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Published in:
Danish Medical Journal

Publication date:
2017

Document version
Publisher's PDF, also known as Version of record

The efficacy of acupuncture on menopausal symptoms (ACOM study): protocol for a randomised study

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ABSTRACT

INTRODUCTION: Around 75% of menopausal women experience hot flushes (HF) and 10-20% of all postmenopausal women find this very distressing. The aim of this study is to evaluate the efficacy of acupuncture on moderate-to-severe menopausal symptoms in general and HF in particular.

METHODS: An un-blinded randomised trial (cross-over) with 1:1 allocation to early (intervention) versus late (control) acupuncture. The included women suffer from moderate-to-severe HF and will receive a weekly treatment during five consecutive weeks in the following predefined acupuncture points: CV-3, CV-4, LR-8, SP-6, SP-9. All acupuncturists will be medical doctors educated in acupuncture. The primary outcome is change in HF from baseline to week 6 measured by the HF scale from the MenoScores Questionnaire (MSQ). Secondary outcomes are change in other menopausal symptoms, in particular day and night sweats and menopausal-specific sleeping problems, also measured by other scales from the MSQ. A total of 68 patients must be enrolled to detect a relevant clinical reduction on the above MSQ scales. Both intention-to-treat and per-protocol analyses will be conducted; four or more treatments are considered adequate adherence.

CONCLUSIONS: In the ACOM study, we explore the potential benefits of acupuncture on moderate-to-severe menopausal symptoms. The cross-over design offers the possibility of examining the legacy effect of acupuncture.

FUNDING: The Idella Foundation, the University of Copenhagen and the Research Foundation of General Practice.

TRIAL REGISTRATION: Clinicaltrials NCT02746497.

Menopause is a normal condition that the majority of women experience in their early fifties [1]. Menopausal symptoms are commonly experienced for four to five years and for some women even longer [1-3]. Around 75% of menopausal women experience hot flushes (HF) [2-4]; and 10-20% of all postmenopausal women find the HF very distressing [2]. Some menopausal women also experience night sweats, emotional vulnerability, sleep disturbances, fatigue, joint pain, cognitive changes, vaginal dryness and loss of sexual desire [1, 2, 5].

Hormone therapy (HT) has been an effective treatment for menopausal symptoms for many years [6]. However, research has shown that long-term HT increases the risk of breast cancer and thromboembolic disorders, among others [7]. Non-hormonal medication such as gabapentin, clonidine and antidepressants may reduce menopausal HF. However, these drugs have frequent side effects, e.g. dizziness, fatigue, dry mouth, constipation and difficulty in sleeping [1, 2, 4, 8]. Other suggested remedies include relaxation, exercise and use of herbal remedies, but currently there is no convincing evidence of any beneficial effect [4, 9].

Acupuncture has been shown to be effective on menopausal HF in several studies [10, 11]. However, many of these studies have been criticised for methodological problems, e.g. poor study design, inadequate control group and individualised treatment (not using standardised acupuncture points) [10, 12]. Moreover, the studies have used different methods and outcome measures (some not validated) and overall comparison of the results is therefore difficult [10, 12]. Consequently, further research and better-designed randomised controlled studies are warranted [10, 12].

An estimate suggests that up to two-thirds of the Danish general practitioners (GPs) are using acupuncture on a regular basis [13]. This large proportion warrants that acupuncture for menopausal symptoms be considered for implementation in general practice, and any beneficial effect of acupuncture on menopausal symptoms may quickly find its way to menopausal women.

Hypothesis:Acupuncture can reduce moderate-to-severe menopausal symptoms. Specifically, acupuncture may produce a clinically meaningful reduction of HF.

Objective: To evaluate the efficacy of a standardised acupuncture approach on women suffering from moderate-to-severe menopausal symptoms; primarily the efficacy on HF measured as change from baseline to week 6.

METHODS

This is a randomised trial (cross-over) with 1:1 allocation to early (intervention) versus late (control) acupuncture. The reporting will follow the STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [14]. The protocol adheres to the SPIRIT 2013 statement; further details are found in the Appendix [15].

PROTOCOL ARTICLE

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Dan Med J 2017:64(3):A5344

TABLE 1

Inclusion and exclusion criteria.

