Title: Effects of acupuncture and Chinese herbal medicine (Zhi Mu 14) on hot flushes and quality of life in postmenopausal women – Results from a four-armed randomized controlled pilot trial.

Running title: Acupuncture and CHM for menopausal symptoms

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Abstract

Objective: The aim of this study was to evaluate the feasibility of a clinical trial investigating the effects of acupuncture (AP) and Chinese herbal medicine (CHM) on hot flushes and quality of life in postmenopausal women.

Methods: 40 postmenopausal women reporting at least 20 hot flushes per week were enrolled in a randomized controlled trial. They were randomly allocated to receive traditional Chinese medicine (TCM) AP, sham AP, verum CHM, or placebo CHM for 12 weeks. Follow-up assessment was conducted 12 weeks after intervention. Primary outcome measures included hot flush frequency and severity. As a secondary outcome measure the severity of menopausal symptoms was assessed using the menopause rating scale (MRS II).

Results: TCM AP induced a significant decline in all outcome measures from pre- to post-treatment compared to sham AP (hot flush frequency: $P = 0.016$; hot flush severity: $P = 0.013$; MRS: $P < 0.001$). In the TCM AP group a larger decrease in MRS-scores persisted from pre-treatment to follow-up ($P = 0.048$). No significant differences were noted between the verum and the placebo CHM group. Compared to the verum CHM group there was a significant decrease in MRS-scores ($P = 0.002$) and a trend towards a stronger decrease in hot flush severity ($P = 0.06$) in the TCM AP group from pre- to post-treatment.

Conclusions: TCM AP was found to be superior to sham AP and to verum CHM in reducing menopausal symptoms, while verum CHM showed no significant improvements when compared to placebo CHM.

Key Words: Menopause – Acupuncture – Chinese herbal medicine – Hot flushes – Vasomotor symptoms – Menopausal symptoms

INTRODUCTION

Menopausal women in western countries including Switzerland frequently report menopausal symptoms such as hot flushes, insomnia, mood swings, and irritability.[1,2] Menopausal symptoms in general and hot flushes in particular are known to affect quality of life.[3,4] To date, hormone therapy (HT) i.e. estrogen therapy (ET) and combined estrogen-progestogen therapy (EPT) is regarded as the most effective treatment for hot flushes.[5-7] Moreover, ET and EPT have been shown to lower the risk for vertebral and non-vertebral fractures, including hip fractures.[8,9] The preliminary report of the Woman's Health Initiative (WHI) that EPT increases the risk for breast cancer, stroke and coronary heart disease[10] has not been confirmed for younger women. In fact, the start of hormone treatment within the so-called "window of opportunity" (i.e. < 10 years after menopause, below the age of 60) results in a decreased risk of cardiovascular diseases[11,12] up to a treatment duration of 10.7 years[13] and a decrease of total mortality.[11,12] In the WHI, ET administered up to 10.7 years was found to decrease the risk for breast cancer,[13] while EPT did not change significantly breast cancer risk up to 7 years in women without prior hormone use.[14,15] With peroral ET and EPT, an increase of venous thromboembolic events has been reported, but not with transdermal ET.[16,17] Stroke and dementia are slightly increased when ET or EPT are administered after the age of 60 years.[8,10,18,19] Nevertheless, concerns about HT safety are an important reason for many women to refuse or discontinue HT.[20,21] In women after breast cancer, HT is contraindicated.[22] Not surprisingly, many symptomatic women are seeking alternative treatment approaches to alleviate their climacteric complaints.[23-25] The use of complementary and alternative medicine (CAM) in Switzerland is widely spread in the general population, with traditional Chinese medicine (TCM) being among the top treatments of the list.[26-29] According to TCM-theory menopausal symptoms are predominantly related to a decline in

kidney Yin, kidney Yang, or a combination of both, often diagnosed with concomitant syndromes associated with deficiencies in other organs e.g. spleen and liver.[30,31] Hence, when applying TCM-treatment modalities such as acupuncture and Chinese herbal medicine (CHM) for menopausal symptoms the main focus of the treatment lies on reinforcing the kidneys.

From a western medical point of view preliminary data are supporting the hypotheses that acupuncture may reduce vasomotor symptoms by inhibiting the impact of the hypothalamic-pituitary-adrenal axis on the hypothalamic-pituitary-ovarian axis[32] and by increasing the release of endogenous opioids[33] potentially influencing the functioning of the hypothalamic thermoregulatory center.[34] Also, for some CHM preparations treating menopausal symptoms, selective activating effects on estrogen receptor-β have been reported with potential synergistic effects of the herbal components.[35,36]

However, clinical trials investigating effectiveness of acupuncture[37-40] and CHM[41-45] on menopause related symptoms revealed mixed results, probably due to the large variability in applied trial methodology, as well as in potential treatment modalities e.g. various acupuncture point selections and CHM formulae.

The main objective of our pilot study was to collect preliminary data in order to assess and compare the effects of two TCM treatment modalities for menopausal symptoms, i.e. a semi-standardized TCM acupuncture treatment, and a standardized 14-herb CHM formula named Zhi Mu 14. This pilot study was also performed to evaluate the feasibility of conducting a larger clinical trial.

METHODS

Study design

We conducted a clinical trial at the Women's Hospital of the University of Bern, using a four-arm prospective, randomized study design investigating the effects of acupuncture (AP) and

Zhi Mu 14, a standardized Chinese herbal medicine (CHM) preparation, in postmenopausal women experiencing twenty or more hot flushes per week (see Figure 1). AP treatment was sham-controlled and single-blinded, while treatment with CHM was placebo-controlled and double-blinded. Participants were in the study for a total of 26 weeks, including a run-in period with diary collection (2 weeks), a treatment period (12 weeks), and a follow-up period after completion of treatment (12 weeks). Recruitment was carried out from December 2009 to March 2011 through advertisement of the study on pin boards and on the websites of the University of Bern and the University Hospital in Bern. The ethics committee of the Canton of Bern, Switzerland has formally approved the research protocol.

