extremely difficult to find women for the second trial. From a total of 50 Dutch women, only 31 passed the stringent selection process conforming to the admittance criteria of the trial (Appendix A.1).

Inclusion criteria were:

- a minimum of 20 hot flushes or night sweats in a week;
- aged 45–65 years;
- FSH (follicle stimulating hormone) level >30 IU/L;
- at least in their peri-menopausal period (marked by irregular cycles and climacteric symptoms);
- no other complaints except those of menopause;
- able to comprehend the context of the trial.

Exclusion criteria were:

- the intake of hormones or medications, that could affect the vasomotoric symptoms;
- serious diseases, like cancer, (auto) immune system diseases, thrombosis and thrombophlebitis;
- blood pressure higher than 160/90;
- endocrinal diseases;
- liver function scores >1.5 of normal values;
- obesity (body weight >30% of normal values);
- hormone intake in interval between first consultation and trial start;
- refusal to take hormone medication Premelle® '5';
- lactation and porphyria (contraindicated to Premelle® '5').

2.3. Treatment intervention and medications

A third party randomised the group by coin flip procedure and the result was 11 women in HRT, 10 in CHM and 10 in Placebo arm. The 'blinded' doctors saw the patients on weeks 0, 2, 4, 12 and 16; for the first four encounters, patient's signs and symptoms had to be evaluated anew each time. Herbal prescriptions were readjusted accordingly. The last 4 weeks was a follow-up period without any medication to see whether or not a rebound effect would occur.

The 'medications' administered were herbal and placebo extracts, HRT and placebo capsules. The basic herbal prescription was a slightly modified classical formula "Zhi Bai Di Huang Wan" from 18th©Zheng Yin Mai Zhi literature (Appendix A.2). This formula was prescribed for the condition of Kidney-yin-deficiency, since all women at menopause suffer from this functional problem. Besides this impairment the person could develop several 'TCM categorical problems', among which are Kidney-yang-deficiency, hyperactivity of Liver-yang stemming from Liver-yin-deficiency, Heart-blood-emptiness, weakness of Spleen and Stomach and Phlegm stagnation (Appendix A.3). So, all patients received additional herbs following the individualised TCM differential diagnosis.

The extracts in this trial were Hydrophilic Concentrate® solutions. HRT was Wyeth Premelle® '5' (0.625 mg conjugated oestrogen plus 5 mg medroxyprogesterone) and double-dummy placebos were a glycerine/water solution with similar colour and taste and a crystalline cellulose. All herbs were screened for arsenic and heavy metal contamination by Moos-Pharma laboratory in Belgium. No products were from animal origin or from endangered species. Patients were instructed to take one capsule and three times 90 drops of liquid extract a day. Remedies and placebos were of same taste and colour.

2.4. Outcome measures

Age, body mass index (kg/m^2), vasomotor symptoms, last period, previous use of HRT or natural therapies for menopausal complaints and quality of life health indicators (SF-36) were documented at baseline. The women were instructed to note the frequencies of hot flushes and night sweats in their daily diary for the whole 16 weeks.

Primary end-point of the trial was the reduction of vasomotor symptoms quantitatively and as night sweat counts during night-time were not always reliable we only chose the reduction of hot flushes during morning, daytime, evening and before bedtime. We noticed that 50% of the women developed their maximum number of hot flushes not at baseline but 2 weeks after start or even longer. For this reason we decided to evaluate the effect of intervention, this being the flush reduction percentage compared to the maximum number encountered.

Secondary end-point was the difference in health indicators between baseline and end of intervention period, measured by the SF-36 (2nd Dutch edition) quality of life questionnaire. It is composed of 36

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questions, organised into 8 multi item scales within 2 main categorical components. The 'Physical'–physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perceptions (GH) and the 'Mental'–general mental health (MH), role limitations due to emotional problems (RE), social functioning (SF) and vitality (VT). All raw data was converted to a 0–100 scale with a higher score indicating a better level of functioning.

2.5. Statistical analysis

Analysis of the primary and secondary end-point was performed using the SPSS 12.0 program.

For 16 weeks, percentage changes in frequency of hot flushes of each participant was calculated compared to the maximum number encountered.

With Kruskall–Wallis non-parametric analysis of variance we tested whether the three treatments modalities data of maximum hot flushes were coming from an identical population and with the Kolmogorov–Smirnov Lilliefors significance test we checked the normal distribution of these data.

Repeated analysis of variance was applied to measure the primary outcome scores differences between treatment modalities for the whole period and these scores were corrected for dispersion within the three groups themselves. All p-value were two-tailed and the α-level of significance was set at 0.05. Missing item scores were not replaced.

