



Review Article

Efficacy Comparison of Different Acupuncture Treatments for Hot Flashes: A Systematic Review with Network Meta-Analysis



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ABSTRACT

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The objective of this study was to conduct a systematic review and network meta-analysis to evaluate and compare the effectiveness of various types of acupuncture for menopausal hot flashes (HF). Randomized controlled trials (RCTs) were retrieved from 8 electronic databases, and the risk of bias was evaluated for the included studies. Pairwise meta-analysis and network meta-analysis were performed using Review Manager and R software for indirect comparison and ranking, respectively. In total, 23 RCTs (2,302 patients) were eligible for systematic review, of which 10 were included in network meta-analysis. Network meta-analysis showed manual acupuncture (MA) had the highest probability of reducing HF frequency and severity, followed by sham acupuncture (SA), electroacupuncture, usual care, or no treatment; furthermore, warm acupuncture significantly improved menopause-specific quality of life compared with MA or electroacupuncture. Compared with hormone replacement therapy, acupuncture had less efficacy in reducing HF frequency but enhanced menopause-specific quality of life. There was no significant difference between MA and SA in mitigating HF. The existing evidence showed that MA could be used for alleviating menopausal HF. However, it is recommended that more high-quality RCTs should be performed.

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Introduction

Hot flashes (HF) are a predominant symptom of menopause, characterized by a sensation of intense heat in the face, neck, or chest [1]. Approximately two thirds of postmenopausal women reportedly suffer from HF, and in 20% or more of all postmenopausal women HF can last for up to 15 years after natural menopause [2]. HF are associated with sleep disorders, depressed mood, poor quality of life, and underlying vascular changes that cause subclinical cardiovascular disease. In addition, HF are among the most common reasons for clinical visits and major healthcare expenses for middle aged women [3].

Estrogen therapy alone or in combination with progesterone is currently the most effective treatment for HF. However, hormone replacement therapy (HRT) has risks of thromboembolic events, cancer, and some side effects, such as breast tenderness and irregular bleeding [4]. For these reasons, many women are

reluctant to take hormones and are concerned about HRT [5,6].

Acupuncture has been widely used to alleviate HF in menopausal women. Acupuncture can reportedly prevent the hypothalamic pituitary adrenal axis from excessively affecting the hypothalamic pituitary ovarian axis; and can increase endogenous opioids release, thus normalizing the function of the hypothalamic thermoregulatory center [7,8].

Reviews on acupuncture for menopausal HF, show controversy over whether acupuncture is effective. There are several reviews stating that traditional acupuncture improves HF [2], or offers results superior to no treatment, but not superior to sham acupuncture (SA) [9,10]. These reviews included various types of acupuncture treatments, such as manual acupuncture (MA), electroacupuncture (EA), warm acupuncture (WA), and acupoint catgut embedding (ACE), but did not evaluate and compare the effects of each individual acupuncture option. Thus, it is difficult to provide clinicians with clear guidelines on what types of

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acupuncture treatments are effective.

Increasingly, many systematic reviews use network meta-analysis to compare 3 or more treatments, even if they have not been directly compared in clinical trials. The methodology of network meta-analysis is a quantitative synthesis of various treatments for the same indication, combining direct and indirect evidence to evaluate potentiality of treatment effect and ranking the available treatments according to the effect size [11,12]. Therefore, a systematic review and network meta-analysis was conducted in this study to examine the effect of acupuncture on menopausal HF and to estimate comparative effectiveness of different types of acupuncture.

Materials and Methods

Search strategy

Eight electronic databases, including PubMed, the Cochrane Library, Embase, China National Knowledge Infrastructure, Korean Medical Database, Korean studies Information Service System, ScienceON, and Oriental Medicine Advanced Searching Integrated System were searched for RCTs until December 9, 2020. In addition, the missing literature was included by reading the reference lists of the retrieved systemic reviews. The languages of the included studies were limited to English, Chinese, or Korean.

The keywords for searching for RCTs were as follows: (“acupuncture” OR “electroacupuncture” OR “acupressure” OR “moxibustion” OR “catgut embedding” OR “warm acupuncture”) AND (“hot flashes” OR “hot flushes” OR “flushing”) AND (“menopausal syndrome” OR “menopause related disorder” OR “climacteric” OR “perimenopause” OR “postmenopause”) AND (“randomized controlled trial” OR “controlled clinical trial”). According to the characteristics of each databases, Chinese or Korean terms were added.

Inclusion criteria

Type of studies

Randomized controlled trials (RCTs) of acupuncture treatment for HF in menopausal women were considered. Non RCT studies, including case studies, quasi RCT, experimental studies, cohort studies, and RCTs published in the form of letters to the editor, and conference abstracts were excluded.

Participants

The patients were diagnosed with perimenopausal or postmenopausal state with HF without restrictions on age, race, duration of condition, and the severity of symptoms. Patients with their menopause caused by radiation or chemotherapy and patients with cancers were excluded.

Intervention and Comparison

In this network meta-analysis, 4 types of acupuncture treatments were included: MA, EA, ACE, and WA. Single use of acupuncture treatment was considered suitable for inclusion in this network meta-analysis. The control group included treatment with HRT, SA, usual care (the use of over-the-counter drugs for symptoms unrelated to HF or supplements), or no treatment (wait list).

Outcome measures

The outcome measure was the reduction in frequency and severity of HF and quality of life. HF frequency was defined as the number of HF per day, and the severity of HF was measured by the hot flash score (HFS). Quality of life was evaluated by the

Menopause-Specific Quality of Life (MENQOL), a questionnaire with scores ranging from 0 to 6 for 29 questions [2].

Study selection and data extraction

All searched studies were imported into Endnote X20 (ISI Research Soft, USA). After reading the titles and abstracts, studies that were duplicates or did not meet the inclusion criteria were excluded. The final included studies were determined by reading the full text of the articles. Data extraction was performed independently by 2 researchers, and discrepancies were resolved through discussion. Study characteristics (author and year of publication), sample size, age range, intervention, treatment frequency, duration, outcomes, results, and adverse events from each of the included RCTs were extracted. For safety, all reported adverse events were recorded regardless of the intervention.