Study participants

Eligible study participants were postmenopausal women who met the following inclusion criteria: hot flushes for at least one year, at least twenty hot flushes per week during the run-in period, normal gynecological status, at least 12 months of self-defined amenorrhea or after hysterectomy, body mass index (BMI = kg/m^2) lower than 30, initial score on the Menopause Rating Scale (MRS II) of at least 20 points, serum concentration of follicle stimulating hormone (FSH) higher than 30 IU/L, and a signed informed consent. The following exclusion criteria were applied: hormone therapy (HT) and/or treatment with traditional Chinese medicine (TCM) and/or any kind of surgical intervention within 12 weeks of recruitment; abnormal genital bleeding; abnormal liver function, bilateral ovariectomy; ongoing pregnancy; chronic and/or acute physical diseases and/or mental disorders; abuse of alcohol and/or any other addictive substances; recent or planned phytoestrogen enriched diet, intake of herbal remedies for treating menopausal symptoms, more than two weeks of planned absence during treatment period, simultaneous participation in any other clinical trial.

Procedure

Women interested in study participation underwent a telephone screening to determine initial eligibility. Informed consent was signed prior to trial start. Initially eligible women received a complete written and oral description of the study and were invited to a clinic visit for medical examination including heart rate, blood pressure, gynecological examination, and laboratory blood tests. Participants received instructions on keeping a 2-week hot flush diary to document the frequency and severity of hot flushes. Diary data, gynecological and laboratory test results were used to verify eligibility. Eligible women were randomized to one of the four study groups. All study participants completed questionnaires at the end of the run-in period (= baseline), 4 weeks after start of treatment, at the end of treatment, as well as 12 weeks after treatment completion (= follow-up). At the end of the follow-up period participants underwent final medical examination. All participants were instructed not to take hormonal medication or to initiate other treatments for their hot flushes during their study participation.

Randomization and blinding

An independent data manager carried out randomization by using a computer generated random allocation sequence. Allocation concealment was achieved through sequentially numbered, opaque and sealed envelopes. After baseline examination was completed, eligible participants were assigned to one of the four study groups by consecutively opening the envelopes as they entered the study. The probability to be allocated to the TCM AP, the sham AP, the verum CHM or to the placebo CHM group was equal (1:1:1:1). Participants were unaware whether they were assigned to a treatment or to a control condition. The study staff in charge of data collection, outcome assessment, and preliminary data analysis was also blinded. Only the acupuncturist was informed regarding the allocation of patients to TCM and sham AP groups. The complete randomization list was placed in a sealed envelope and kept there until the study was completed.

Interventions

AP groups

A licensed acupuncturist (PJ) with 30 years of clinical experience has performed all AP treatments in both AP study groups. Participants in the TCM and sham AP group were scheduled for 12 weekly treatments. On the first treatment session, women received a TCM diagnosis. The standard treatment for women in the TCM AP group comprised the following acupuncture points: CV-4, GV-20, GB-20, PC-6, ST-36, SP-6, LI-4, and KI-3. Except for CV-4 and GV-20, which are located on the median of the body, all standard treatment points were needled bilaterally. In addition to this standardized treatment 7 to 10 supplementary acupuncture points were needled based on a persons' TCM diagnostic category (i.e. "kidney Yang with spleen Yang deficiency": BL-20, BL-23, SP-9, and CV-6 or "kidney Yin with liver Yin deficiency": BL-18, BL-23, HT-6, KI-6, and LR-3) or in accordance to the physicians clinical judgment. No more than 24 points were needled during any treatment. Needles were inserted through the skin to a depth of 0.2 cm to 1.5 cm depending on target site. With each needle insertion the acupuncturist attempted to elicit a de Qi sensation, which is characterized as a feeling of soreness, numbness, heaviness, or distention around the stimulated acupuncture point. Retention time of the sterile, single-use stainless-steel acupuncture needles (needle type: SEIRIN; 0.25 x 30 mm and 0.25 x 40 mm) was 30 min without any additional stimulation.

In the sham AP group acupuncture needles were inserted superficially without attempting to elicit a de Qi sensation on seven bilateral target sites that do not correspond to established TCM-acupuncture points (see Table, Supplemental Digital Content 1, which describes sham acupuncture points in detail). These sham acupuncture points have been previously defined [46] and used in large clinical trials.[47,48]

CHM groups

Participants in the verum and placebo CHM group were scheduled for clinic visits at week 1, 4, 8, and 12 of the treatment period. During these visits a licensed TCM-therapist (LT) with 20 years of clinical experience set a TCM diagnosis, observed the course of menopausal symptoms, inquired whether treatment related side effects occurred, and assessed treatment compliance by controlling participants' daily diary entries and weighting the remaining capsules. Women in both CHM groups were instructed to take 3 capsules orally with water twice per day i.e. postprandial in the morning and in the evening, and to report daily medication intake in their hot flush diary. Women in the CHM group received Zhi Mu 14, a standardized CHM preparation comprising 14 plant materials (see Table, Supplemental Digital Content 2, which describes the composition of the CHM formula Zhi Mu 14 in detail) that has been approved by the Swiss Agency for Therapeutic Products (Swissmedic) for therapeutic use. The formulation of Zh Mu 14 is based on two modified classic formulas i.e. "Gan Mai Da Zao Tang" and "Qing Hao Bie Jia Tang" designed to treat hot flushes, night sweats, insomnia, mood swings, irritability, and emotional instability resulting from kidney yin deficiency.[49] The administered dosage of 3 g of herbal extract granules per day is equivalent to 15g of dry herb. Participants in the placebo CHM group received placebo capsules containing starch (Amylum Maydis) and caramel as a color tracer. This placebo mixture has no known effects on menopausal symptoms. Both placebo and CHM capsules were identical in their appearance and were prepared by Sheng Foong Pharmaceutical Ltd., Taiwan on behalf of China Medical Ltd., Switzerland. In accordance with herbal Good Manufacturing Practice (GMP) genuineness and quality of each herbal component was controlled by conducting thin-layer chromatographic analysis and tests for heavy metal contamination, microbial traces, and pesticide residues.