To correct the significance level set-point for multiple comparisons setting we chose the Tukey-HSD test for not inadvertently rejecting the zero-hypothesis—the Bonferroni one being too strict. For treatments effect size (partial η^2 factor) calculation, we used Univariate General Linear model.

Quality of life SF-36 secondary outcome scores were compared between baseline and week 12 data using the Student's t-test. Extra analysis of covariance was done to see the interaction effect of baseline and maximum hot flush frequencies on the final effect of the interventions.

Finally, for a power of 80% and $\alpha = .05$ (one-tailed test), we estimated that 50 participants in each group were needed to detect a minimum of 25% difference on the primary outcome scores between the CHM and Placebo groups.

3. Results

3.1. Baseline data and participants flow

The baseline data were presented according to intention-to-treat protocol. Although the characteristics of the three groups were similar, one exception was the poor general mental health condition of the Placebo group compared to the other two. We did not have any specific explanation for this (Appendix A.4).

During the study, one woman from the CHM group experienced a serious problem. She experienced a strong aggravation of her asthma for two episodes and needed heavy corticosteroid medications (Appendix A.1). This event was obviously not related to the study-circumstances.

Consequently, we excluded this person from our evaluation and presented our outcome measures as per protocol analysis.

3.2. Hot flushes

On average Placebo scored 30% effective in reduction of hot flushes. Compared to Placebo, CHM had a 29% higher average score ($p < 0.05$ and 95% CI: 1.2–56.0%) and HRT 50% higher ($p < 0.01$ and 95% CI: 24.0–76.1%). In time-course, the significant effect of CHM was seen for weeks 5–11 (with the exception of week 6) and HRT for weeks 4–13 (Fig. 1). The CHM and HRT large confidence interval values were taken from the week 7 data, since those data corresponded next to the average effect figures.

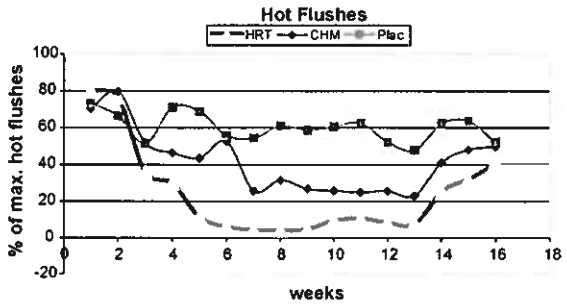

Fig. 1. Primary end-point: hot flushes.

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3.3. Quality of life scale SF-36

Although quantitatively there was a significant difference in hot flush reduction between groups, qualitatively there was no overall improvement at all by the end of trial intervention.

3.4. Effect of baseline hot flush and maximum hot flush frequencies on study outcomes

Statistically there was no significant covariates contribution of baseline hot flush and maximum hot flush frequencies on the final effect of all interventions.

3.5. Adverse events

For all interventions, no serious adverse events were reported.

Some patients disliked the taste of the extracts, but it was without any consequences.

4. Discussion

This pilot (although classified as phase I) study proved clearly that CHM could help women with their menopausal problems. The negative outcome on week 6 and the rebound effect of CHM parallel to HRT at follow-up were due to some slow responders and short-term intake of the herbs. We did not measure the incidences in the period preceding the trial start and almost 50% of the subjects developed their maximum hot flush frequencies 2 weeks or more after it. One explanation of the latter could be the result of a 'doctor's effect' and the eagerness of the women to participate in the study. The former is not a real issue, since as we mentioned before, the baseline hot flush frequency as a covariate factor showed no interaction effect. Our trial had a positive effect for CHM compared to Placebo, as distinct to the Australian study [7]. Two reasons are probable; the different Chinese herbal compositions used and a noteworthy methodological difference such as the individualised Chinese diagnosis plus accordingly adjusted prescriptions, instead of one standard CHM formula. The chosen trial methodology with its TCM differential diagnosis after the orthodox medicine diagnostic procedure is fully compatible with TCM practice and hence acceptable for western and Chinese medical practitioners.

For our final calculation we excluded the woman who used the strong corticosteroid medications for several weeks because of her asthma aggravation. Although corticosteroids do not interfere with vasomotor symptoms, all strong orthodox medications like antibiotics, corticosteroids and others do block the therapeutic actions of the herbs and therefore our decision was to exclude the woman from our evaluation and to present our outcome measures as per protocol analysis.

