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Effects of Gua Sha therapy on perimenopausal syndrome: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objective: In East Asia, Gua Sha therapy is widely used in patients with perimenopausal syndrome. The goal of this systematic review was to evaluate the available evidence from randomized controlled trials (RCTs) of Gua Sha therapy for the treatment of patients with perimenopausal syndrome.
Methods: Databases searched from inception until June 2017 included: PubMed, Embase, the Cochrane Central Register of Controlled Trials and four Chinese databases [WanFang Med Database, Chinese BioMedical Database, Chinese WeiPu Database, and the China National Knowledge Infrastructure (CNKI)]. Only the RCTs related to the effects of Gua Sha therapy on perimenopausal syndrome were included in this systematic review. A quantitative analysis of RCTs was employed using RevMan 5.3 software. Study selection, data extraction, and validation were performed by two independent reviewers. Cochrane criteria for risk-of-bias were used to evaluate the methodological quality of the trials.
Results: A total of 6 RCTs met the inclusion criteria, and most were of low methodological quality. When compared with Western medicine therapy alone, meta-analysis of 5 RCTs indicated favorable statistically significant effects of Gua Sha therapy plus Western medicine on the Kupperman Menopausal Index (KMI) Score [mean difference (MD) = -4.57, 95% confidence interval (CI) (−5.37, −3.77), $p < 0.01$; heterogeneity: $Chi^2 = 29.57$ $p < 0.01$, $I^2 = 86\%$]. Moreover, study participants who received Gua Sha therapy plus Western medicine therapy showed significantly greater improvements in serum levels of follicle-stimulating hormone (FSH) [MD = −5.00, 95% CI (−9.60, −0.40), $p = 0.03$], luteinizing hormone (LH) [MD = −4.00, 95% CI (−7.67, −0.33), $p = 0.03$], and E_2 [MD = −6.60, 95% CI (−12.32, −0.88), $p = 0.02$] compared to participants in the Western medicine therapy group, with a low heterogeneity ($Chi^2 = 0.12$, $p = 0.94$, $I^2 = 0\%$ in FSH; $Chi^2 = 0.19$ $p = 0.91$, $I^2 = 0\%$ in LH; $Chi^2 = 0.93$, $p = 0.63$, $I^2 = 0\%$ in E_2). In addition, the pooled results displayed favorable significant effects of Gua Sha therapy plus the Western medicine therapy on the MENQOL scale when compared with the Western medicine therapy alone [MD = −5.13, 95% CI (−7.45, −2.81), $p < 0.01$] with low heterogeneity ($Chi^2 = 0.66$, p = 0.42, $I^2 = 0\%$).
Conclusion: Preliminary evidence supported the hypothesis that Gua Sha therapy effectively improved the treatment efficacy in patients with perimenopausal syndrome. Additional studies will be required to elucidate optimal frequency and dosage of Gua Sha.

Contents

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1. Introduction

Perimenopause is defined as “the time period prior to menopause and 1 year after final menstruation” [1]. During this period, ovarian failure and changes in serum estrogen levels can cause perimenopausal syndrome [2]. Perimenopausal syndrome most frequently presents with clinical symptoms, which include hot flashes, sweating, urinary stress incontinence, musculoskeletal pain, fatigue, insomnia, vaginal dryness, sexual dysfunction, and formication [2,3]. In addition, with disease progression, perimenopausal syndrome significantly diminished a patients' normal quality of life, increased their social distress and emotional embarrassment [4,5].

Currently, international and local guidelines recommended the use of hormone replacement therapy (HRT) as a gold standard treatment of perimenopausal syndrome, especially for vasomotor symptoms [6,7]. However, according to recent studies, this therapy cannot be used for the primary and secondary prevention of cardiovascular diseases [8]. HRT is frequently associated with several undesired side effects, and increases the long-term risk of serious adverse events (AEs) involving endometrial cancer [9], breast cancer [10], stroke [11], and coronary heart disease [12]. Therefore, due to consequences of AEs from HRT, over half of the women have tried alternative therapies for managing their perimenopausal syndrome [13,14].