Outcome measures

Primary outcome measures were severity and frequency of hot flushes per week. An adapted form of a daily hot flush diary frequently used in prior studies was used for data collection.[50] A hot flush severity score has been calculated as the sum of the number of self-reported hot flushes multiplied by severity. The applied hot flush severity rating scale ranged from 1 to 3 to distinguish between mild (= 1; heat sensation without sweating and disruption of activity), moderate (= 2; heat sensation accompanied by sweating but no disruption of activity), and severe (= 3; heat sensation accompanied by sweating and disruption of activity) hot flushes. Participants were asked to record the occurrence and severity of each hot flush during the run-in, the treatment, as well as during the 4th, 8th and 12th week of the follow-up period of the trial. During the follow-up period participants were reminded by phone call to re-uptake their diary entries.

As a secondary outcome measure menopause related quality of life was assessed using the validated Menopause Rating Scale (MRS II).[51-54] This self-report instrument comprises 11 items and assesses the presence and intensity of menopausal symptoms on a 5-point rating scale ranging from 0 (= no symptom) to 4 (= very severe symptom). The MRS II sum score represents an overall index of severity of climacteric related complaints, i.e. MRS II sum score of 0 to 4 (= no, little), of 5 to 8 (= mild), of 9 to 16 (= moderate), of ≥ 17 (= severe). Additionally to the MRS II sum score, three independent subscales i.e. psychological, somato-vegetative, and urogenital subscale indicate domain specific symptom severity.

Mean reference values for the MRS II scores in European populations are 7.2 for MRS II sum score, 2.9 for the psychological, 3.3 for the somato-vegetative, and 1.0 for the urogenital subscale. These values are comparable to the mean MRS II reference values for North America.[54]

Statistical analyses

Data analysis was conducted using SPSS (version 20) statistical software package for Macintosh (IBM SPSS Statistics, Somers, NY, USA). The level of significance was set at $P < 0.05$. Differences in group characteristics and baseline values were analyzed using χ^2 Tests for dichotomous variables, Kurskal-Wallis Tests for continuous variables with skewed distributions, and ANOVAs for normally distributed continuous variables. To compare treatment effects on primary and secondary outcome measures between the TCM and sham AP group, between the verum and placebo CHM group, as well as between the TCM AP and the verum CHM group mean change values have been calculated for each study group by subtracting pre-treatment baseline values from post-treatment values, and from follow-up values. Between group differences in mean change values have been analyzed using Mann–Whitney U Tests. Within group changes in outcome measures have been analyzed using Wilcoxon Tests.

RESULTS

Participants

Of the 63 applicants who underwent a telephone screening, 40 participants fulfilled eligibility criteria and successfully completed baseline assessment. They were randomly assigned to one of the four study groups. Study retention was excellent with 39 out of 40 women (97.5%) remaining in the study. Only one participant of the placebo CHM group discontinued prior to treatment start due to lack of motivation. Complete data sets of 39 participants have been considered in statistical analysis (Figure 1). Except for the frequency of TCM diagnoses, the four study groups did not significantly differ in group and baseline characteristics (Table 2).

14 women had other TCM diagnoses with 12 of them being diagnosed of kidney yin and spleen qi deficiency. On average participants in the verum CHM group took 92.3% (SD ± 10.0) and those in the placebo CHM group 89.5% (SD ± 14.2) of the prescribed capsules. The compliance rate for the weekly regimen in the TCM AP group was 94.2% (SD ± 6.9) and 92.6% (SD ± 6.2) in the sham AP group.

Changes in hot flushes

Figures 2a and b show the course of weekly hot flush severity scores and weekly hot flush frequencies in all four study groups. As within group analyses revealed participants in the TCM AP group reported a significant decrease of hot flush severity and frequency from pre- to post-treatment ($Z = -2.803$, $P = 0.005$; $Z = -2.701$, $P = 0.007$, respectively) as well as from pre-treatment to follow-up assessment ($Z = -2.497$, $P = 0.013$; $Z = -2.191$, $P = 0.028$, respectively). In the sham AP group a trend towards a decrease of hot flush severity and frequency was observed from pre- to post-treatment (P's = 0.09). In this group decrease in hot flush severity from pre-treatment to follow-up assessment was significant ($Z = -2.497$, $P = 0.013$), while decrease in hot flush frequency from pre-treatment to follow-up assessment remained on a trend level ($P = 0.06$). In the verum CHM group participants reported a significant decrease of hot flush severity from pre- to post-treatment ($Z = -1.988$, $P = 0.047$) as well as from pre-treatment to follow-up assessment ($Z = 2.040$, $P = 0.041$), while this was not the case for hot flush frequency (P's > 0.08). No significant changes in hot flush measures have been found in the placebo CHM group (P's > 0.40).

Between group analyses showed, that in comparison to the sham AP group participants in the TCM AP group reported a significantly greater decline in hot flush severity ($P = 0.013$) and frequency ($P = 0.016$) from pre- to post-treatment but not from pre-treatment to follow-up assessment (P's > 0.24; see Table 2a). No significant differences have been found between the verum and the placebo CHM group in any hot flush mean change value (P's > 0.42; see Table

2b). When compared to the verum CHM group a trend towards a greater decline of hot flush severity from pre- to post-treatment has been observed in the TCM AP group (P = 0.06), while no significant group differences have been found for the remaining hot flush mean change values (P's > 0.13).

Changes in menopause related quality of life (MRS II scores)

Within group analyses revealed the strongest decrease in MRS II sum score in the TCM AP group from pre- to post-treatment, and from pre-treatment to follow-up (P's = 0.005). Significant decreases in MRS II sum score from pre- to post-treatment (P's ≤ 0.025) and from pre treatment to follow-up assessment (P's ≤ 0.019) have also been found in the verum CHM and the sham AP group, while in the placebo CHM group a significant reduction of the MRS II sum score was observed for the period from pre-treatment to follow-up assessment (P = 0.036) but without significant changes in any MRS II subscale scores. In the TCM AP group all MRS II subscale scores decreased significantly from pre- to post-treatment (P's ≤ 0.007) and to follow-up assessment respectively (P's ≤ 0.013). In the sham AP group the psychological and somato-vegetative MRS II subscale scores decreased significantly from pre- to post-treatment (P's ≤ 0.017) and to follow-up assessment respectively (P's ≤ 0.005), while the MRS II urogenital subscale score decreased significantly from pre-treatment to follow-up assessment only (P = 0.012). In the verum CHM group a significant decrease from pre- to post-treatment and to follow-up assessment respectively was found in MRS II somato-vegetative subscale scores (P's ≤ 0.021), while the scores of the MRS II psychological and urogenital subscales decreased significantly from pre-treatment to follow-up assessment only (P's ≤ 0.020). In the placebo CHM group a significant decrease in the MRS II sum score (P = 0.036) but not in the subscale scores (P's ≥ 0.08).

