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Factors Associated with Conflicting Findings on Acupuncture for Tension-Type Headache: Qualitative and Quantitative Analyses

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Abstract

Objectives: This study aimed to identify the factors that might have contributed to the conflicting outcomes about the efficacy of acupuncture for tension-type headache (TTH) through systematically reviewing relevant randomized controlled trials.

Methods: Thirteen (13) databases were searched from their inception until August 2010. There were no restrictions on language or year of publication. Included studies were randomized controlled trials comparing real with sham acupuncture, with patient selection guided by the International Headache Classification, and reported headache days. Meta-analyses and subgroup analyses were undertaken to compare the effects of real and sham acupuncture interventions and the effects of acupuncture with various needling techniques and treatment modes.

Results: Forty-three (43) studies were retrieved for further assessment from 120 potential studies. Finally, five studies of high methodological quality were included in this review. Standard mean difference (SMD) of the included studies showed no statistical significance between real and sham acupuncture (-0.31 ; 95% confidence interval [CI] -0.72 to 0.09), however, the heterogeneity among the studies was high ($I^2=81\%$). Subgroup analyses reduced heterogeneity, and showed that electro-acupuncture (SMD -1.60 ; 95% CI -2.33 to -0.88) to be more efficacious than manual acupuncture (SMD -0.13 ; 95% CI -0.41 to 0.14); needle retention with 30 minutes (SMD -0.46 ; 95% CI -0.87 to -0.06) being better than no needle retention (SMD 0.45 ; 95% CI -0.11 , 1.01); and twice-a-week treatment (SMD -0.46 ; 95% CI -0.87 to -0.06) was better than once-a-week treatment (SMD 0.45 ; 95% CI -0.11 , 1.01).

Conclusions: Acupuncture stimulation mode, needle retention, and treatment frequency could be important factors contributing to the outcome of acupuncture for TTH. Further studies are warranted to determine treatment parameters to ensure effective translation of RCTs outcomes of acupuncture for patients with TTH.

Introduction

ACUPUNCTURE HAS BEEN WIDELY USED to relieve headache, but trials on acupuncture for tension-type headache (TTH) have produced conflicting results. A recent Cochrane Library Systematic Review concludes that acupuncture is valuable for the management of TTH.¹ Results of sham-acupuncture controlled trials, however, showed inconsistent results. Some trials conclude that real acupuncture is significantly better than sham intervention,^{2,3} whereas others have not found a statistically significant difference between the two.^{4–7} A consensus on whether real acupuncture is superior to sham acupuncture has not been reached.^{8–12}

Acupuncture is a complex intervention. Its active ingredients are not well defined.^{13,14} A recent Delphi study of expert opinions on the essential components of quality acupuncture treatment has identified 14 domains with 26 items, including needle stimulation mode, treatment duration, frequency of treatment, practitioner training, and trial monitoring.¹⁵

To improve the quality of efficacy research on acupuncture for TTH, there is a need to identify factors contributing to the inconsistent outcomes (for instance, the adequacy and administration of trial acupuncture treatments). This systematic review aimed to identify the factors contributing to conflicting findings through conducting a meta-analysis and

subgroup analyses comparing the effects of real and sham acupuncture on TTH. Specifically, this review explored the effect of the factors that have been considered to have direct impact on the quality of acupuncture trial as described elsewhere.¹⁵ These factors are mode of acupuncture, manipulation of needle, frequency of treatment, and the number of trial centers, and other factors identified through qualitative assessment of the included studies.

Methods

Search strategy

Thirteen (13) major databases were searched consisting of four leading Chinese databases (CNKI, CQVIP, Wanfang database, and CBM) and nine English databases (Pubmed, Embase, CINAHL, Proquest, Cochrane library, Acubriefs, Science direct, SCOPUS, Informit) up to August 2010. There were no restrictions on year or language of publication. The search terms were the following: tension-type headache, acupuncture, randomized controlled trial, and their variations. A sample strategy is included in Table 1.