Inclusion criteria
Woman
Age 40-65 yrs
"Quite a bit" or "a lot" bothered by hot flushes: score ≥ 4 on a validated scale measuring hot flushes, MenoScores questionnaire
No conflicts of interests and have provided informed consent
Have an e-mail address
Exclusion criteria
Hysterectomized and/or bilateral oophorectomized
Systemic hormone therapy for menopausal symptoms within the past 4 weeks
Hormonal intrauterine device within the past 4 weeks
Treatment with antidepressants and/or antiepileptics within the past 4 weeks
Other medical treatment for hot flushes, e.g. clonidine, within the past 4 weeks
Other herbal remedies/alternative treatment for menopausal symptoms, e.g. Black Cohosh, Red Clover, Evening Primrose oil, Melbrosia, within the past 4 weeks
Alcohol consumption exceeding 21 drinks per week
Using prescribed sleeping pills and/or prescribed sedatives
Treatment with corticosteroids within the past 4 weeks, inhaled steroids not excluded
Previously diagnosed with breast cancer, endometrial cancer, cervical cancer or ovarian cancer
Diagnosed with other severe cancer disease within the past 5 yrs
Heart valve disease
Insulin dependent and/or poorly controlled diabetes mellitus
Diagnosed with thyroid disease
Under investigation for serious disease e.g. cancer
Pregnancy or breast-feeding within the past 2 yrs
Received acupuncture treatment within the past 6 mo.s
Participating in another trial or participated in another trial in the past 2 weeks before screening

ABBREVIATIONS

ABD = abdominal symptoms
DMAS = Danish Medical Acupuncture Society
DNS = day and night sweats
DSEA = Danish Society for Evidence-based Acupuncture
EM = emotional symptoms
GP = general practitioner
GS = general sweating
HF = hot flushes
HT = hormone therapy
MEM = memory changes
MSQ = MenoScores Questionnaire
MSSP = menopausal specific sleeping problems
PHY = physical symptoms
SEX = sexual symptoms
SH = skin and hair symptoms
URIN = urinary and vaginal symptoms
WMA = Western Medical Acupuncture

Recruitment

The study subjects will primarily be recruited through GPs, GPs/medical doctors who are members of the Danish Society for Evidence-based Acupuncture (DSEA) or the Danish Medical Acupuncture Society (DMAS), groups for menopausal women on the social media and local newspapers.

Study subjects

The inclusion and exclusion criteria are presented in **Table 1**.

Screening and informed consent

Potential study subjects will be screened based on the validated HF scale from the MenoScores Questionnaire (MSQ). Included study subjects will have a score of 4 (quite a bit) or above 4 (a lot) on the HF scale. Study subjects will receive oral and written information and must sign an informed consent form before enrolment.

Baseline

In a baseline questionnaire, information will be obtained about age, marital status, children living at home, education level, gynaecological and obstetric history, urinary incontinence, comorbidity, use of medication, use of alternative treatment, previous use of acupuncture or alternative treatment, exercise, alcohol consumption and smoking status. Moreover, MSQ must be completed at baseline (week 0). Thereafter, the study subjects will be randomised.

Randomisation

The allocation sequence is generated using the computer software SAS (version 9.4, SAS Institute, Cary, NC, USA). Study subjects are allocated to one of the two randomisation groups, Group E (early intervention) and Group L (late intervention) by an independent person (independent of the project organisation). Randomisation is done in blocks, stratified by age and level of symptoms ("quite a bit" or "a lot" HF) using random block sizes.

Intervention and settings

The study will take place in Danish medical clinics. All study subjects will be offered a weekly treatment during five consecutive weeks. In study weeks 1-5, Group E will receive treatment and Group L will act as a control group. After study week 5, the groups trade places: Group L will then receive treatment for five weeks (trial week 6-10) and Group E will act as a follow-up group (**Table 2**).