Risk of bias in individual studies

Two researchers independently conducted quality assessments using the “risk of bias” (RoB) tool of Cochrane Collaborations. The RoB tool evaluates 7 areas: random sequence generation, allocation concealment, participant and personnel blinding, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. In each category, the assessment result was categorized into “low risk,” “high risk,” and “unclear” [13]. If the 2 researchers had a difference of opinion, the final evaluation was conducted through mutual discussion.

Statistical synthesis

Pairwise meta-analysis was performed using Review Manager (RevMan, Version 5.4, the Nordic Cochrane Center, the Cochrane Collaboration, 2020 Copenhagen, Denmark). A randomized effects model was used for each pair of interventions, using a 95% confidence interval (CI) and a standardized mean difference (SMD) for synthesizing continuous results. The heterogeneity among the studies was measured using I^2 statistics and p values. According to the Cochrane handbook, when $p > 0.05$ and $I^2 < 50\%$ no statistical heterogeneity is indicated [13].

A frequentist method was adopted to perform network meta-analysis for indirectly comparing efficacy and the ranking of different acupuncture treatments, using R software (<http://www.r-project.org/>; version 4.0.3). Consistency between direct and indirect evidence was estimated by the z-test, and $p > 0.05$ indicated inconsistency. The results of interventions were ranked through the surface under the cumulative ranking curves and this value indicated the possibility of efficacy of the intervention [14].

Results

Characteristics of included studies

In total, 564 studies retrieved using databases, and a further 10 studies were added manually. There were 391 duplicate records removed, after reading the article title and abstract leaving 112 records. Based on full text assessments, a further 89 articles were excluded. There were 23 RCTs included in the systematic review, of which 10 were included in network meta-analysis (Fig. 1).

Of the 23 included RCTs, 9 studies were performed in China [15-23], 4 from the United States [24-27], 3 from Sweden [28-30], and 1 each from Italy [31], Iran [32], Brazil [33], Australia [34], United Kingdom [35], Korea [36], and Denmark [37].

The total sample size of the included RCTs involved 2,302

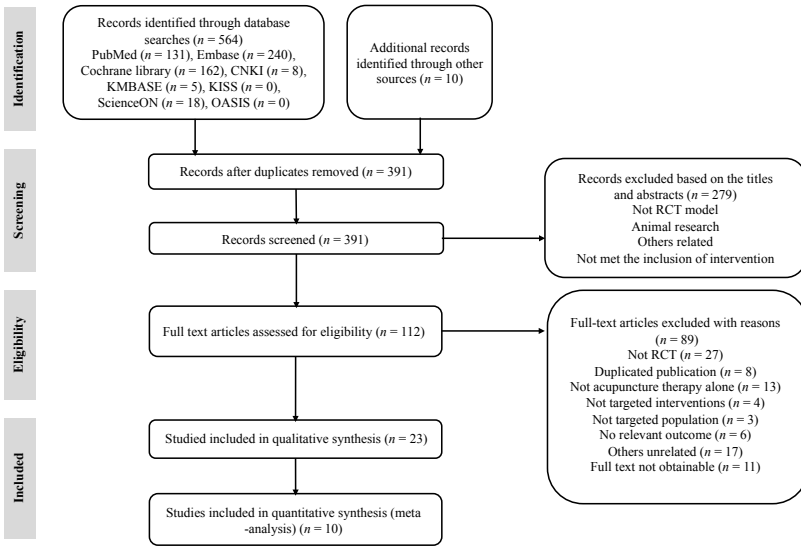


Fig. 1. Flow chart of article retrieval of selection. RCT, randomized controlled trial.

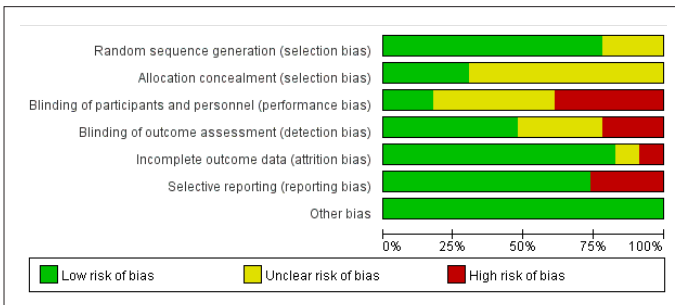


Fig. 2. Risk of bias graph.

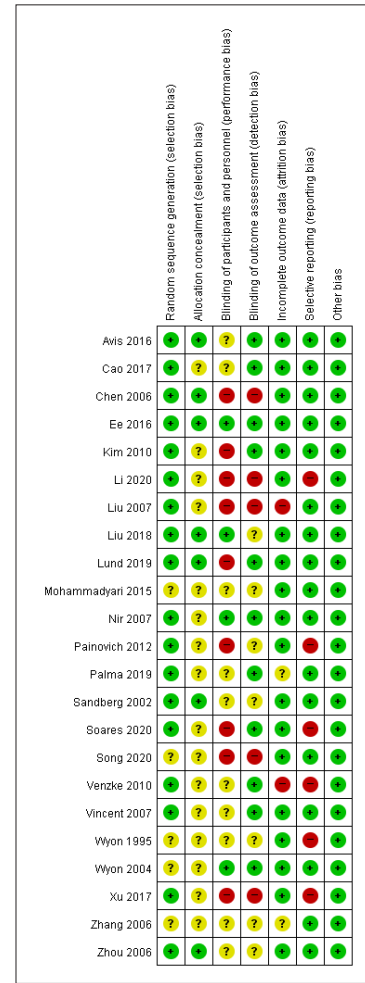


Fig. 3. Risk of bias of the included randomized controlled trials.

patients ranging from 20 to 360 patients per study, the average of which was 100 patients. There were 19 2-arm RCTs, whereas 4 employed a 3-arm group design. Among the 2-arm trials, there were 6 trials comparing acupuncture treatment with HRT [15,16,20-22,32], 6 trials comparing it with SA [18,24-26,33,34], 1 trial comparing it with usual care [36], and 2 trials comparing it with no treatment [27,37]. The remaining 4 studies evaluated a comparison between different acupuncture treatments [17,23,29,30]. Among the 3-arm trials, 1 trial investigated MA versus HRT versus dietary supplements [31], 1 compared MA versus SA versus no treatment [35], 1 compared EA versus MA versus HRT [16], and 1 evaluated ACE versus EA versus HRT [19].