Selection criteria

Included studies (1) were randomized or quasirandomized controlled trials (RCTs or quasi-RCTs); (2) had adult patients with TTH diagnosed according to International Headache Society (IHS) criteria or Ad Hoc committee's criteria; (3) reported headache days as an outcome mea-

surement; (4) employed invasive acupuncture needling; and (5) needled acupoints, Ashi point, and/or trigger/tender points. Studies were excluded if (1) they did not have a sham acupuncture control group; (2) point injections were used because it is difficult to differentiate if the efficacy was from medication or acupuncture itself; (3) dry-needling was employed because its theory and practice is not in accordance with traditional acupuncture; or (4) results about participants with TTH were reported separately from those with other types of headache, such as migraine.

Outcome measure

The outcome measure was headache days¹⁶ at the end of the treatment and follow-ups.

Data extraction

Two (2) reviewer authors (XYH, LD) extracted data from eligible trials independently. Major characteristics including methods, participants, interventions, and outcome measures were recorded for analysis. Other information including protocols of treatment and selection criteria was also extracted for study comparisons. Disagreements were solved by discussion and consult with a third reviewer (ZZ).

Assessment of methodological quality

The methodological quality of each study was assessed by 2 reviewers (XYH and LD) using Jadad Scale,¹⁷ Internal Validity Scale (IVS),¹⁸ and the Oxford Pain Validity Scale (OPVS).¹⁹ Additionally, allocation concealment was ranked as A: adequate, B: unclear, C: inadequate, and D: not used.²⁰ A study with a score of 3 or more points on a Jadad scale is considered high quality. Similarly, with IVS and OPVS rating, studies reaching 60% of the total scores can be regarded as high quality.²¹

Data analysis and synthesis

Review Manager 5.1 was used for meta-analysis. Assessment of heterogeneity was evaluated using the I^2 test; a low, moderate, and high I^2 value was indicated by 25%, 50%, and 75%, respectively.²² A random-effect model was used if significant heterogeneity ($I^2 \geq 50\%$) among the trials was detected. For continuous data, weight or standard mean difference (SMD) was used. When different scales were used for assessing one outcome measure, SMD was calculated.

Subgroup analysis

When heterogeneity was high, qualitative data were examined to identify the potential sources. Subgroup analyses were then conducted to verify the sources.²⁰

Results

Search result and eligibility

Five (5) of 120 trials involving 838 TTH participants^{3-5,23,24} were selected, and the remaining were excluded because they reported invalid outcome measures, were duplications, had invalid interventions, or did not use IHS diagnostic criteria (see Supplementary Table online at www.liebertpub.com/acm). Figure 1 outlines the study selection.

TABLE 1. SAMPLE STRATEGY OF SEARCHING DATABASES

A. Search strategy to locate "tension-type headache"	# 1. tension-type headache [MeSH]
	# 2. tension headache [tw]
	# 3. headache [MeSH]
	# 4. TTH [tw]
	# 5. TH [tw]
	# 6. or/# 1-# 5
B. Search strategy to locate acupuncture interventions	# 7. acupuncture [MeSH]
	# 8. acupuncture therapy [MeSH]
	# 9. electroacupuncture [MeSH]
	# 10. electro-acupuncture [tw]
	# 11. brief needling [tw]
	# 12. dry needling [tw]
	# 13. electrical acupuncture [tw]
	# 14. acupuncture points [MeSH]
	# 15. body acupuncture [tw]
	# 16. scalp acupuncture [tw]
	# 17. routine acupuncture [tw]
	# 18. manual acupuncture [tw]
C. Search strategy to locate RCTs or semi-RCT	# 19. abdomen acupuncture [tw]
	# 20. or/#7-#19
	# 21. Randomized Controlled Trial [MeSH]
	# 22. RCT [tw]
	# 23. Controlled Trial [tw]
	# 24. CT [tw]
D. Search strategy to locate studies for this review	# 25. or/#21-#24
	#6 AND #20 AND #25

RCTs, randomized controlled trials.

FIG. 1. Flowchart of study selection. RCTs, randomized controlled trials.

Study characteristics

The characteristics of the five trials are listed in Table 2. Three (3)^{5,24,25} were conducted in Germany, and the remaining two^{3,23} were from the United Kingdom and Australia, respectively. The sample size ranged from 40 to 409, with three multicenter trials^{5,24,25} having a larger sample size. There were more females than males in the studies. The average age of the participants ranged from 30 to 50 years.^{3,5,23,25}

Quality of the trials

Scores of Jadad, IVS, and OPVS are presented in Table 2. Based on the Jadad scores, all five studies were of high

methodological quality. There was a high correlation between Jadad and IVS scores ($r=0.97$ $p=0.006$), but not between either Jadad and OPVS or IVS and OPVS. There was no correlation between methodology quality and treatment effect.