We could not detect any oestrogen content in our herbal formulae. Oestrogen level is associated with thermoregulatory stability in the body and when the level declines this stability is compromised. One possible explanation is that a low oestrogen level may increase brain catecholamine, norepinephrine. The higher norephinephrine concentration narrows the hypothalamic thermoneutral regulation zone of a body's core temperature, hence an increase in hot flush frequency.

But several epidemiological studies reported, that external factors could – direct or indirect – influence this thermoregulation as well. Therefore, one reasonable explanation for the CHM positive effect was, that individualised treatment might modify the women complex mind-body imbalance, since the herbal composition chosen were in accord with the exhibited overall symptoms and signs. This statement would need further researching.

Another explanation from Chinese studies [8] referred by Dharmananda in his review [5], claimed that the positive effect of some formulae were indeed due to the pharmacological active constituents in the herbs. They interacted with the adrenal cortex and other endocrine glands, resulting in the decline of serum FSH and LH and an increase of oestradiol. We had not measured these parameters at the end of our study.

Emotional factors, like stress, excitement and fear can strengthen or induce flushes. The modification of these psychic elements might for the greater part be responsible for the high score of the Placebo intervention, a score that corresponds with figures (between 18 and 40%) in the literature on the subject matter [9].

In western societies, vasomotor symptoms are the main complaints of menopausal women. But epidemiological and symptomatic data across cultures report

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quite a different pattern. For example, in Malaysia up to 70% of menopausal women never suffer from vasomotor symptoms and in Japan their main complaint is shoulder stiffness and hot flushes count as number four after fatigue and headache [10]. Having this knowledge, socio-economic and cultural factors need to be taken into consideration for an appropriate medical intervention.

Most women in the West experience hot flushes for 3–5 years before they taper off and many of them do not like to use HRT for such a long period [11]. Therefore CHM could supplement HRT for the remaining problematic years, but to ascertain our positive result we need to conduct a larger trial and with a more menopause specific questionnaire, like the Menopause Rating Scale (see: http://www.menopause-rating-scale.info).

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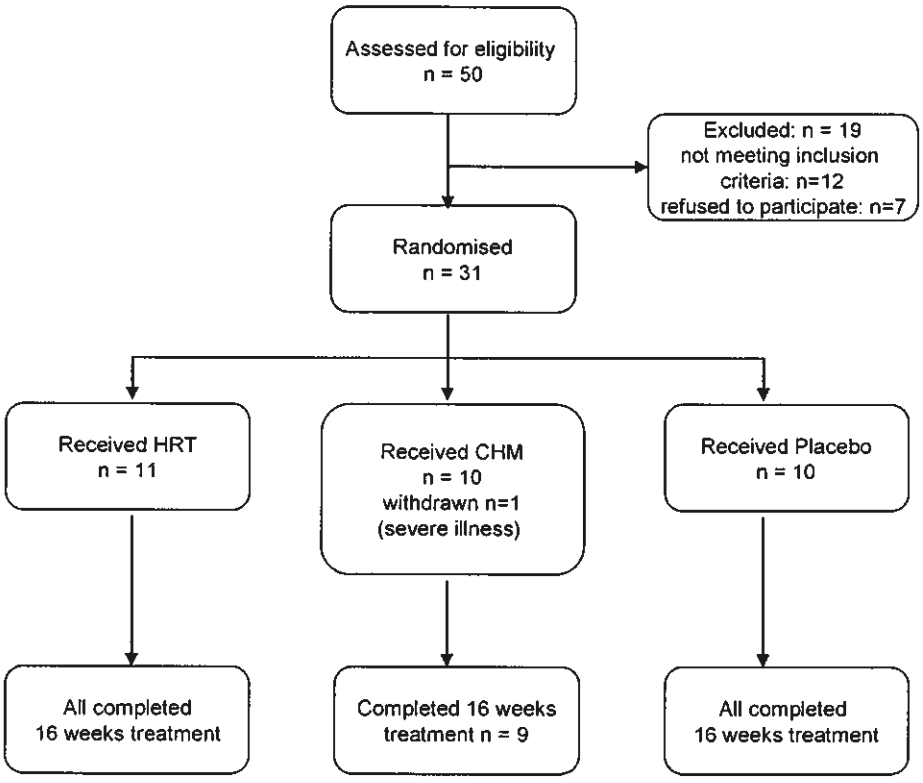
Appendix A

A.1. Flow diagram



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HRT: hormone replacement therapy; CHM: Chinese herbal medicines.