Participants in the TCM AP group reported a significantly higher decrease in the MRS II sum

score from pre- to post-treatment ($P < 0.001$), as well as from pre-treatment to follow-up assessment ($P = 0.048$) when compared to the sham AP group. In the TCM AP group a significantly greater decline in all MRS II subscale scores was measured from pre- to post-treatment ($P's < 0.004$). At follow-up assessment significant group differences in mean change values of the MRS II somato-vegetative and the urogenital subscales persisted ($P = 0.014$, $P = 0.035$ respectively; see Table 2a). Between the verum and the placebo CHM group no significant group differences in MRS II related mean change values have been found ($P's \geq 0.10$; see Table 2b). In comparison to the verum CHM group participants in the TCM AP group indicated a significantly higher decrease in the MRS II sum score ($U = 9.5$, $Z = -3.072$, $P = 0.002$), as well as in all three MRS II subscale scores from pre- to post-treatment (psychological subscale: $U = 12.5$, $Z = -2.866$, $P = 0.004$; somato-vegetative subscale: $U = 16.0$, $Z = -2.591$, $P = 0.010$; urogenital subscale: $U = 15.0$, $Z = -2.675$, $P = 0.007$). No significant differences in MRS II mean change values between the verum CHM and the TCM AP group have been found from pre-treatment to follow-up assessment ($P's \geq 0.10$).

Adverse events

In one participant in the verum CHM group a dysplasia of the squamous epithelium was diagnosed at the final gynecological examination at follow-up assessment. This serious adverse event, however, is not thought to be related to the trial medication. Only one participant in the sham AP group reported a mild adverse event by stating pain sensation at needle insertion.

Blinding

At follow-up assessment all participants were asked to indicate to which study group they believe they were assigned to. In the TCM AP group 50% of the participants guessed correctly, 40% could not tell, and 10% guessed incorrectly. In the sham AP group 10% of the

participants guessed their group allocation correctly, 40% could not tell, and 50% guessed incorrectly. In the verum CHM group 40% of the participants guessed their group assignment correctly and 60% guessed incorrectly. In the placebo CHM group 89% of the participants guessed their group allocation correctly, only 11% made a wrong guess.

DISCUSSION

Our findings demonstrate a significant improvement of hot flush severity and frequency, as well as other menopausal symptoms in postmenopausal women after 12 weeks of TCM AP treatment in comparison to sham AP. Moreover we measured persisting long-term effects of TCM AP on attenuation of overall, somato-vegetative and urogenital menopausal symptom severity at 12 weeks follow-up assessment. When comparing the effects of TCM AP with verum CHM, TCM AP was found to be superior to CHM in terms of significantly stronger decreases in all MRS II subscale scores, and a trend towards a stronger reduction in hot flush severity from pre- to post-treatment. No significant effects were found for verum CHM compared to placebo CHM. Interventions in all study arms were well tolerated.

Unlike several sham-controlled AP studies[32, 34, 37,55-58] our data suggest that TCM AP is superior to sham AP in reducing severity and frequency of menopause related symptoms. This preliminary finding is in line with results from two recently published randomized sham-controlled AP trials emphasizing not only clinical effectiveness of TCM AP by reducing hot flush frequency and overall menopausal symptom severity by 60 to 95% but also underlining its treatment specific efficacy.[38,39] Taken into account that sham AP interventions are not considered to be physiologically inert control interventions[59] physiologic treatment effects of AP are likely to be underestimated. In our trial a semi-standardized treatment protocol was applied by a highly experienced acupuncturist, which might have contributed to the

pronounced treatment effects of TCM AP.[60] With respect to the reported postmenopausal HT induced reduction of hot flush severity and frequency by approximately 87% and 75% respectively,[61] and of MRS II sum score by 30% to 36% from baseline,[53,62] the observed attenuation in menopausal symptoms in the TCM AP treatment group (i.e. reduction of hot flush severity and frequency by 64.3% and 55.9% respectively, and of MRS II sum score by 66.3% from baseline) plead for acupuncture as a clinically meaningful intervention for alleviating menopausal symptoms. However, further comparative effectiveness research is needed to prove its clinical significance.

Even though within group analyses revealed a significant decrease of hot flush severity and frequency as well as of MRS II scores in the verum but not in the placebo CHM group, both study groups did not differ significantly in outcome measures when compared with each other. A possible explanation for this finding could be the limits of our clinical trial setup. Since we used a predefined CHM prescription (Zhi Mu 14 capsules) we did not have the possibility to individually adapt the treatment provision, i.e. formula and dosage of the formula depending on the patients' diagnoses, like we did in the TCM AP group. In fact, only three out of ten women in the verum CHM group were diagnosed of kidney yin and liver yin deficiency, while five women were diagnosed of kidney yin and spleen qi deficiency. Therefore a more individually tailored approach with adaptable herbal formula or inclusion criteria determined according to a specific TCM diagnosis (hot flushes can be based on different TCM diagnoses) would be more accurate for further studies. Despite the good treatment compliance in the verum CHM group it might be that the standard dosage of the trial medication was inadequate. Also, taken into account the small sample size of our pilot study, this non-significant finding should be treated with care, as we cannot rule out a type II error. Further basic and clinical studies investigating the effects of Zhi Mu 14 are warranted, as potential therapeutic effects of some herbal components of the trial medication have

already been documented, e.g. estrogenic activity of Rhizoma Anemarrhenae (Zhi Mu)[63] and sedative-hypnotic effects of Semen Ziziphy Spinosae (Suan Zao Ren).[64]

TCM AP was found to be superior in reducing menopausal symptoms when compared to the verum CHM. This result might be due to different mode of actions of the two treatment approaches. Hence, future research would strongly benefit from including the assessment of biological markers related to the postulated mechanistic pathways.