Characteristics of acupuncture treatments

Details of acupuncture treatments are presented in Table 3. One (1) study³ used electroacupuncture (EA) and selected distal points only, whereas the rest^{5,23-25} chose manual acupuncture (MA) using both local and distal points.

Four (4) studies^{3,5,24,25} had 30 minute-needle retention with *de qi* sensation, whereas one applied 15 seconds of

TABLE 2. CHARACTERISTICS OF THE INCLUDED STUDIES

	Study (author & year)				
	White 2000	Karst 2001	Xue 2004	Melchart 2005	Endres 2007
Country	England	Germany	Australia	Germany	Germany
Sample size	50	69	40	270	409
Age range	41-50	41-50	41-50	41-50	30-40
Gender ratio	18/7	17/17	13/7	95/37	163/46
(f/m)	20/5	21/14	13/7	46/17	158/42
TTH type	ETTH	ETTH+CTTH	ETTH+CTTH	ETTH+CTTH	ETTH+CTTH
Diagnosis standard	IHS 1997 ICD-10	IHS 1988 ICHD-I	IHS 1988 ICHD-I	IHS 1988 ICHD-I	IHS 2004 ICHD-II
Setting	Multiple health centers	Not mentioned	Research clinic in university	28 outpatient centers	122 outpatient family practice
Design	Multicenter trial 2-arm parallel RCT	Single site trial 2-arm parallel RCT	Single site trial crossover RCT	Multicenter trial 3-arm parallel RCT	Multicenter trial 3-arm parallel RCT
Interventions	Active: Acupuncture Control: Sham acupuncture	Active: Acupuncture Control: Sham acupuncture	Active: Electroacupuncture Control: Sham acupuncture	Active: Acupuncture Control: Sham acupuncture	Active: Acupuncture Control: Sham acupuncture
Outcome variables	Headache days; VAS; Frequency of headache; GHQ; SF-36 Acu: <i>n</i> = 1 Sham: <i>n</i> = 1	Headache days; VAS; CGI; Frequency of headache; ELQ; LS; D-S; NHP Not reported	Headache days; VAS; PTH; HDI; SIP	Waiting list Number of headache days; Pain disability index; SES; ADS SF-36; Acu: <i>n</i> = 6 Sham: <i>n</i> = 1 Waiting list: <i>n</i> = 6	Amitriptyline group Headache days; medication use; SF-12; Von Korff chronic pain grade scale; Global patient assessment Acu: <i>n</i> = 1 Sham: <i>n</i> = 5
Dropout	No significant differences between the groups.	No significant differences between the groups.	Real acupuncture produces a significantly better outcome than sham acupuncture.	Acupuncture was more effective than no treatment, but not significantly more effective than minimal acupuncture.	Verum acupuncture was superior to sham for most secondary endpoints.
Summary of results	Jadad: 5 (2-2-1) IVS: 6 (1-1-1-1-1-1) OPVS: 14 (6-1-2-1-1-1-1)	Jadad: 3 (1-2-0) IVS: 3.5 (0.5-0-1-0.5-0.5-1) OPVS: 12 (3-2-2-1-1-1-1-1)	Jadad: 5 (2-2-4) IVS: 5.5 (1-1-1-1-0.5-1) OPVS: 14 (6-1-2-1-1-1-1-1)	Jadad: 5 (2-2-1) IVS: 5.5 (1-1-1-1-0.5-1) OPVS: 16 (6-3-2-1-1-1-1-1)	Jadad: 5 (2-2-1) IVS: 6 (1-1-1-1-1-1-1) OPVS: 13 (3-3-2-1-1-1-1-1)
Quality assessment	A - Adequate	B - Unclear	A - Adequate	A - Adequate	A - Adequate
Allocation concealment					

IHS, International Headache Society; CGI, Clinical Global Impressions; NHP, Nottingham health profile; SIP, sickness impact profile; ICD, International Classification of Diseases; D-S, von Zerssen Depression Scale; ELQ, Everyday-Life-Questionnaire; PTH, Mechanical pain threshold; VAS, visual analogue scale; ICHD, International Headache Classification; GHQ, General Health Questionnaire; PPT, pressure pain thresholds; IVS, Internal Validity Scale; CTTH, Chronic Tension-type Headache; HDI, Headache disability index; SES, Schmerzempfindungs-Skala; OPVS, Oxford Pain Validity Scale; ETTH, Episodic Tension-type Headache; LS, Life-Quality scale; ADS, depression scale (Allgemeine Depressionsskala); RCT, randomized controlled trial; SF-36-item, Short Form Quality of Life Survey; SF-12, 12-item Short-Form Health Survey.