The selection of acupuncture points in the included RCTs was diverse, and the main choices included SP 6 (Sanyinjiao), CV 4 (Guanyuan), BL 23 (Shenshu), PC 6 (Neiguan), HT 8 (Shaofu), SP 9 (Yinlingquan), and GV 20 (Baihui). The treatment period ranged from 3 to 48 weeks, and the average frequency of intervention was about 3 times per week. In 2 studies [19,28], the frequency was not reported, and in 6 trials [25,28-30,33,34], the intervention was initially performed twice per week and then once per week. The outcome measurements included the changes in frequency and severity of HF, quality of life, and follicle stimulating hormone (FSH), estradiol (E₂), and luteinizing hormone (LH) levels (Table 1).

Assessment of risk of bias

Although 5 studies [15,19,28,30,32] did not report specific methods of randomization, there was no high risk of bias in random sequence generation. As methods of randomization in the RCTs, 11 [18,23,25-27,31,33-35,36,37] used computer programs, 3 [16,24,29] used envelopes, 1 [20] used drawing lots, and the other 3 [17,21,22] used random number tables. In terms of allocation in the RCTs, 7 [16,18,21,27,29,34,37] mentioned that the assignment was not known to the researchers due to the management of randomization by an independent manager, which resulted in a low risk of bias in allocation concealment. Nine RCTs [19-23,32,35-37] had a high risk of bias in the blinding of the participants due to the nature of the interventions, and 4 [18,25,28,34] were assessed as a low risk of bias because researchers and patients were reportedly blinded to the allocated intervention. Moreover, 11 RCTs [17,24-28,31,33,34,36,37] with an independent assessor for interventions had a low risk of blinding of outcome assessment. In terms of attrition bias, 2 studies [19,24] were judged to be at high risk of bias because “As treated” analysis and a large number of missing data. In addition, 2 studies [15,31] had an unclear risk of attrition bias because no reasons for the missing data were provided. Six RCTs [22,23,24,30,33,35] did not report complete results, and therefore had a high risk of reporting bias. All included RCTs appeared to be free of other sources of bias (Figs. 2 and 3).

Table 1. Characteristics of Included Studies.

Study ID	Sample size (E/C)	Mean age (y) (E/C)	Intervention (acupuncture points)		Frequency, duration	Treatment period (wk)	Outcome	Results	Adverse event (n)
			Experimental group	Control group					
Acupuncture									
Palma 2019 [31]	24/25/23	54.8 ± 5.2 / C1: 51.2 ± 2.6 C2: 53.0 ± 6.4	MA (NR)	C1: HRT (Estrogen 0.3 mg + medroxy progesterone acetate 1.5 mg 1×/d) C2: Dietary supplement (soy isoflavones 75 mg 2×/d)	1×/d	12	1. Effective rate 2. GCS 3. MENQOL	1. E = C1 C1 > C2 (p < 0.05) 2. E = C1 C1 > C2 (p < 0.05) 3. E = C1 E > C2 (p < 0.05)	E: cutaneous erythema (3)
Mohammadyari 2015 [32]	10/10	total 50.6 ± 2.5	MA (NR)	HRT (Estrogen 0.625 mg + medroxy progesterone acetate 12.5 mg 1× d)	2×/wk, 40 min	5	1. Effective rate 1) HF frequency 2) Palpitation 3) Perspiration 4) Headache	1. 1) E = C 2) E = C 3) E = C 4) E = C	NR
Zhang 2006 [15]	33/32	50.2 ± 2.0 / 49.0 ± 6.0	MA (BL 23, ST 36, SP 6, PC 6, HT 7, LR 3, DU 20, RN 17; BL 18, KI 3, KI 12, BL 20, RN 4 were added for yang deficiency)	HRT (Oryzanol 20 mg 3×/d)	6×/wk, 30 min	4	1. Effective rate 2. KMI	1. E > C (p < 0.05) 2. E > C (p < 0.05)	NR
Soares 2020 [33]	50/50	47.74 ± 4.26 / 47.32 ± 4.81	MA (EX-HN1, LI4, HT7, PC6, TE5, CV12, CV6, CV4, ST36, SP6, SP9, GB34, LR3, LU7, LR5, KI3, KI6, Scalp)	SA (same points)	1×/wk (10 wks), 1×/2 wks (until end point), 40 min	48	1. KMI 2. HF frequency/d	1. E > C (p = 0.019) 2. E > C (p < 0.01)	None
Ee 2016 [34]	163/164	55.2 ± 4.3 / 54.8 ± 4.2	MA (KI6, KI7, SP6, HT6, CV4, LR3)	SA (non acupuncture points on abdomen, limbs)	2×/wk (2 wks), 1×/wk (until end point), 20 min	8	1. HFS 2. HF severity/wk 3. HF frequency/wk 4. MENQOL 5. HADS	1. E = C 2. E = C 3. E = C 4. E = C 5. E = C	E: pain (6), tingling (1), bleeding or bruising (8), syncope/presyncope (2), worsening symptoms (2), heat/sensitivity (1), swelling and itching around acupuncture point (1) C: pain (1; unrelated), syncope/presyncope (1), worsening symptoms (1), nervousness (1), essential tremor (1)
Painovich 2012 [35]	12/12/9	57.2 ± 5.2 / C1: 56.8 ± 6.5 C2: 54.9 ± 6.4	MA (GV20, PC6, HT 7, LR3, LI4, LI11, KI3, SP6, ST36, CV17, CV6, GV14, BL15, BL18, BL20, BL23, GB34, KI3)	C1: SA (proximate to MA points) C2: No treatment (wait)	3×/wk, 30 min	12	1. HF frequency/wk 2. HF severity/wk 3. MENQOL 4. PSQI 5. BDI-II 6. State-Trait Anxiety Inventory 7. 24 hours urinary cortisol and metabolites 1) Dehydroepiandrosterone 2) Cortisol 3) Total F metabolites 4) Adrenal androgens	1. E = C1 = C2 2. E = C1 = C2 3. E > C1 > C2 (p = 0.07) 4. E = C1 = C2 5. E = C1 = C2 6. E = C1 = C2 7. 1) E > C1 > C2 (p = 0.04) 2) E > C1 > C2 (p = 0.05) 3) E > C1 > C2 (p = 0.03) 4) E > C1 > C2 (p = 0.09)	NR

Table 1. Continued.