The acupuncture style used will be Western Medical Acupuncture (WMA) with standardised treatment in predefined points. In WMA theory, acupuncture acts mainly by simulating the nervous system. The classic acupuncture points may be the best sites to needle, but not the only place to stimulate the nervous system; and sham acupuncture is rather perceived as another, but less effective form of therapeutic needling than an inert (placebo) treatment [16, 17]. Moreover, earlier studies have shown that sham acupuncture is associated with a

TABLE 2

Trial flow and time schedule: enrolment, interventions and assessments.

			Study period											
			post-allocation											long-term
	Enrolment, time $-t_1$	Allocation, time 0	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W26
Enrolment														
Eligibility screen	x													
Informed consent	x													
Screening questionnaire	x													
Allocation		x												
Intervention														
Group E			x	x	x	x	x							
Group L								x	x	x	x	x		
Assessment[c]														
Screening questionnaire incl. HF scale	x													
Baseline data	x													
MSQ		x[a]			x			x[b]		x			x	X

HF scale = hot flushes scale from MSQ; MSQ = MenoScores Questionnaire; Wx = study week no. x.
a) MSQ is completed before allocation and 1st treatment.
b) Group E completed MSQ 1 week after final treatment (week 6), Group L completed MSQ before 1st treatment (week 6).
c) Intermediate assessment at week 3, main comparison of primary outcome at week 6 before cross-over, assessment of legacy effect at week 11, assessment of long-term effect at week 26.

moderately large non-specific effect that might be larger than other inert placebo interventions [18]. Thus, in this study we use a control group rather than a placebo group.

Acupuncturists

Acupuncturists must be medical doctors educated in acupuncture by the DSEA, the DMAS or similar. An information meeting will be held with the acupuncturists and all are offered a two and a half-hour course concerning the study design and a review of the selected acupuncture points and techniques. The acupuncturists are instructed to give the acupuncture treatment and to provide no other treatment or counselling. The acupuncturists will receive a manual with instructions, including an overview of the specific acupuncture points. We expect that the study will include ten acupuncturists.

Needle information

The needles will be sterile disposable needles (Plandent) size 0.30 × 30 mm. The needles will be inserted perpendicularly and rotated manually between index finger and thumb for a few seconds to elicit "de-qi" (needle sensation). The needle retention time will be ten minutes. Afterwards, the needle will be removed.

Acupuncture points

The acupuncture points (CV-3, CV-4, LR-8, SP-6, SP-9) [19] are listed in **Table 3**. In total, 8 points are used as LR-8, SP-6 and SP-9 are given bilaterally.

TABLE 3

Acupuncture points and location.

Point	Location
CV-3	Anterior midline, 1 cun proximal to the symphysis Insertion depth: perpendicularly 0.5-1 cm
CV-4	Anterior midline, 1 cun proximal to CV-3 and 3 cun inferior to the umbilicus Insertion depth: perpendicularly 0.5-1 cm
LR-8	Medial side of the knee, in the depression anterior/medial to the tendons of semimembranosus and the semitendinosus muscles, at the medial end of the popliteal crease Insertion depth: perpendicularly 1.5-2 cm
SP-9	Under the medial condyle of tibia in a depression between the posterior tibia and m. gastrocnemius Insertion depth: perpendicularly 2-3 cm
SP-6	3 cun proximal to the prominent part of the medial malleoli, on the medial and posterior border of the tibia Insertion depth: perpendicularly 1-3 cm

Cun = an acupuncture measurement unit, 1 cun corresponds to the width of the study subject's thumb.

Outcome

Outcomes will be evaluated using the MSQ. This questionnaire was developed and validated based on a literature review, two focus groups, four single interviews, four pilot tests and a cross-sectional validation study including 1,504 women's completion of a draft version of the questionnaire. Data collected for this validation study were analysed using item response theory Rasch models. The MSQ encompasses 11 scales and one single item, measuring different dimensions of menopausal symptoms. The scale score refers to the sum of the scores of the items in the scale. **Table 4** presents the MSQ scales.

TABLE 4

Outcome evaluated by the MenoScores Questionnaire (MSQ) scales[a].