TABLE 3. COMPARISON OF REAL ACUPUNCTURE TREATMENT PROTOCOLS

	Study				
	White 2000	Karst 2001	Xue 2004	Melchart 2005	Endres 2007
Stimulation style <i>De qi</i> elicited	Manual acupuncture <i>De qi</i> or manipulate for 15 s	Manual acupuncture Not reported	Electroacupuncture <i>De qi</i>	Manual acupuncture <i>De qi</i>	Manual acupuncture <i>De qi</i>
Number of applied needles	Only a single needle in succession	6–10; max 15 needles	8	Maximum 25	10–25
Uni/bilateral	Bilateral	Not reported	Bilateral	Bilateral	Bilateral
Depths of insertion	Not reported	Not reported	Not reported	Not reported	2–30 mm
Needle retention time	No retention (15 s or until <i>de qi</i> if sooner)	30 min	30 min	30 min	30 min
Total treatment sessions (treatment duration)	8 sessions (6 weeks)	10 sessions (5 weeks)	8 sessions (4 weeks)	12 sessions (8 weeks)	10–15 sessions (6 weeks)
Point selection	Local + distal points	Local + distal points	Distal points only	Local + distal points	Local + distal points
Treatment Frequency	Once a week for 6 weeks then once a month for 2 months	Twice a week	Twice a week	Twice a week in the first 4 weeks then once a week in the remaining 4 weeks	Twice a week
Points used in real acupuncture	Obligatory points + supplementary points <i>Obligatory points</i> : GB20; LI4	Fixed points GB 20; LI 4; LR 3; GB 8; GB 14; GB 21; GB 41; UB 2; UB 10; UB 60; LU 7; TW 5; ST 8; ST 36; ST 44; DU 20; Extra1	Four types of formula: 1): LI 4; SJ 5; ST40; GB60 2): LR 3; LR 2; LI 4; LU 7 3): SP 6; ST 36; LI 4; SJ 5 4): LR 3; LI 4; KI 3; SJ 5	Obligatory points + supplementary points <i>Obligatory points</i> : GV 20; LI 4; LR 3 (or LR 2); GB 20 (or BL 10)	Obligatory points + supplementary points <i>Obligatory points</i> : GV 20; LI 4; LR 3 (or LR 2); GB 20 (or BL 10)
CM (Chinese Medicine) diagnosis applied	No	No	Yes	Yes	Yes
Practitioner's background	Accredited acupuncturists	Not reported	Registered acupuncturist	Physicians received > 140-h training	Physicians received > 140-h training
No. of practitioners	5	Not reported	1	43	122
No. of patients received real acupuncture	25	34	20	132	209
Rationale for treatment*	B	C	A	A	A

*Rating on Rationale for Treatment:

A: rationale for treatment has been clearly stated in text.

B: rationale for treatment can be assumed through the text.

C: rationale for treatment can be assumed through the text but not clear.

D: didn't mention the rationale for design of the treatment protocol at all.

needling stimulation without intention to obtain *de qi* or needle retention.²⁵

Treatment sessions range from 8 to 15 over 4–8 weeks, with weekly or twice-a-week treatment. Three (3) studies applied pulse and tongue diagnosis or Chinese medicine (CM) diagnostic questionnaires.^{3,5,24} All trials reported number and training background of practitioners except for one.²⁵ Four (4) studies intended to achieve individualized treatment through semistructured protocols,^{3,5,23,24} and one used fixed points for all patients.²⁵

A comparison of sham acupuncture is provided in Table 4. All studies used nonacupuncture points and applied the same needle retention time as that in the real acupuncture treatment. Three (3)^{3,5,24} avoided using any points on the head. Three (3)^{3,4,24} used an invasive method, by means of superficial insertion onto on nonpoints without *de qi*. The other two studies^{23,25} used a noninvasive method.