Study ID	Sample size (E/C)	Mean age (y) (E/C)	Intervention (acupuncture points)		Frequency, duration	Treatment period (wk)	Outcome	Results	Adverse event (n)
			Experimental group	Control group					
Venzke 2010 [24]	27/24	54.1 ± 4.67 / 52.6 ± 2.87	MA (BL23, BL20, BL 15, BL17, GV9, GV4, SP9, SP6, right LU7, left KI6, KI3, KI7, HT6, HT7, LR3, GV24, GB20)	SA (non acupuncture points on back, limbs)	2×/wk (4 wks), 25 min	12	1. BDI 2. BAI 3. HFS/d 4. GCS	1. E = C 2. E = C 3. E = C 4. E = C	None
Nir 2007 [25]	12/17	56.92 ± 1.73 / 53.71 ± 4.24	MA (5-7 points based on TCM diagnose)	SA (non acupuncture points)	2×/wk (2 wks), 1×/wk (5 wks), 20 min	7	1. HF frequency/d 2. HF severity/d 3. MENQOL	1. E = C 2. E > C (p = 0.042) 3. E = C	E: bleeding/bruising (8), discomfort (7), insomnia (2), pain (1), itchiness (1), twitching (1) C: bleeding/bruising (1), discomfort (6), insomnia (2), irritability/restlessness (3), low energy (1), flatulence (1), resentment (1), pain (1)
Vincent 2007 [26]	51/52	52.0 / 52.0	MA (SP4, SP6, HT7, LI11, LV2, KI6, LU7, PC6, GB34, LV3, CV4, GB20)	SA (non acupuncture points)	2×/wk, 30 min	5	1. Residual HFS/d 2. Residual HFS ratio	1. E = C 2. E = C	None
Kim 2010 [36]	116/59	51.4 ± 2.9 / 51.2 ± 3.7	MA (ST36, SP6, LI4, PC6, HT7, HT8, CV4)	Usual care	3×/wk, 20 min	4	1. HFS/d 2. HF severity/d 3. HF frequency/d 4. MRS	1. E > C (p < 0.0001) 2. E > C (p = 0.0038) 3. E > C (p = 0.0089) 4. E > C (p < 0.0001)	E (unrelated to MA): common cold (5), muscle pain (2), mild joint pain (2), urine glucose increased (2), headache (1), nausea (1),
Lund 2019 [37]	36/34	55.3 ± 4 / 54.1 ± 5	MA (CV3, CV4, LR8, SP9, SP6)	No treatment (wait)	1×/wk, 10 min	5	1. MSQ 1) HF scale 2) Day/night sweating 3) General sweating 4) Menopausal specific sleeping problems 5) Emotional symptoms 6) Memory changes 7) Physical symptoms 8) Urinary and vaginal symptoms 9) Abdominal symptoms 10) Skin and hair symptoms 11) Sexual symptoms 12) Tiredness	1. 1) E > C (p < 0.0001) 2) E > C (p = 0.0056) 3) E > C (p = 0.0086) 4) E > C (p < 0.0001) 5) E > C (p = 0.0008) 6) E = C 7) E > C (p = 0.01) 8) E = C 9) E = C 10) E > C (p = 0.0021) 11) E = C 12) E = C	E: more HF (1), tiredness and headache (1), tingling in leg (1), urinary frequency (1)
Avis 2016 [27]	170/39	53.8 ± 3.5 / 53.6 ± 3.6	MA (NR)	No treatment (wait)	determined by practitioner	24	1. HF frequency/wk 2. HFS/wk 3. HF Related Daily Interference Scale 4. Center for Epidemiologic Studies Depression scale 5. WHQ 1) Depression 2) Anxiety 3) Attractiveness 4) Somatic 5) Memory 6) Sexuality 7) Vasomotor 8) Sleep 6. PSQI 7. Generalized Anxiety Disorder 8. Perceived Stress Scale 9. PROMIS 1) Anxiety 2) Depression 3) Sleep 10. SF-36 11. Global Quality of Life	1. E > C (p < 0.001) 2. E > C (not mentioned) 3. E > C (p < 0.001) 4. E = C 5. 1) E = C 2) E > C (p = 0.02) 3) E = C 4) E > C (p < 0.001) 5) E > C (p = 0.001) 6) E > C (p = 0.04) 7) E > C (p = 0.002) 8) E > C (p < 0.001) 6. E > C (p = 0.01) 7. E = C 8. E = C 9. 1) E > C (p = 0.07) 2) E = C 3) E > C (p = 0.002) 10. E = C 11. E = C	NR

Table 1. Continued.