A non-specific treatment effect of approximately 30% reduction in hot flush severity from pre- to post-treatment was observed in the sham AP group, which is in line with the reported effects of sham AP in some previously conducted randomized sham-controlled trials (reduction of 20 to 40%).[55-57] Interestingly, unlike other randomized placebo-controlled CHM trials in postmenopausal women, where placebo effects of approximately 30% reduction of hot flush severity were documented[42-44] we have found no such effect in our placebo CHM group. This might be due to participants' potentially lower treatment expectations in this study group. Furthermore, the fact that eight of nine participants correctly assumed to be allocated to the placebo CHM group supports the notion of a reduced treatment expectation in this group. Future trials should consider repeated measuring of treatment expectations. Moreover, blinding of treatment allocation is likely to be enhanced by ensuring high similarity between placebo and verum CHM medication not only in look but also in taste and smell.[42,65] The significant decrease in the MRS II sum score from pre-treatment to follow-up assessment in the CHM placebo group is likely to reflect the natural course of menopause related symptom severity. However, to obtain precise data about the natural course a further control group receiving usual care should have been included in the study design, which would also allow a more accurate estimation of the sum of unspecific treatment effects other than time effects.[66]

The main strength of our trial is the four-armed placebo- and sham-controlled study design with a follow-up period of 12 weeks. Moreover, as study groups did not differ neither in their

group characteristics nor in baseline values randomization of participants is considered to be successful. Also, participants' adherence to the study protocol was excellent.

The following limitations need to be considered when interpreting the findings of this pilot study. First, we investigated the effects of a standardized CHM preparation and did not take into account TCM-treatment principles where the administered formula would have been modified at the beginning, as well as in the course of the treatment according to participants' individual constitution, overall symptoms, and CHM treatment responses. To the best of our knowledge, to date only one randomized placebo-controlled CHM trial with an individualized TCM based treatment approach has been conducted in postmenopausal women showing stronger symptom reducing effects in the verum CHM group.[43] A comparison of the efficacy of both a standardized and an individualized treatment approach would certainly elucidate this issue. Second, since hepatotoxic adverse events have been reported in association with the intake of CHM[67] we conducted laboratory blood analyses prior to treatment onset to rule out pre-existing abnormal liver functions. As analyses were not repeated until the end of the follow-up period the impact of the Zhi Mu 14 compound on liver functioning during the treatment could not have been evaluated. However, regarding CHM treatment safety no adverse events were reported in the verum CHM group during and after the treatment and no abnormal laboratory results were noted at follow-up assessment 12 weeks after treatment completion indicating long-term safety of the investigated CHM formula. Third, for the same reason as stated above no treatment effect on hormone levels from pre- to post-intervention was evaluated. Finally, the comparison of the two interventions TCM AP and verum CHM is suboptimal, since participants in the TCM AP group had significantly more treatment visits than those in the verum CHM group. Also the extent to which TCM treatment principles could have been considered was larger in the semi-standardized TCM AP treatment compared to the prescription of a standardized CHM preparation. Therefore these findings should be interpreted with care.

CONCLUSIONS

In this pilot study TCM AP treatment of 12 weeks has led to a general attenuation of menopausal symptoms including a substantial reduction in hot flush severity of more than 60% in postmenopausal women. This treatment type was found to be superior to sham AP and verum CHM. Former did not differ from placebo CHM. Due to the small sample size the generalizability of our results is limited. Our pilot data, however, support the feasibility of conducting a large scale multicenter trial to validate the preliminary findings.

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FIGURE LEGENDS

Legend to Figure 2a and 2b:

TCM = traditional Chinese medicine; AP = acupuncture; CHM = Chinese herbal medicine; a) = within group changes from baseline to post intervention; b) within group changes from baseline to follow-up; c) between groups changes within the same intervention method from baseline to post intervention; d) between groups changes within the same intervention method from baseline to follow-up; ns = not significant; * = $P < 0.05$; ** = $P < 0.01$.

LIST OF SUPPLEMENTAL DIGITAL CONTENT

- Supplemental Digital Content 1. Table that describes sham acupuncture points in detail. pdf
- Supplemental Digital Content 2. Table that describes the composition of the Chinese herbal medicine formula Zhi Mu 14 in detail. pdf

Figure 1: Flow diagram for the progress through the phases of the randomized trial based on the CONSORT recommendations