Efficacy of acupuncture in headache days

All five studies^{3,5,23–25} were included in the meta-analysis. SMD was calculated because one study reported headache days per week²³; two studies^{3,25} reported headache days per month; and the other two studies^{5,24} reported headache days per 4 weeks.

Results are presented in Figure 2. Real and sham acupuncture groups were not statistically different at any time point with regard to headache days. A high heterogeneity ($p=0.0004$; $I^2=81\%$) was identified at the end of the treatment. Low heterogeneities were presented for analyses of short-term and long-term follow-up periods ($I^2=33\%$ and $I^2=30\%$, respectively).

Subgroup analyses and investigation of heterogeneity

Subgroup analyses were conducted to examine the source of heterogeneity according to qualitative data of the features of acupuncture treatments (Table 5).

TABLE 4. COMPARISON OF SHAM ACUPUNCTURE PROCEDURES

	Study				
	White 2000	Karst 2001	Xue 2004	Melchart 2005	Endres 2007
Invasive needling method used?	No	No	Yes	Yes	Yes
Stimulation style	Blunted cocktail-stick tapped in by avoiding tender area and acupoints	Blunt needle inserted on the real points in real group through a cube-shaped elastic foam to cause a pricking sensation without actually puncturing the skin	Superficial insertion by same needle with real intervention with very low frequency	Superficial needling by same type of needle with real group	Superficial insertion by same type of needle with real group
Points on head?	Yes Sham points are 4 standard areas (2 selected from the occipital protuberances, spines of scapula, vertex of skull and spinous process of 6th cervical vertebra, and 2 areas at the middle of 2nd metacarpal bone of each hand)	Yes Same points as the real acupoints. include: GB20 LI4 LR3 GB8 GB14 GB21 GB41 BL2 BL10 BL60 LU7 TE5 ST8 ST36 ST44 GV20 Extra1 (<i>Yintang</i>)	No	No	No
Location of points	5–10 mm away from real points	Same points used in real group	5–10 mm away from real points	Nonacupoints	Nonacupoints
Manipulation on needle	Gentle pressure while rotating for 15 seconds on each	Not mentioned	No further manipulation	Avoid manual stimulation	No stimulation
Needle retention time	Manipulate for 15 seconds (without retention)	30 minutes	30 minutes	30 minutes	30 minutes
<i>De qi</i> elicited	Not mentioned	Not mentioned	Avoid <i>de qi</i>	Avoid <i>de qi</i>	Avoid <i>de qi</i>

FIG. 2. Forest plot: Acupuncture versus sham acupuncture, outcome: Headache days. SD, standard deviation; CI, confidence interval.

Type of acupuncture (EA versus MA). When four^{5,23–25} MA studies were compared with one EA study, there was a statistically significant subgroup difference favoring EA. The overall heterogeneity was moderate ($I^2=57\%$) (Fig. 3A). After the removal of White's study, which had no needle retention, the heterogeneity was reduced. The subgroup

difference remained statistically significant ($\chi^2=12.69$, $p=0.0004$) (Fig. 3B).

Needle retention (30 minutes versus no retention). Four (4) studies^{3,5,24,25} with 30-minute needle retention with *de qi* sensation were compared with one study with 15 seconds of

TABLE 5. RESULTS OF SUBGROUP ANALYSES (AFTER TREATMENT)