Study ID	Sample size (E/C)	Mean age (y) (E/C)	Intervention (acupuncture points)		Frequency, duration	Treatment period (wk)	Outcome	Results	Adverse event (n)
			Experimental group	Control group					
Electroacupuncture									
Zhou 2006 [16]	45/45	49.90 ± 3.80 / 50.03 ± 3.20	EA (SP6)	HRT (Nylestriol 2 mg 1×2 wks); for post-menopause add medroxy progesterone 2 mg 3×/d from third month for 7 d)	3×/wk, 30 min	3	1. KMI 2. HFS 3. mental symptoms score	1. E = C 2. E > C (p < 0.05) 3. E > C (p < 0.01)	None
Wyon 2004 [28]	15/13/15	54.5 / C1: 53.4 C2: 50.9	EA (BL15, BL23, BL32, HT7, SP6, SP9, LR3, PC6, GV20)	C1: MA (the upper points of BL15, BL23, BL32) C2: HRT (17 β-estradiol 2 mg 1×d)	2×/wk (2 wks), 1×/wk (10 wks), 30 min	12	1. HF frequency/d 2. HF severity/d 3. KMI 4. VAS for general climacteric symptom	1. E = C1, E = C2 2. E = C1, E = C2 3. E = C1, E = C2 4. E = C1, E = C2	NR
Cao 2017 [17]	23/27	48 ± 4 / 48 ± 4	EA (CV4, EX-CA1, ST25, SP6)	MA (same points)	3×/wk, 30 min	8	1. HFS/d 2. MENQOL 3. MRS 4. Serum level 1) E2 2) FSH 3) LH	1. E = C 2. E = C 3. E = C 4. 1) E = C 2) E = C 3) E = C	NR
Sandberg 2002 [29]	15/15	54.4 ± 3.6 / 53.6 ± 3.0	EA (BL15, BL23, BL32, SP6, SP9, LR3, HT3, PC 6, GV20)	MA (same points)	2×/wk (2 wks), 1×/wk (10 wks), 30 min	12	1. Mood scale 2. SCL-90 3. VAS for general climacteric symptom	1. E > C (p < 0.01) 2. E = C 3. E = C	NR
Wyon 1995 [30]	12/12	total 54.0	EA (UB 15, UB 23, UB 32, GV 20, H7, P6, LIV3, SP6, SP9)	MA (same points)	2×/wk (2 wks), 1×/wk (6 wks), 30 min	8	1. HF frequency/d 2. KMI 3. VAS for general climacteric symptom 4. Sleep Dysfunction Scale 5. Psychological General Well-Being index	1. E = C 2. E = C 3. E = C 4. E = C 5. E = C	NR
Liu 2018 [18]	180/180	48.7 ± 4.0 / 48.1 ± 3.8	EA (RN4, ST25, EX-CA1, SP6)	SA (non acupuncture points)	3×/wk, 30 min	8	1. HFS/d 2. MENQOL 3. MRS 4. Serum level 1) E2 2) FSH 3) LH 4) FSH/LH ratio 5. Use of other treatment during study	1. E > C (p = 0.0001) 2. E > C (p = 0.0033) 3. E > C (p = 0.0002) 4. 1) E = C 2) E = C 3) E = C 4) E > C (p = 0.0024) 5. E = C	E: dizziness (1), fatigue (1), severe needling pain (4), abdominal discomfort (1) subcutaneous hematoma (2) C: fatigue (2)
Acupoint catgut embedding									
Song 2020 [19]	30/30/30	51.6 ± 3.3 / C1: 49.0 ± 6.0 C2: 51.9 ± 3.4	ACE (BL23, CV4, EX-CA1, SP6)	CG1: EA (same points) CG2: HRT (Premarin 0.625 mg/d)	EG: 1×/d, 30 min CG1: 1×/2 d, 30 min	8	1. Effective rate 2. KMI 3. Serum level 1) E2 2) FSH 3) LH	1. E > C2 (p < 0.05) C1 > C2 (p < 0.05) 2. E > C2 (p < 0.05) C1 > C2 (p < 0.05) 3. E = C1 = C2	NR
Liu 2007 [20]	86/80	46.16 ± 6.14 / 45.75 ± 5.2	ACE (BL23, GV4, CV4, BL15, BL18, SP6)	HRT (Ethinyll estradiol pentyl ether 2.5 mg 1×/2 wks + Oryzanol 25 mg 3×/d)	1×/wk	12	1. Effective rate 2. Average number of days to effect onset 3. Average number of days until symptoms disappear 4. Menopausal symptom score 1) Flashes and sweating 2) Irritability 3) Dizziness and fatigue 4) Vaginal dryness 5) Urinary infection 5. Serum level 1) E2 2) FSH 3) LH 6. Endometrial thickness	1. E > C (p < 0.05) 2. E > C (p < 0.01) 3. E > C (p < 0.01) 4. (all p < 0.05) 1) E > C 2) E > C 3) E > C 4) E > C 5) E > C 5. (all p < 0.01) 1) E < C 2) E < C 3) E < C 6. E < C (p < 0.05)	NR

Table 1. Continued.

Study ID	Sample size (E/C)	Mean age (y) (E/C)	Intervention (acupuncture points)		Frequency, duration	Treatment period (wk)	Outcome	Results	Adverse event (n)
			Experimental group	Control group					
Chen 2006 [21]	33/32	total 53.94 ± 2.94	ACE (SP6, BL23, CV4 + BL18 for Liver and Kidney yin deficiency, ST36, BL20 for Spleen and Kidney yang deficiency)	HRT (Estrogen 1.25 ug + Progesterone 0.5 mg 1x/d)	1x/2 wks	12	1. Menopausal symptom score 1) Flashes and sweating 2) Parasthesia 3) Insomnia 4) Irritability 5) Depression 6) Dizziness 7) Fatigue 8) Joint and muscle pain 9) Headache 10) Palpitation 11) Tingling 12) Vaginal dryness 13) Urinary symptoms 2. KMI 3. SF-36 1) Physical functioning 2) Role physical 3) Bodily pain 4) General health 5) Vitality 6) Social functioning 7) Role emotional 8) Mental health 4. Effective rate 5. Serum level 1) E2 2) FSH 2) LH	1. 8) E > C (p = 0.001) 12) E < C (p < 0.001) Otherwise, E = C 2. E > C (p > 0.05) 3. 3) E > C (p < 0.05) 8) E > C (p < 0.05) Otherwise, E = C 4. E = C (p > 0.05) 5. 1) E > C (p < 0.05) 2) E > C (p < 0.01) 3) E > C (p < 0.01)	E: redness/swelling (1) C: nausea and lethargy (8), breast distention (7)
Warm acupuncture									
Li 2020 [22]	35/35	45.78 ± 12.83 / 46.47 ± 14.20	WA (SP6, CV4, EX-CA1)	HRT (Nilestriol 2 mg 1x/2 wks)	1x/d	4	1. Effective rate 2. KMI 3. MENQOL 4. Serum level 1) E2 2) FSH 3) LH	1. E > C (p < 0.05) 2. E > C (p < 0.05) 3. E > C (p < 0.05) 4. 1) E > C (p < 0.05) 2) E > C (p < 0.05) 3) E > C (p < 0.05)	NR
Xu 2017 [23]	30/30	49.53/ 50.16	WA (CV4, ST25, EX-CA1, SP6, e.t.c., based on TCM diagnose)	MA (CV4, ST25, EX-CA1, SP6, e.t.c., based on TCM diagnose)	1x/2 d	8	1. MRS 2. Serum level 1) E2 2) FSH 3) LH	1. E > C (p < 0.05) 2. 1) E = C 2) E = C 3) E = C	NR

E, experimental group; C, control group; Effectiveness rate = (total points of symptom before treatment - total points of symptom after treatment)/total points of symptom before treatment × 100%.

Total effective rate was calculated for the number of cured and improved cases.