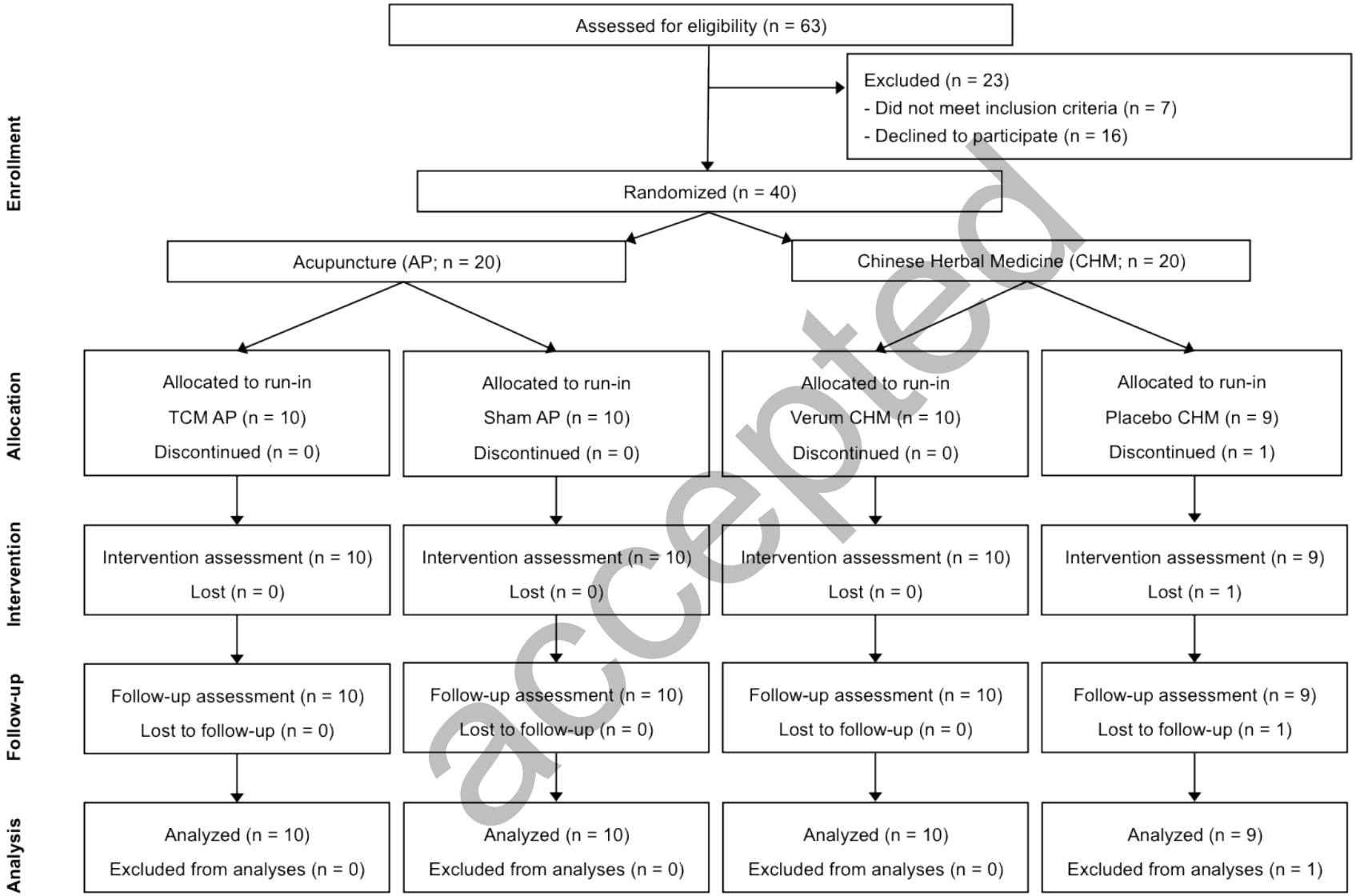

Figure 2a: Mean weekly hot flush severity scores as percentage of baseline

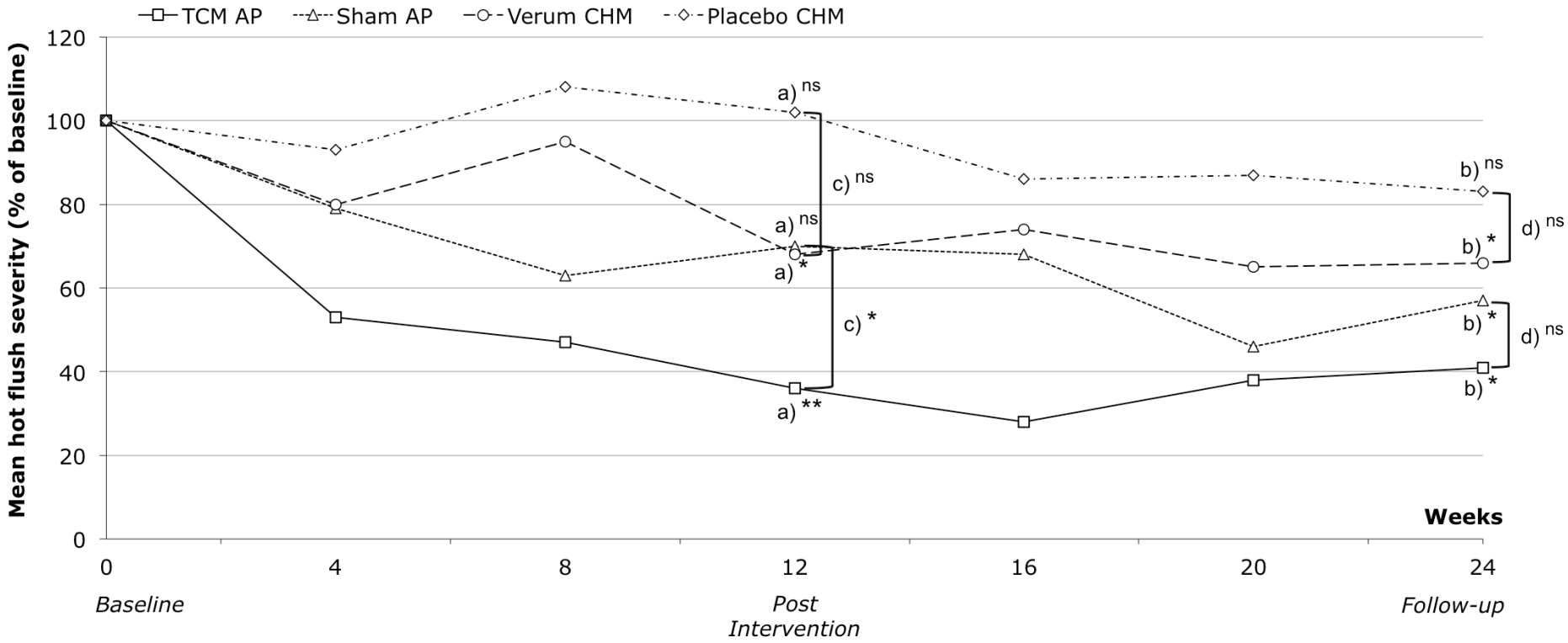

Figure 2b: Mean weekly hot flush frequency scores as percentage of baseline

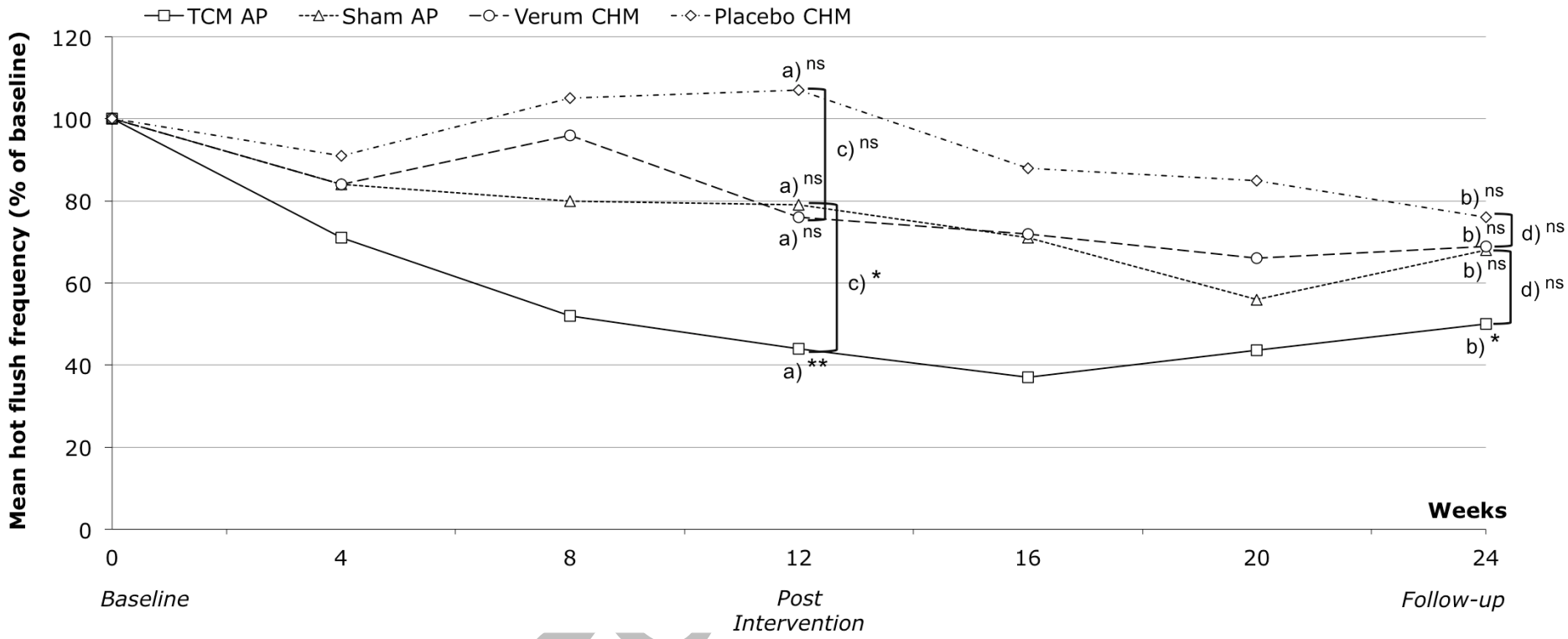

Table 1: Group and baseline characteristics of the four study groups

Characteristics	**TCM AP** (n = 10)	**Sham AP** (n = 10)	**Verum CHM** (n = 10)	**Placebo CHM** (n = 9)	**Complete sample** (n = 39)	**P**
Current age (years)	54.70 ± 4.11	51.20 ± 2.86	53.10 ± 2.81	53.44 ± 3.39	53.10 ± 3.45	0.15
BMI (kg/m^2)	24.03 ± 2.34	21.58 ± 2.12	21.72 ± 2.03	23.03 ± 2.72	22.58 ± 2.44	0.07
Smoking (yes / no)	1 / 9	1 / 9	1 / 9	3 / 6	6 / 39	0.41
Years since last menstruation	4.4 ± 2.7	5.8 ± 6.7	6.4 ± 5.2	7.2 ± 5.8	5.9 ± 5.2	0.69
Frequency of hot flushes (per week)	63.20 ± 43.77	54.80 ± 31.71	65.50 ± 36.57	54.83 ± 34.43	59.71 ± 35.80	0.88
Severity of hot flushes (per week)	119.55 ± 79.31	102.75 ± 73.21	121.00 ± 63.65	119.67 ± 107.97	115.64 ± 78.95	0.95
MRS II sum score	25.20 ± 3.29	24.00 ± 3.86	25.70 ± 6.43	23.11 ± 2.62	24.54 ± 4.29	0.56