Gua Sha, also known as ‘coining’, ‘skin-scraping’ or ‘pressured-stroking’, is an ancient invasive healing technique that is widely used in East Asian [15]. Literally, ‘Gua’ refers to the instrument-assisted press-stroking of a lubricated body surface, while ‘Sha’ refers to the transitory therapeutic petechiae at the treated area [16]. In general, Gua Sha is defined as a technique that involves various smooth-edged instruments (historically a spoon) to create unidirectional press-stroking on the patient's lubricated skin at the back until therapeutic petechiae appear at the treated area [17]. These therapeutic petechiae fade and normally resolve within 3–5 days [18]. From the perspective of Traditional Chinese Medicine (TCM), Qi (form and function)-stagnancy and blood stasis are characteristics of a variety of diseases. The expression of therapeutic petechiae and their subsequent fading are associated with upregulation of heme-oxygenase-1 (HO-1) and its anti-inflammatory and immunomodulatory effect. In TCM, the expression and resolution of Sha petechiae resolves pain and features of disease that are associated with Qi and 'blood' stagnation. As a traditional folk remedy, Gua Sha has been widely accepted by TCM practitioners and the Chinese population with a cultural background [20]. According to a 2008 cross-sectional study, Gua Sha therapy was considered the second most widely used manipulative therapy in Taiwan next to Chinese Tuina [21]. Moreover, roughly 71% of TCM practitioners in Taiwan have applied this technique for treating musculoskeletal pain, allergic asthma, common cold, influenza, and insomnia [22]. In addition, a community-based survey conducted in Hong Kong revealed that about one-fourth of the general population employed Gua Sha therapy for treating diverse chronic illnesses, especially those involving pain conditions [23]. Although Gua Sha is popular in East Asian countries, this type of therapy has not attracted much attention in the Western world. On the one hand, most acupuncture and oriental medicine schools in the West do not teach Gua Sha therapy. On the other hand, cultural differences between East Asian and Western values have influenced clinical applications of Gua Sha therapy.

Recently, a bibliometric analysis of studies published in China between 1994 and 2012 indicated that Gua Sha therapy has been widely used in the treatment of a wide spectrum of gynecological diseases, including perimenopausal syndrome [24]. Nowadays,

other systematic reviews have studied the effects of Gua Sha therapy on musculoskeletal pain [25] and low back pain [26]. Moreover, in 2014, Peng et al. [27] summarized current evidence to evaluate the effect of TCM on perimenopausal syndrome (including one RCT, to test the effect of Gua Sha therapy for perimenopausal syndrome). However, no systematic reviews are available that specifically focus on the Gua Sha therapy in perimenopausal syndrome.

Therefore, the aim of this study is to update and critically evaluate the evidence from randomized controlled trials (RCTs) that have tested the efficacy and safety of Gua Sha therapy in treating perimenopausal syndrome.

2. Materials and methods

This study was employed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The protocol used in this systematic review has been registered in PROSPERO funded by the United Kingdom (UK) National Institutes of Health Research (Registration Number: CRD 42017059790).

2.1. Data sources

The following databases were searched from inception until June 2017: PubMed, Embase, the Cochrane Central Register of Controlled Trials and four Chinese databases [WanFang Med Database, Chinese BioMedical Database, Chinese WeiPu Database, and China National Knowledge Infrastructure (CNKI)]. Search strategies are presented in Appendix A, and search terms were slightly modified for other databases. In addition, the reference lists of review articles were also searched to identify RCTs for any possible titles matching the inclusion criteria. Furthermore, to identify grey literature/unpublished studies, relevant studies were identified via a review of Registry ClinicalTrials.gov, Chinese Clinical Trial, and WHO International Clinical Trials Registry Platform (ICTRP).

2.2. Selection of studies

Only RCTs that focused on the effects of Gua Sha therapy in perimenopausal syndrome were included in this systematic review. Trials published as dissertations were also selected as eligible studies. All studies included in this review met the following inclusion criteria using the PICOS principle (population, intervention, comparison, and outcome). No language restrictions were imposed.

P (population): Patients diagnosed with perimenopausal syndrome using definitive World Health Organization (WHO) diagnostic criteria were included [28].

I (intervention): Studies were included if Gua Sha therapy was used as the sole intervention or as an adjunct therapy in conjunction with routine care for perimenopausal syndrome. Therefore, studies were excluded when other TCM therapies, such as acupuncture, moxibustion, massage, Chinese herbals, and Chinese Patent Medicine were utilized as an adjunct treatment in conjunction with routine care.

C (comparison): The routine care for perimenopausal syndrome in the control group should follow the North American Menopause Society guidelines [29]. Routine care involved appropriate physical exercise, a healthy lifestyle modification, a reasonable diet, as well as psychological adjustment and cognitive behavioral therapy (CBT). HRT was used according to a physician's prescription. Studies were excluded if treatments in the control group were not relevant to routine care based on the North American Menopause Society guidelines or other TCM therapies, such asacupuncture, moxibustion, massage, Chinese herbals, and Chinese patent medicine that were used as an adjunct treatment in conjunction with routine care.

O (outcomes): The primary outcome included in this systematic review was the Kupperman Menopausal Index (KMI) score and Menopause-Specific Quality of Life (MENQOL) scale. The KMI score was used to assess patients with perimenopausal syndrome in a clinical settings [30]. This questionnaire included 11 items, including hot flashes, paresthesias, insomnia, depression, urinary infection and low sex drive, dizziness, fatigue, arthralgia and myalgia, headache, palpitations, and skin formication. For each item, the four possible response options were as follows: none, mild, moderate, and severe. The equivalent scores were 0, 1, 2 and 3, respectively. The total KMI score ranged from 0 to 63 and a higher score indicated worse perimenopausal syndrome symptoms. In addition, MENQOL is an internationally used validated questionnaire to determine the quality of life of patients with perimenopausal syndrome [30]. The questionnaire consisted of 29 items in four dimensions, including vasomotor (3 items), psychosocial (7 items), physical (16 items), and sexual (3 items). Each dimension received a score ranging from 0 to 6. The lower the MENQOL score, the less quality of life was influenced by perimenopausal syndrome. The secondary outcome included serum levels of FSH, LH, and E_2.