Outcome title	Number of studies	Number of patients	Effect size SMD (95% CI)	Test for overall effect p-value	Heterogeneity
1. Type of acupuncture (EA vs. MA)					
Before removal EA	1	40	-1.60 [-2.33, -0.88]	$p < 0.0001$	N/A
MA	4	689	-0.13 [-0.41, 0.14]	$p = 0.33$	$I^2 = 57\%$; $\tau^2 = 0.04$
After removal of White 2000 MA	3	639	-0.26 [-0.42, -0.10]	$p = 0.001$	$I^2 = 0\%$; $\tau^2 = 0.00$
2. Needle retention (No retention vs. 30 minutes retention)					
Before removal Needle retention not applied	1	50	0.45 [-0.11, 1.01]	$p = 0.12$	N/A
Needle retention applied for 30 minutes	4	679	-0.46 [-0.87, -0.06]	$p = 0.02$	$I^2 = 78\%$; $\tau^2 = 0.12$
After removal of Xue 2004 Needle retention applied for 30 minutes	3	639	-0.26 [-0.42, -0.10]	$p = 0.001$	$I^2 = 0\%$; $\tau^2 = 0.00$
3. Treatment frequency (twice a week vs. once a week)					
Before removal Once a week	1	50	0.45 [-0.11, 1.01]	$p = 0.12$	N/A
Twice a week	4	679	-0.46 [-0.87, -0.06]	$p = 0.02$	$I^2 = 78\%$; $\tau^2 = 0.12$
After removal of Xue 2004 Twice a week	3	639	-0.26 [-0.42, -0.10]	$p = 0.001$	$I^2 = 0\%$; $\tau^2 = 0.00$
4. Center of study (multicenter vs. single site)					
Before removal Single-site trial	2	109	-0.92 [-2.20, 0.35]	$p = 0.15$	$I^2 = 88\%$; $\tau^2 = 0.75$
Multicenter trial	3	620	-0.07 [-0.43, 0.28]	$p = 0.69$	$I^2 = 70\%$; $\tau^2 = 0.07$
After removal of White 2000 Multicenter trial	2	570	-0.25 [-0.44, 0.06]	$p = 0.01$	$I^2 = 17\%$; $\tau^2 = 0.00$

SMD, standard mean difference; CI, confidence interval; EA, electroacupuncture; MA, manual acupuncture; N/A, not applicable.

A

B

C

FIG. 3. Exploration of the sources of heterogeneity. **A** and **B**: Type of acupuncture (electroacupuncture [EA] versus manual acupuncture [MA]). **C** and **D**: Needle retention (30 minutes versus no retention). Frequency of treatment (twice a week versus once a week). **E** and **F**: Number for study center (multicenter versus single site). SD, standard deviation; CI, confidence interval.

needling.²⁵ There was a high heterogeneity ($I^2=78\%$) (Fig. 3C). After the removal of the EA study, heterogeneity was reduced ($I^2=0\%$). Among the remaining four MA studies, there was a statistically significant subgroup difference between studies having 30-minute retention and those with no needle retention ($\chi^2=5.70$, $p=0.02$) favoring longer needle retention (Fig. 3D).

Frequency of treatment (twice a week vs. once a week). Four (4) studies^{3,5,24,25} with twice-a-week treatment sessions were compared with one study having weekly treatment.²⁵ This subgroup analysis involved exactly the same studies as in the comparison of needle retention, and the same result was obtained (Figs. 3C and 3D).

D **E** **F**

FIG. 3. (Continued).

Number for study center (multicenter versus single site). Three (3) multicentered trials were compared with two single-site studies. There was no statistically significant difference ($\chi^2 = 1.60$, $p = 0.21$). Heterogeneity was high among the two single site-studies ($I^2 = 88\%$) because EA and MA were used, respectively. Removal of the one study with short-needle retention did not change the results (Figs. 3E and 3F).

A comparison of two multicenter trials

A detailed comparison was conducted of the two multicenter studies^{5,24} (Table 6). Information about the trial

methods of the two studies were extracted from another two publications.^{26,27} They were similar in their design, but differed in outcomes, with one study showing significantly less headache days reported in the real acupuncture group than the sham group²⁴ (SMD -0.31; 95% CI -0.51 to -0.12) and the other reporting no group difference⁵ (SMD -0.10; 95% CI -0.42 to 0.21).

The two studies differed in treatment protocol and administration. In Endres' study, protocol adherence was enforced with trial monitors visiting the centers regularly; in Melchart's study, this was not described. In that study, one center did not use two out of three mandatory points as the