A.2. *The basic Chinese herbal formula 'Zhi Bai Di Huang Wan' or 'Anemarrhena, Phellodendron and Rehmannia combination' modified by Dr. Kwee Swan Hoo*

Rhizoma Anemarrhenae, Zhi Mu	5.1%
Cortex Phellodendri, Huang Bai	5.1%
Radix Rehmanniae Praeparata, Shu Di Huang	20.5%
Fructus Corni, Shan Zhu Yu	10.3%
Rhizoma Dioscoreae Oppositae, Shan Yao	10.3%
Sclerotium Poriae Albae, Fu Ling	7.7%
Os Draconis Ustum, Duan Long Gu	10.3%
Concha Ostreae Usta, Duan Mu Li	10.3%
Cortex Moutan Radicis, Mu Dan Pi	7.7%
Rhizoma Alismatis, Ze Xie	7.7%
Fructus Lycii, Gou Qi Zi	5%

Additional materia medica following the TCM differential diagnosis (see Section 2.3). For individuals who are interested herein, please contact the author.

A.3. *Menopause—TCM differential diagnosis [12]*

Key clinical symptoms and signs.

(1) Kidney-yin-deficiency: night sweating, backache, tinnitus, dry mouth at night, etc. *Tongue*: normal colour without coating; *pulse*: floating-empty.
(2) Kidney-yang-deficiency: backache, feeling of cold, abundant clear urination, weak legs and knees, etc. *Tongue*: pale and wet; *pulse*: deep-weak.
(3) Hyperactivity of Liver-yang: headache, irritability, insomnia, outburst of anger, etc. *Tongue*: pale or slightly red on sides; *pulse*: wiry.
(4) Heart-blood-deficiency: palpitations, insomnia, poor memory, anxiety, etc. *Tongue*: pale, thin and slightly dry; *pulse*: choppy or fine.
(5) Spleen/Stomach-Qi-deficiency: poor appetite, epigastric discomfort, tiredness, pale complexion, etc. *Tongue*: pale; *pulse*: empty, especially on right middle position.
(6) Phlegm stagnation: (among others) a feeling of oppression of the chest, heaviness of body, nausea, dizziness, etc. *Tongue*: swollen with sticky coating; *pulse*: slippery or wiry.

A.4. *Baseline characteristics*

Baseline characteristics[a]	HRT (2)	CHM (1)	Placebo (0)	$p_{2,1}$	$p_{2,0}$	$p_{1,0}$
Numbers	11	10	10			
Age (years)	53.6 (50.0–57.3)	53.2 (51.5–55.0)	54.9 (51.6–58.2)	0.81	0.57	0.32
BMI (kg/m^2)	22.3 (20.7–24.0)	23.8 (21.9–25.6)	23.3 (20.8–25.8)	0.20	0.45	0.75
Amenorrhea (years)	3.91 (1.23–6.59)	2.84 (0.11–5.58)	3.33 (0.48–6.18)	0.54	0.74	0.78
Previous use of						
HRT	27%	25%	0			
Natural therapies	9%	25%	10%			
Hot flushes (per week)						
at start	88.9 (31.7–146.2)	95.6 (46.7–144.5)	74.0 (56.0–98.1)	0.85	0.61	0.38
at max[b]	100.5 (60.1–160.8)	126.6 (68.5–184.7)	102.9 (81.2–124.6)	0.64	0.76	0.40
SF-36 = quality of life						
Physical health						
PF: physical function	82.7 (70.8–94.7)	84.5 (71.6–97.4)	78.5 (58.1–98.9)	0.82	0.68	0.58
RP: role physical	61.4 (37.2–85.5)	70.0 (45.0–95.0)	80.0 (49.8–110.2)	0.58	0.29	0.57
BP: bodily pain	25.5 (11.6–39.3)	31.0 (15.8–46.2)	22.0 (5.5–38.5)	0.55	0.72	0.38
GH: general health	68.2 (60.3–76.0)	64.0 (52.3–75.7)	57.5 (47.8–67.2)	0.50	0.07	0.35
Mental health						
VT: vitality	54.5 (47.0–62.1)	50.0 (44.7–55.3)	56.0 (43.3–68.7)	0.30	0.82	0.34
SF: social function	52.3 (35.6–69.0)	43.7 (36.2–51.3)	48.7 (39.9–57.6)	0.33	0.69	0.35
RE: role emotional	69.7 (44.3–95.1)	86.7 (70.0–103.3)	100.0 (51.0–149.0)	0.23	0.22	0.57
MH: mental health	62.5 (54.3–70.8)	55.2 (50.4–60.0)	75.6 (64.7–86.5)	0.11	0.04	0.01

[a] Values are mean (95% confidence interval).
[b] Delayed max hot flushes.

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