AE, adverse event; BAI, Beck anxiety inventory; BDI-II, Beck depression inventory-II; EA, electroacupuncture; GCS, Greene climacteric scale; HADS, hospital anxiety and depression scale; HF, hot flash; HFS, hot flash scores; HRT, hormone replacement therapy; KMI, Kupperman menopausal index; MA, manual acupuncture; MENQOL, menopause-specific quality of life questionnaire; MRS, menopause rating scale; MSQ, MenoScores questionnaire; NR, not reported; PROMIS, patient-reported outcomes measurement information system; PSQI, Pittsburgh sleep quality index; SA, Sham acupuncture; SCL-90, symptom checklist-90; SF-36, short form 36 health survey; TCM, traditional Chinese medicine; VAS, visual analog scale; WA, warm acupuncture; WHQ, women's health questionnaire.

Systematic review

MA

Twelve RCTs examined the effectiveness of MA. In the 3 studies comparing MA with HRT, the 2 interventions showed no significant differences [31,32], whereas Zhang [15] observed MA to be more effective than HRT at improving the Kupperman menopausal index (KMI) score and effective rates. Among the 6 RCTs [24-26,33-35] which compared MA and SA, those evaluating HF frequency, severity, MENQOL, and Beck Depression Inventory

showed no significant difference between MA and SA, except for 1 RCT [33]. Painovich et al [35] reported that 24 hour urinary cortisol and metabolites, such as dehydroepiandrosterone, cortisol, total F metabolites, and adrenal androgens, were significantly lower in MA than in SA. Data of 3 RCTs which compared MA to usual care [36] or no treatment [27,37], showed that MA had a significantly better effect in reducing HF frequency, severity, and other menopause symptoms as indicated by the Menopause Rating Scale (MRS) and Meno Scores Questionnaire (Table 1).

EA

Six RCTs evaluated the effectiveness of EA in comparison with HRT, MA, and SA. Zhou et al [16] when comparing EA to HRT, reported the HFS and mental health symptoms score was significantly better with EA, whereas the KMI scores did not significantly differ between the 2 interventions. Among the 4 RCTs comparing MA and EA [17,28-30], there were no significant differences between the 2 groups in most outcomes. In 1 RCT [32] comparing EA and SA, EA was significantly more effective in terms of the HFS, MENQOL, and MRS scores, but not in terms of serum levels of E₂, FSH and LH (Table 1).

ACE

All 3 RCTs [19-21] assessing the effects of ACE were compared with HRT. The results indicated that ACE had a higher effective rate and was more effective at improving the KMI score, but contradictory in altering the serum levels of E₂, FSH, LH, and vaginal dryness symptoms score. Liu et al [20] reported the endometrium was significantly thicker in patients treated with HRT than in patients treated with ACE (Table 1).

WA

There were 2 RCTs that explored the effectiveness of WA, compared with HRT [22] and MA [23] respectively. In comparison with HRT, WA was significantly more effective in terms of effective rate, KMI and MENQOL scores, but less effective for beneficially altering serum levels of E₂, FSH, LH [22]. In terms of comparing

the effects of WA and MA, WA significantly reduced MRS, but there were no significant differences in alterations of serum E₂, FSH, and LH levels [23] (Table 1).

Pairwise meta-analysis

Reduction in the frequency of HFs

Six pairwise meta-analyses were performed to evaluate the effect of acupuncture treatment on reducing the frequency of HF (Table 2). MA showed more significant effects than usual care (1 RCT, SMD -0.47, 95% CI -0.78 to -0.15; $p = 0.004$) and no treatment (1 RCT, SMD -8.61, 95% CI -9.60 to -7.61; $p < 0.001$). Conversely, MA (1 RCT, SMD 0.81, 95% CI 0.04 to 1.59; $p = 0.04$) and EA (1 RCT, SMD 1.01, 95% CI 0.25 to 1.78; $p = 0.01$) reduced the frequency of HF to a greater extent than HRT. No significant difference was noted between MA and EA, or between MA and SA. It was judged that there was no heterogeneity between MA and SA ($I^2 = 0$).

Reduction in the HFS

There were 4 pairwise meta-analyses performed to compare the HFS (Table 3). MA was more effective than usual care at improving the HFS (1 RCT, SMD -0.59, 95% CI -0.91 to -0.27; $p = 0.0003$). However, no significant difference was reported in others.

Reduction in MENQOL score

Six pairwise meta-analyses were generated to investigate the improvement in MENQOL scores with different acupuncture

Table 2. Pairwise Meta-Analysis of the Frequency of Hot Flashes.

Comparison	Number	SMD (95% CI)	<i>p</i>	<i>I</i> ²
A vs B	1	-0.04 [-0.79, 0.70]	0.910	-
A vs D	1*	0.81 [0.04, 1.59]	0.040	-
A vs E	2	-0.05 [-0.26, 0.16]	0.640	0
A vs F	1*	-0.47 [-0.78, -0.15]	0.004	-
A vs G	1*	-8.61 [-9.60, -7.61]	< 0.001	-
B vs D	1*	1.01 [0.25, 1.78]	0.010	-

*A significant result.

A: manual acupuncture; B: electroacupuncture; D: hormone replacement therapy; E: sham acupuncture; F: usual care; G: no treatment.

Table 3. Pairwise Meta-Analysis of Hot Flash Score.

Comparison	Number	SMD (95% CI)	<i>p</i>	<i>I</i> ²
A vs B	1	-0.07 [-0.62, 0.49]	0.8100	-
A vs E	1	0.02 [-0.20, 0.23]	0.8800	-
A vs F	1*	-0.59 [-0.91, -0.27]	0.0003	-
B vs E	1	0.15 [-0.05, 0.36]	0.1500	-

*A significant result.

A: manual acupuncture; B: electroacupuncture; E: sham acupuncture; F: usual care. CI, confidence interval; SMD, standardized mean difference.

therapies (Table 4). MA significantly enhanced MENQOL scores compared with no treatment (1 RCT, SMD -0.97, 95% CI -1.89 to -0.05; $p = 0.04$). WA showed a greater significant reduction in MENQOL scores compared with HRT (1 RCT, SMD -0.58, 95% CI -1.06 to -0.11; $p = 0.02$). SA significantly improved MENQOL scores compared with no treatment (1 RCT, SMD -1.32, 95% CI -2.29 to -0.35; $p = 0.008$). No significant difference was reported between MA and EA, between MA and HRT, and between MA and SA. When comparing MA and SA, there was no heterogeneity ($I^2 = 0$).