TABLE 6. DIFFERENCES OF THE TWO MULTICENTER TRIALS

	Study	
	Melchart 2005	Endres 2007
<i>De qi</i>	Required to achieve if possible	<ul style="list-style-type: none"> • <i>De qi</i> was required on all points • Repeated <i>de qi</i> was required (2–3 times)
Literature support	No description	40 acupuncture textbooks were analyzed
Requirement on point selection	No description	Had to be formulated as precisely as possible based on the appropriate TCM principles
Classification of optional points selection	<ul style="list-style-type: none"> • Classical acupoints • Microsystem points • <i>Ah-Shi</i> points • Trigger points 	<ul style="list-style-type: none"> • Channels • Internal level Chinese syndrome • <i>Ah-Shi</i> points • Symptomatic points
CM diagnosis	<ul style="list-style-type: none"> • A traditional Chinese syndrome diagnosis was requested, but not mandatory 	<ul style="list-style-type: none"> • Identifying affected meridians • Identification of TCM syndrome patterns • Tongue diagnosis was used additionally • A predefined questionnaire was designed • Mimicking an individualized TCM acupuncture procedure
Administration	<ul style="list-style-type: none"> • Physicians were free to choose needle length and diameter • Recommendations for additional points were made, but practitioners were free to choose others • One center did not use basic points on patients 	<ul style="list-style-type: none"> • Type of needles and intensity of needle stimulation, minimum and maximum number of needles to be inserted were consistent during treatment • Independent clinical monitors were set

CM, Chinese Medicine; TCM, Traditional Chinese Medicine.

points were considered unnecessary by the trial practitioners at the center. Data from the center were excluded from the final outcome. Nevertheless, the incident highlighted the importance of protocol adherence and trial monitoring.

Discussion

Results from meta-analysis showed no statistically significant difference between real and sham acupuncture on headache days. Through subgroup analyses, it was found that mode of acupuncture stimulation, duration of needle retention, and frequency of treatment could be the contributing factors to a lack of difference. In clinical practice, a typical acupuncture treatment involves 20–30 minutes of needling retention, repeated *de qi* sensation or stimulation, and daily or twice-weekly treatment. This review conforms to the importance of these factors. Trials with acupuncture treatment that neglect these factors might have provided suboptimal treatments, leading to a lack of difference between real and sham acupuncture.

The impact of the number of trial centers on the outcome of acupuncture treatment for TTH is not clear. Through qualitative analysis of two multicenter trials, it was further identified that adherence to treatment protocol could be another key contributing factor for multicenter trials.

A comparison with other reviews

Among four existing meta-analyses comparing the effectiveness of real with sham acupuncture intervention,^{1,4,10,28,29} only two used the headache days as one of the outcome

measures,^{1,10} including the latest Cochrane review by Linde and colleagues finding that real acupuncture was significantly better than sham acupuncture on reducing headache days (WMD –1.56; 95% CI –3.02 to –0.10), and the other by Davis that reported no difference between the two interventions, the same as ours.

The Linde review restricted trials to those with 8 weeks or more observation period after randomization. As a result, they included four out of five studies selected for the current review and excluded one EA study with a 6-week treatment period. This EA study was included because it meets the authors' criteria, and a 6-week observation period was considered sufficient to detect the short-term effect of acupuncture. The Davis review included the same five studies as those of the current review. The EA study increased the heterogeneity of the meta-analysis, resulting in no difference between real and sham acupuncture. The Linde review reported small heterogeneity of $I^2 = 13\%$, and we reported a large heterogeneity of $I^2 = 81\%$.

The main aim of this review was to utilize subgroup analyses to explore the source of heterogeneity, which was not conducted in either of the two reviews. Subgroup analyses are frequently used to extract valuable information from RCTs.^{30–32} It has also been applied in acupuncture systematic reviews to investigate and interpret heterogeneity.³³ To ensure that only high-quality studies were included, this review employed three commonly used scales (i.e., Jadad, IVS, and OPVS), considering selection bias, performance bias, and attrition bias, as well as the sample size and outcome measures used in pain studies. All five studies were found to be of high reporting and methodological quality.

Adequacy of acupuncture treatment and reporting of treatment details

Adequacy of acupuncture treatment is as important as methodological quality when considering the validity of the conclusions.^{34–37} However, the adequacy and quality of treatment was seldom assessed in the existing systematic reviews of acupuncture.³⁴ A recent study using the Delphi method¹⁵ identified contributing factors as recommended by experts. Mode of acupuncture, frequency of treatment, and needle manipulation, identified in the current review, were also recommended by experts as key contributing factors.