Heart rate (beats per minute)	64.9 ± 8.0	67.2 ± 8.6	63.6 ± 8.9	67.4 ± 8.8	65.7 ± 8.4	0.72
Systolic blood pressure (mmHg)	106.7 ± 19.1	111.3 ± 17.6	109.5 ± 11.6	112.8 ± 18.9	110.0 ± 16.5	0.88
Diastolic blood pressure (mmHg)	73.6 ± 13.9	71.5 ± 10.6	71.1 ± 8.2	70.6 ± 12.3	71.7 ± 11.0	0.94
FSH (IU/L)	85.33 ± 21.84	93.71 ± 31.49	71.61 ± 16.51	89.20 ± 29.16	84.85 ± 25.74	0.26
LH (IU/L)	39.76 ± 14.35	46.86 ± 15.60	37.30 ± 9.71	41.49 ± 12.32	41.35 ± 13.18	0.43
Estradiol (pmol/L)	27.70 ± 13.15	58.70 ± 54.40	41.50 ± 23.47	67.56 ± 48.21	48.38 ± 40.02	0.12
ALP (IU/L)	74.20 ± 25.99	61.00 ± 9.37	69.80 ± 10.12	68.11 ± 11.16	68.28 ± 15.97	0.32
ASAT (IU/L)	25.00 ± 4.50	25.50 ± 4.17	26.50 ± 5.62	25.78 ± 7.54	25.69 ± 5.36	0.94
ALAT (IU/L)	23.50 ± 8.46	18.20 ± 5.05	21.70 ± 13.65	24.33 ± 22.78	21.87 ± 13.49	0.77
Creatinin (µmol/L)	68.70 ± 9.89	62.50 ± 9.72	62.00 ± 8.18	66.56 ± 6.58	64.90 ± 8.87	0.27
TCM diagnoses (yes / no)						
- kidney yin and liver yin deficiency	4 / 6	7 / 3	3 / 7	1 / 8	15 / 24	0.06
- kidney yang and spleen yang deficiency	6 / 4	3 / 7	1 / 9	0 / 9	10 / 29	0.014
- other TCM diagnoses	0 / 10	0 / 10	6 / 4	8 / 1	14 / 25	<0.001