Network meta-analysis

Network plot for different interventions

In the network meta-analysis plot, the thickness of the line shows the number of comparisons between the 2 interventions. Network meta-analysis included 6 interventions for the frequency of HF (Fig. 4A), 4 interventions for the HFS (Fig. 4B), and 6 interventions for MENQOL scores (Fig. 4C).

Evaluation of statistical inconsistency

The results of heterogeneity assessment of the HFS and MENQOL scores did not show statistically significant heterogeneity; therefore, the consistency model was selected ($p =$

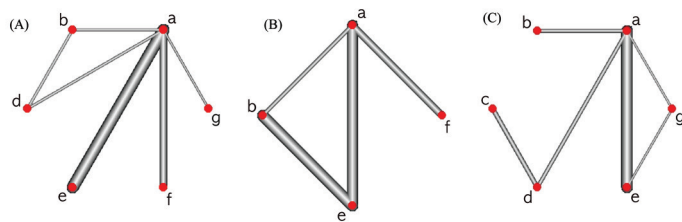


Fig. 4. (a) manual acupuncture, (b) electroacupuncture, (c) warm acupuncture, (d) hormone replacement therapy, (e) sham acupuncture, (f) usual care, (g) no treatment. The thickness of the line shows the number of comparisons between the two interventions. (A) Manual acupuncture and sham acupuncture had the largest number of comparisons followed by the comparisons of manual acupuncture and usual care. (B) Manual acupuncture and sham acupuncture, electroacupuncture and sham acupuncture were the most compared, followed by manual acupuncture usual care. (C) The number of comparisons between manual acupuncture group and sham acupuncture is remarkably greater than other comparisons.

0.699, 0.785). In network meta-analysis of changes in a reduction in frequency, the inconsistency either at the global level of the whole network or at the local level for a specific comparison could not be evaluated because of the small number of studies involved in each intervention. Network meta-analysis under the inconsistency model (design by treatment interaction model) for global inconsistency was conducted and used as the node splitting method for the assessment of local inconsistency.

Comparative results of different interventions

(1) Frequency of HFs

A league table was produced for the 6 interventions, including 5 RCTs (Table 5). Compared with no treatment, the other 5 interventions were significantly more effective (Table 5). Furthermore, HRT, MA, and SA showed a significant reduction in the frequency of HF compared with usual care, but there was no significant difference between usual care and EA (Table 5).

HRT had the highest efficacy (98.9%) for reducing the frequency of HF, which was significantly better than the efficacy of the other 5 interventions; MA (65.1%), SA (56.4%), EA (56.1%), usual care (23.5%), and no treatment (0%).

(2) HFS

There were 4 RCTs including 4 interventions which reported on the HFS (Table 6). The results showed that MA, SA, and EA were more effective than usual care at reducing the HFS (Table 6). Furthermore, MA had the highest efficacy (83.8%) in relieving HF severity, followed by SA (76.0%), EA (39.4%), and usual care (0%).

(3) MENQOL questionnaire

The network meta-analysis data from 5 RCTs involving 6 interventions showed that WA, SA, and MA significantly improved quality of life compared with no treatment (last row of Table 7). In addition, WA was more effective at improving MENQOL scores compared with HRT (SMD -0.58, 95%CI -1.06 to -0.11). WA was the most efficacious at enhancing quality of life (86.1%), followed by SA (79.3%), MA (54.7%), EA (45.0%), HRT (31.7%), and no treatment (0%).

Safety

Overall, 11 RCTs [16,18,21,24-26,31,33,34,36,37] including 1,442 patients reported on the safety of interventions. Based on these studies, the therapies included were MA, EA, ACE, SA, and

Table 4. Pairwise Meta-Analysis of Menopause-Specific Quality of Life Questionnaire.

Comparison	Number	SMD (95% CI)	p	I^2
A vs B	1	-0.13 [-0.68, 0.43]	0.660	-
A vs D	1	-0.25 [-0.82, 0.31]	0.380	-
A vs E	2	0.15 [-0.05, 0.35]	0.150	0
A vs G	1*	-0.97 [-1.89, -0.05]	0.040	-
C vs D	1*	-0.58 [-1.06, -0.11]	0.020	-
E vs G	1*	-1.32 [-2.29, -0.35]	0.008	-

*A significant result.

A: manual acupuncture; B: electroacupuncture; C: warm acupuncture; D: hormone replacement therapy; E: sham acupuncture; G: no treatment. CI, confidence interval; SMD, standardized mean difference.

Table 5. Network Meta-Analysis Comparisons of Effectiveness for Reducing the Frequency of Hot Flashes.

D					
-0.82 (-1.59, -0.04)*	A				
-0.87 (-1.67, -0.06)*	-0.05 (-0.26, 0.16)	E			
-0.87 (-1.62, -0.11)*	-0.05 (-0.79, 0.69)	0.00 (-0.77, 0.77)	B		
-1.28 (-2.12, -0.44)*	-0.47 (-0.78, -0.15)*	-0.42 (-0.80, -0.04)*	-0.42 (-1.22, 0.39)	F	
-9.42 (-10.69, -8.16)*	-8.61 (-9.60, -7.61)*	-8.56 (-9.57, -7.54)*	-8.56 (-9.80, -7.32)*	-8.14 (-9.19, -7.10)*	G

*A significant result.

A: manual acupuncture; B: electroacupuncture; D: hormone replacement therapy; E: sham acupuncture; F: usual care; G: no treatment.

Table 6. Network Meta-Analysis Comparisons of Effectiveness for Reducing Hot Flash Score.

A					
-0.02 (-0.23, 0.18)	E				
-0.15 (-0.34, 0.05)	-0.12 (-0.39, 0.14)	B			
-0.62 (-1.00, -0.24)*	-0.59 (-0.91, -0.27)*	-0.47 (-0.89, -0.06)*	F		

*A significant result.

A: manual acupuncture; B: electroacupuncture; E: sham acupuncture; F: usual care.

Table 7. Network Meta-Analysis Comparisons of Effectiveness for Improving Menopause-Specific Quality of Life Questionnaire.