	MSQ				
	scale	single item	MSQ + 1 item	Items, n	Scale score
Outcome					
Primary	Hot flushes			2	0-6
Secondary	Day and night sweats			2	0-6
	General sweating			2	0-6
	Menopausal specific sleeping problems			2	0-6
	Emotional symptoms			12	0-36
	Memory changes			2	0-6
	Skin and hair symptoms			8	0-16
	Physical symptoms			8	0-24
	Abdominal symptoms			4	0-8
	Urinary and vaginal symptoms			4	0-12
	Sexual symptoms			4	0-8
		About tiredness		1	0-3
Enquiring					
After last acupuncture treatment			About the overall effect		
Week 11			About use of other treatments for menopausal symptoms		
Asking					
Week 26			If the study subject has started any treatment for menopausal symptoms after week 11		

a) 11 scales and 1 single item, 51 items in total.

All study subjects will receive the MSQ by e-mail in study weeks 0, 3, 6, 8, 11 and 26 and are asked to complete the MSQ within 1-2 days. The MSQ is completed electronically. Study subjects not returning a completed questionnaire within the scheduled time will receive a reminder within 1-2 days. When receiving the planned acupuncture treatment, the MSQ must be completed one or two days before the third treatment and one week after the fifth (the last) treatment (Table 2).

Primary outcome

Primary outcome is change in HF means from baseline to week 6 expressed by a score on the HF scale from the MSQ. The HF scale consists of two items with four response categories (no, a bit, quite a bit, a lot); and the range of score is 0 to 6, where six expresses "a lot" HF and nobody expresses "no" HF.

Secondary outcome

The secondary outcomes are change from baseline in the remaining MSQ scales covering the following domains: *day and night sweats* (DNS), *general sweating* (GS), *menopausal specific sleeping problems* (MSSP), *emotional symptoms* (EM), *memory changes* (MEM), *skin and hair symptoms* (SH), *physical symptoms* (PHY), *abdominal symptoms* (ABD), *urinary and vaginal symptoms* (URIN), *sexual symptoms* (SEX) and a single item about *tiredness*. While the scales have different ranges (Table 4), they all have a minimum of 0 denoting no symptoms; and for each of these scales higher scores express more symptoms. After the final acupuncture treatment, the study subjects are asked to evaluate the overall effect of their acupuncture treatments along with completing the MSQ at week 6 (Group E) or week 11 (Group L). At week 11, all study subjects are also asked if during the study period and despite recommendations, they have used any other treatment for menopausal symptoms. Finally, when completing the MSQ in week 26, the study subjects are asked if they have started any treatment for menopausal symptoms after ending the study in week 11. Drop-outs will be contacted in order to clarify the causes of drop-out.

Power calculations

The power calculation was based on data from the MSQ validation study. We used the primary outcome HF and the two secondary outcomes DNS and MSSP to establish the sample size. A reduction in a scale score corresponding to a reduction from "a lot" to "quite a bit" on a global item about whether the respondent was bothered by menopausal symptoms was considered a clinically relevant reduction. Women who were "a lot" both-

ered by menopausal symptoms scored a mean of 4.98 on the HF scale, and women who were "quite a bit" bothered scored a mean of 3.48 on the HF scale; both groups with a standard deviation (SD) around 1.4. To detect this reduction at 90% power, 5% level of significance, and accounting for 20% dropouts, 40 + 8 = 48 study subjects need to be included; 24 study subjects in each group. To detect a similar reduction in DNS and MSSP, a total number of 56 and 68 study subjects, respectively, need to be included (including dropouts). Hence, we aim to include a total of 68 study subjects in the ACOM study.

Statistical analysis

Outcomes will be analysed in linear mixed models including a subject-random effect so as to adjust for repeated measurements on the same individual. The main comparisons will be the mean difference in the outcomes between the randomisation groups from baseline to week 6, assessed by Wald tests. Outcomes in week 11 express the legacy effect and outcomes in week 26 express any longer-lasting effect.

The analyses will be adjusted for age and level of symptoms so as to account for the stratification in the randomisation procedure. Comparisons of the outcomes at baseline will be done along with the outcome analyses in the linear models to assess the randomisation. Additionally to this aim, covariates at baseline will be compared between randomisation groups with t-tests (continuous covariates) or chi-squared tests (categorical covariates). A logistic regression model will be used to investigate whether there are factors that influence dropout; these factors will then be added as adjustments to the linear mixed models in additional analyses so as to account for any attrition.