All continuous data are presented as mean ± SD; P-values for continuous data refer to ANOVA, and for dichotomous data to X^2-Test; TCM = traditional Chinese medicine; AP = acupuncture; CHM = Chinese herbal medicine; BMI = body mass index; FSH = follicle stimulating hormone; LH = luteinizing hormone; MRS = Menopause Rating Scale; ALP = alkaline phosphatase; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase

Table 2a: Changes in hot flushes and MRS II scores in acupuncture (AP) groups

Variable	Mean change values ± SD Δ TCM AP (n = 10)	 Δ Sham AP (n = 10)	U	Z	P[a]
Hot flushes severity					
- week 12 (post intervention)	- 76.9 ± 49.6	- 31.7 ± 57.6	17.0	- 2.495	0.013
- week 24 (follow-up)	- 70.4 ± 70.5	- 44.3 ± 57.0	34.5	- 1.172	0.24
Hot flushes frequency					
- week 12	- 35.3 ± 30.2	- 11.3 ± 21.7	18.0	- 2.420	0.016
- week 24	- 31.3 ± 40.0	- 16.8 ± 27.5	35.5	- 1.097	0.27
MRS II total score					
- week 12	- 16.7 ± 5.5	- 4.2 ± 4.3	0.0	- 3.788	<0.001
- week 24	- 14.2 ± 6.1	- 9.5 ± 3.7	24.0	- 1.975	0.048
MRS II psychological subscale					
- week 12	- 5.7 ± 3.2	- 1.3 ± 2.2	12.5	- 2.861	0.004
- week 24	- 4.3 ± 4.3	- 3.8 ± 1.9	38.5	- 0.880	0.38
MRS II somatio-vegetative subscale					
- week 12	- 7.3 ± 3.0	- 1.9 ± 2.2	5.0	- 3.422	0.001
- week 24	- 6.4 ± 2.2	- 3.7 ± 1.6	18.0	- 2.462	0.014
MRS II urogenital subscale					
- week 12	- 3.7 ± 1.3	- 1.0 ± 1.8	11.0	- 2.982	0.003
- week 24	- 3.5 ± 1.2	- 2.0 ± 1.9	22.5	- 2.111	0.035

[a] P-values refer to Mann-Whitney U Test

Table 2b: Changes in hot flushes and MRS II scores in Chinese herbal medicine (CHM) interventions

Variable	Mean change values ± SD		U	Z	P[a]
	Δ Verum CHM (n = 10)	Δ Placebo CHM (n = 9)			
Hot flushes severity					
- week 12 (post intervention)	- 36.8 ± 49.3	- 2.4 ± 82.9	36.5	- 0.695	0.49
- week 24 (follow-up)	- 41.4 ± 69.2	- 24.4 ± 65.2	38.5	- 0.531	0.60
Hot flushes frequency					
- week 12	-15.4 ± 21.84	3.2 ± 44.5	39.0	- 0.490	0.62
- week 24	- 20.2 ± 41.24	- 4.8 ± 24.8	31.0	- 0.800	0.42
MRS II total score					
- week 12	- 5.6 ± 6.70	- 4.1 ± 7.0	41.5	- 0.287	0.78
- week 24	- 8.9 ± 9.39	- 4.6 ± 5.3	32.5	- 1.022	0.31
MRS II psychological subscale					
- week 12	- 1.5 ± 2.5	- 1.9 ± 4.2	44.5	- 0.041	0.97
- week 24	- 2.2 ± 3.2	- 2.7 ± 3.7	41.0	- 0.330	0.74
MRS II somato-vegetative subscale					
- week 12	- 3.0 ± 3.3	- 1.11 ± 3.5	30.0	- 1.232	0.22
- week 24	- 4.7 ± 4.5	- 0.78 ± 2.0	25.0	- 1.665	0.10
MRS II urogenital subscale					
- week 12	- 1.1 ± 2.2	- 1.1 ± 0.9	40.5	- 0.384	0.70
- week 24	- 2.0 ± 2.8	- 1.1 ± 1.2	34.0	- 0.914	0.36

[a] P-values refer to Mann-Whitney U Test

Supplemental Digital Content 1: Table that describes sham acupuncture points

Name of the sham acupuncture point	Location
Deltoideus	In the middle of the insertion line of M. deltoideus (LI-14) and Acromion
Upper Arm	2 cun laterally (radial) of LU-3
Forearm	1 cun ulnar of the proximal third of the line between HT-3 and HT-7
Spina Iliaca	2 cun above the spina iliaca anterior superior in vertical line to the arch of left ribs
Upper Leg I	6 cun above the upper edge of the patella (between the spleen and stomach meridian)
Upper Leg II	4 cun above the upper edge of the patella
Upper Leg III	2 cun dorsally of GB-31 (avoidance of bladder meridian)

cun = an acupuncture term for "body inch" corresponding to the width of the inter-phalangeal joint of patient's thumb; LI = large intestine meridian; LU = lung meridian; HT = heart meridian; GB = gall bladder meridian

Supplemental Digital Content 2: Table that lists details of the Chinese herbal medicine (CHM) formula Zhi Mu 14

Herb name		
Latin name	Chinese name	Amount in %
Radix Rehmanniae	Sheng Di Huang	11%
Rhizoma Anemarrhenae	Zhi Mu	10%
Semen Ziziphi Spinosae	Suan Zao Ren	10%
Radix et Rhizoma Cynanchi Atrati	Bai Wei	10%
Radix et Rhizoma Glycyrrhizae	Gan Cao	8%
Caulis Polygoni Multiflori	Shou Wu Teng	7%
Radix Paeoniae Alba	Bai Shao	7%
Cortex Lycii	Di Gu Pi	6%
Cortex Phellodendri Chinensis	Huang Bo	6%
Fructus Tritici Levis	Fu Xiao Mai	5%
Cortex Moutan	Mu Dan Pi	5%
Herba Artemisiae Annuae	Qing Hao	5%
Radix Bupleuri	Chai Hu	5%
Fructus Jujubae	Da Zao	5%