C					
-0.18 (-0.95, 0.58)	E				
-0.33 (-1.07, 0.41)	-0.15 (-0.35, 0.05)	A			
-0.46 (-1.38, 0.47)	-0.27 (-0.87, 0.32)	-0.13 (-0.68, 0.43)	B		
-0.58 (-1.06, -0.11)*	-0.40 (-1.00, 0.20)	-0.25 (-0.82, 0.31)	-0.13 (-0.92, 0.66)	D	
-1.31 (-2.44, -0.19)*	-1.13 (-1.98, -0.28)*	-0.98 (-1.83, -0.13)*	-0.86 (-1.87, 0.16)	-0.73 (-1.75, 0.29)	G

*A significant result.

A: manual acupuncture; B: electroacupuncture; C: warm acupuncture; D: hormone replacement therapy; E: sham acupuncture; G: no treatment.

HRT. Acupuncture most frequently caused minor subcutaneous bleeding. In addition, pain, tingling, heat, swelling, abdominal discomfort, urinary frequency, tiredness, headache, and insomnia were also reported. In terms of SA intervention, bleeding, discomfort, insomnia, irritability, pain, fatigue, and flatulence were reported, whereas nausea, lethargy and breast swelling were caused by HRT. However, there were no severe adverse events associated with any intervention.

Discussion

Acupuncture therapy is widely used to treat menopausal symptoms and other gynecological conditions [1,2]. Developed from traditional MA, EA and WA are combination therapies: EA is where a micro electric current is passed through acupuncture needles and WA adds the thermal stimulation of moxibustion during acupuncture treatment [22,23,38]. ACE is also an integrative therapy that maximizes its therapeutic action with long retention time by implanting absorbable catgut sutures into acupuncture points [39]. Many studies have reported that MA, EA, WA,

ACE, and even SA are effective at improving HF in menopausal women [2,22,23,38,40,41]. The lack of a direct comparison among different acupuncture treatments makes it difficult to choose the clinically best treatment. Thus, the effectiveness of different types of acupuncture therapies were compared and ranked using network meta-analysis according to treatment capacity to reduce the frequency and severity of HF, and improve the quality of life of menopausal women.

In this review, 23 RCTs including 2,302 patients suffering from menopausal HF were enrolled in a systematic review, and a network meta-analysis was conducted using 10 of these RCTs. The results of network meta-analysis showed that MA had a higher probability of reducing HF frequency and severity compared with EA, SA, usual care, or no treatment. Furthermore, WA improved quality of life of menopausal women significantly more than MA or EA. However, studies related to ACE were only included in the systematic review due to their high heterogeneity and were not included in the network meta-analysis. In terms of ranking interventions, acupuncture therapy had a higher probability of reducing HF compared with usual care or no treatment. When comparing with HRT, acupuncture was less effective at lowering the frequency of HF, but was better at increasing quality of life. SA had a similar effect or slightly less than MA but had a better effect than EA.

Comparing the effects of MA and SA, the results for changes in frequency of HF are consistent with previous reviews [1,2,41] but show a difference in change of HF severity. In previous reviews [1,2,41], MA did not significantly reduce HF frequency, but it significantly reduced the severity of HF when compared with SA. Notably, in the analysis, only nonpenetrating needles as in SA were included because of the difference in the effect between shallow needling and nonpenetrating needling [42]. Therefore, there was little evidence to support differences between the 2 interventions at reducing HF severity, showing that both interventions were effective, and MA and SA did not show significantly different efficacy.

Previous studies [43,44] have demonstrated that acupuncture therapy, regardless of the type, may alleviate menopausal symptoms by increasing the level of E₂ and decreasing the level of LH. However, in several studies [18,23] included in this systematic review, serum E₂ and LH levels showed no significant change comparing before and after treatment. Several studies [45,46] have suggested that estrogen reduction alone is not sufficient to explain the occurrence of HF. Indeed, there is no relationship between HF with plasma, urinary, or vaginal levels of estrogens, and furthermore, there is no difference in serum levels between women with and without HF [46]. In addition, although a temporal relationship between HF and LH was observed [47,48], HF are also observed in women without LH, such as in women with pituitary insufficiency and pituitary gland resection [49, 50].

In menopausal women, HF are caused by core body temperature elevations acting within a greatly narrowed thermoneutral zone [51]. The lowering of the upper threshold in menopause changes peripheral blood flow even with a slight rise in core body temperature, which results in HF. Basic scientific investigations [52] have determined that narrowing of the thermoneutral zone is caused by increased brain norepinephrine levels. Acupuncture can stabilize the thermoregulatory center by influencing serotonin and norepinephrine in the central nervous [41,53,54]. In this regard, the changes in E₂ or LH make it difficult to clearly assess changes in HF, and a measurement of factors that affect the thermoregulatory center, such as norepinephrine, will be needed.

This review has several limitations. Firstly, a small number of studies were included in network meta-analysis, particularly in

the analysis of HF frequency changes. In addition, few studies with small sample size had a greater influence on the estimation of effects. Although there was no significant difference between direct and indirect comparisons, it seemed that the effect size of each intervention was overestimated compared with a direct comparison. Secondly, most studies included in this review had an unclear or high risk of bias in allocation concealment and blinding, which reduced the reliability of the study. In this respect, when the results of this study were interpreted, the important effect modifiers, such as treatment duration, acupuncture points, and severity of symptoms, were considered, and differences in the relative effects between interventions were acceptable. However, the estimated effect size was not taken as it was. Finally, it was difficult to synthesize the outcome measurements for symptom evaluation due to high heterogeneity in the RCTs. In the included studies, HFS, visual analog scale, or individual clinical symptom scores were used to assess the severity of HF, and the assessment period also varied from 1 to 7 days. Despite these limitations, this study would be meaningful as an initial review comparing and ranking the effects of various interventions for menopausal HF. It is highly recommended to seek further evidence through a high quality RCTs with unified clinical rating scale.

Conclusion

Herein, 23 RCTs were included in the quantitative analysis of which 10 studies were included in network meta-analysis to compare the effects of various types of acupuncture treatments on menopausal HF. It was determined that MA was the best option for alleviating the frequency and severity of HF, and WA for reducing MENQOL. There was no statistical difference between MA and SA in terms of HF frequency, severity, and MENQOL scores. The findings of this review should be interpreted with caution due to the small number of included studies and the risk of bias in the original research.

Conflicts of Interest

The authors have no conflicts of interests to declare.

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