Stimulation mode: EA versus MA. In this review, the study with EA produced a better result in headache reduction than MA did. EA has found by other researchers to be effective in reducing pain.^{38,39} Up to now, there has not been any study directly comparing EA with MA on TTH. However, comparisons were made in some health conditions, and EA was better than MA in treating patients with tennis elbow,⁴⁰ knee osteoarthritis,⁴¹ and fibromyalgia syndrome.³³

When measured with functional magnetic resonance imaging, EA produced a more widespread signal increase in the brain than MA did.⁴² In addition, a greater analgesic effect was found when comparing EA with MA or sham acupuncture.⁴³

Needle retention and treatment frequency. In most acupuncture clinical trials for headache, 20–30-minute treatments with more than 10 minutes of needle retention per session were applied.^{44–48} However, standards or guidelines of needle retention time are not available for TTH treatment currently. A study for cerebral palsy reported that the group with needle retention of 30 minutes had better results than the group with 5-minute needle retention.⁴⁹ One recent study also identified EA of 15–20 minutes was better than that of 5 or 10 minutes.⁵⁰

Another factor is the frequency of treatment. One (1) study in this review applied weekly treatment, which was regarded as being insufficient to produce an analgesia effect.⁵¹ Short needle retention time together with inadequate acupuncture treatment frequency (e.g., weekly 5-minute treatment) could underestimate the treatment effect.⁵²

Other factors identified. Other potential factors identified through qualitative analyses of the data in this reviews are *de qi*, point selection, CM diagnosis, background of trial acupuncturist, and adherence to trial protocol. Due to insufficient data, subgroup analyses were not conducted.

de qi is regarded as the essential part of acupuncture and the predictor of a positive outcome during an acupuncture treatment.⁵¹ A strong correlation between *de qi* and analgesic effect was found in healthy humans.⁵³

Studies included in this review had two categories of point selection (i.e., fixed or semistandardized point selection) like many other acupuncture studies^{54–59}. However, fixed, a pre-determined acupuncture treatment protocol was not suggested in headache clinical trials,⁶⁰ given the varieties of headache presentations.

Individualized or semistandardized point selection requires standard CM diagnosis of TTH. Variations in these studies indicate a need to establish the CM differentiation diagnosis of TTH before further trials are conducted.

Multicenter studies inevitably encounter more problems than single-center trials, especially in nonpharmacological studies. As described previously, delivery of intervention could vary from one center to another even when the same protocol is used. In addition, the quality of non-pharmacological treatment largely relies on the skills and experience of the trial practitioners. As a result, skilled practitioners and reporting and assessment on protocol adherence are imperative.⁶¹ Careful monitoring is necessary for ensuring the credibility of the results.⁶²

Strengths and limitations

This review is among the first studies that explore the contributing factors to inconsistent findings from systematic reviews of acupuncture on TTH. It does not aim to assess the effect and safety of acupuncture for TTH as other systematic reviews aimed to achieve. As a result, all sham-acupuncture controlled trials were included without including studies comparing real acupuncture with no acupuncture or other active treatments. Authors of two studies with insufficient data^{23,25} were contacted, but no reply was obtained from them. Also, Chinese literature was systematically searched from the leading Chinese databases, but none met the selection criteria.

The limitation of this review is the small sample size with only five studies meeting the selection criteria. As a result, some potential factors, such as obtaining *de qi* during the treatment, CM diagnosis, and point selection were not able to be explored. Furthermore, the conclusion of the current review is limited by the weakness of subgroup analyses, which help identify the source of heterogeneity, but do not provide definite answers as studies that directly compare the factors do. For instance, EA was found to be better than MA in the current review. A definite conclusion can only be drawn when EA and MA are compared in a study.

A consensus on quality acupuncture needs to be reached. The Delphi study by Smith and colleagues has provided the first step. The present review illustrates the importance of some factors. The factors identified from the Delphi and this review should be assessed via subgroup analyses planned in systematic reviews of acupuncture and purposely designed trials in patients and healthy humans.

Implications and Conclusions

Stimulation mode, needle retention, and treatment frequency are important factors contributing to the outcome of acupuncture treatment for TTH. For clinical practice, the ideal acupuncture treatment protocol for TTH could be EA with 30 minutes needle retention and twice-weekly treatment. Further studies comparing EA with MA and comparing individualized treatment with standard formula are needed. Researchers also need to consider number of trial sites, practitioner training, and protocol adherence. To ensure that systematic reviews and trials of acupuncture are of high quality, consensus on quality acupuncture treatment and administration need to be established with evidence-based approaches.

Disclosure Statement

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