The primary analyses will be intention-to-treat analyses. Additionally, per-protocol analyses will be conducted in which non-compliers will be omitted; four or more treatments are considered adequate adherence. A p-value < 0.05 will be considered significant. The statistical significance for the secondary outcomes will be assessed with a false discovery rate of 5%. SAS v9.4 will be used for the analyses.

Blinding

The statisticians and outcome assessors will be blinded until all analyses have been completed. Study subjects and acupuncturists cannot be blinded.

Adverse events

We expect no risk for the study subjects. Adverse events are expected to be minimal and may be bruises or irritation at the needle-insertion site and for few study subjects transient fatigue, pruritus, nausea or briefly intensified symptoms following treatment. Along with completing the MSQ at weeks 3, 6, 8, 11 and 26, the study subjects are asked about adverse events in relation to the treatments. Adverse events will be presented along with the outcomes.

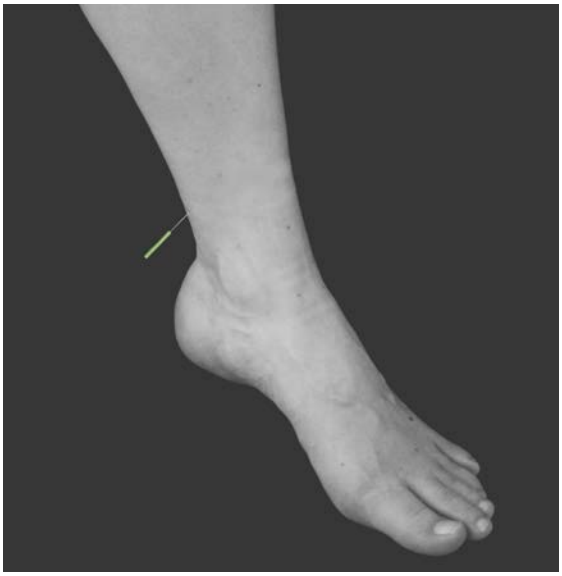
Ethics, regulatory authorities and registration

Approvals from the Committees on Health Research Ethics (H-16016365), the Committee of Multipractice Studies in General Practice (MPU 08-2016) and the Danish Data Protection Agency (SUND-2016-24) are obtained. The study will be conducted in accordance with the Declaration of Helsinki.

Trial registration: clinicaltrials.gov (NCT02746497).

DISCUSSION

Earlier studies have shown effect of acupuncture on menopausal HF. Unfortunately, these studies have methodological deficiencies and the quality of the evidence is generally low [10, 12]. If sham acupuncture is not inert, a comparison of acupuncture with sham acupuncture is more likely a comparison of two different types of acupuncture, and claiming that such a study is a placebo-controlled study would be incorrect. At the present time, no proper acupuncture placebo comparator exists [16-18] and blinding is obviously difficult. Both of these issues constitute limitations in acupuncture studies, this study included. However, a strength in our study is the use of a control group to demonstrate the different impact of acupuncture treatment versus no treatment. Moreover, our statisticians and outcome assessors will be blinded until all analyses have been completed.



Acupuncture needle in SP-6.

A specific strength of this study is the use of a validated and reliable outcome measure (the MSQ) with high content validity and adequate psychometric properties. The MSQ was developed and validated in an earlier validation study, and data from this validation study were used to generate a power calculation for this study.

This study will use a standardised intervention in the same predefined acupuncture points. Individualised tailored treatment might be closer to a real clinical setting and could be more effective than standardised treatment, but when testing a specific treatment in a scientific trial, aiming for high applicability of findings, we believe that the treatment should be standardised. Furthermore, as an attempt to avoid that other interventions affect the results, we exclude all subjects who are included in other studies or are using other interventions against menopausal symptoms. Finally, the cross-over design makes it possible to survey a potential legacy effect in group E and may improve the adherence of the control group L since they will be also offered acupuncture.

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ACCEPTED: 9 January 2017

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

AKNOWLEDGEMENTS: The authors would like to extend their gratitude to *Palle Rosted* and Danish Society for Evidence-based Acupuncture for inspiration and counselling.

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