2.3. Data extraction, quality, and validation

The full text of each included article was read by two independent reviewers (Ren and Yu) who extracted relevant data based on predetermined criteria. The following data were extracted from each original manuscript: (1) author and publication year; (2) sample size; (3) therapeutic intervention (types of Gua Sha therapy, duration of treatment, treatment acupuncture points, acupoints' rational theory); (4) control groups (types of Western medicine, methods of administration, and the duration of treatment); (5) follow-up (6) main outcomes (7) AEs. The Cochrane risk-of-bias tool [31] was used to evaluate the methodological quality of each included trial, and each RCT was assessed for the following characteristics: (1) selection bias; (2) performance bias; (3) detection bias; (4) attrition bias; (5) reporting bias. The terms 'Low', 'Unclear', and 'High' referred to *low*, *uncertain*, and *high* risks of bias, respectively. In most cases, disagreements were settled by discussion between the two reviewers. If disagreement remained after discussion, a third reviewer (Zhou) was consulted prior to the final decision on the disagreements.

2.4. Quantitative data analysis

In our review, meta-analysis was performed using software RevMan 5.3 (Cochrane Collaboration, Oxford, UK, freely available on the following website: http://www.ccims.net/revman/download [31]. For dichotomous data, results were presented as risk ratio (RR) with 95% confidence intervals (CIs). For continuous data, mean difference (MD) was included in the meta-analysis. In each meta-analysis, the Chi-square and I^2 tests were used to evaluate statistical heterogeneity [32]. When $I^2<50\%$ and $p>0.1$, a fixed effect model was applied. In addition, the random effect model was used if articles were clinically similar in nature [32]. If a sufficient number of studies were available (at least 10 studies), publication bias was assessed using funnel plot analysis [33].

3. Results

3.1. Trial flow and study characteristics

In this study, the literature search of databases generated a total

of 220 citations. After excluding duplicate manuscripts, titles, and abstract, a total of 47 full text articles were evaluated. Of these 47 articles, 41 were excluded as they did not meet the inclusion criteria. Therefore, 6 eligible RCTs [34–39] involving 438 participants were included for systematic review (Fig. 1). The six included RCTs all originated in China and had a relatively small sample size. In all trials, cointervention of Gua Sha therapy and HRT was compared, using a control of HRT alone. Moreover, except for one RCT [36], the duration of the interventions was 4 weeks. The number of sessions per week varied from 1 to 7, resulting in a total of 4–28 sessions. The site of Gua Sha therapy varied according to TCM theory. Among all included trials, two trials did not specify the points. The most commonly site of Gua Sha therapy, which was used in four studies, were Taiyang Bladder Meridian of the Foot. Du Meridian was used in two trials. The other studies used additional sites of Gua Sha therapy (BL11 to BL18, Shaoyin Heart Meridian of Hand, Shaoyin Kidney Meridian of Foot) according to TCM pattern identification. Details regarding the six RCTs [34–39] included in our meta-analysis are shown in Tables 1 and 2.

3.2. Risk of bias

The Cochrane risk-of-bias is presented in Figs. 2 and 3. Two of the included trials [34,36] reported appropriate sequence-generation methods for randomization, whereas in the remaining trials [35,37–39] the methods of sequence generation were not described. One of the included trials [36] conducted concealment of allocation by sealed envelopes, while three RCTs [37–39] used inappropriate methods. In the remaining trials [34,35], the methods of sequence generation were not described. In addition, the authors reported that none of the included trials employed patient-blinding methods, whereas assessor blinding was not mentioned in 5 RCTs [34,35,37–39]. Of the 6 included RCTs, two RCTs [34,36] stated the risk of bias for participant dropout or withdrawal. Considering other sources of bias, funding agencies were shown in three RCTs [37–39]. The sources of direct funding included medical universities or Ministry of Health research foundations. These trials were deemed to be free from the risk of bias posed by a financial conflict of interest.

3.3. Outcomes meta-analysis

3.3.1. Kupperman Menopausal Index score

Five RCTs (involving 438 patients) [34,36–39] were identified using the outcome measurement of the KMI Score. The meta-analysis showed superior effects of Gua Sha therapy combined with Western medicine therapy on KMI Score when compared with Western medicine alone [MD = −4.57, 95% CI (−5.37, −3.77), $p < 0.01$], with high heterogeneity ($Chi^2 = 29.57$ $p < 0.01$, $I^2 = 86\%$) (Fig. 4).

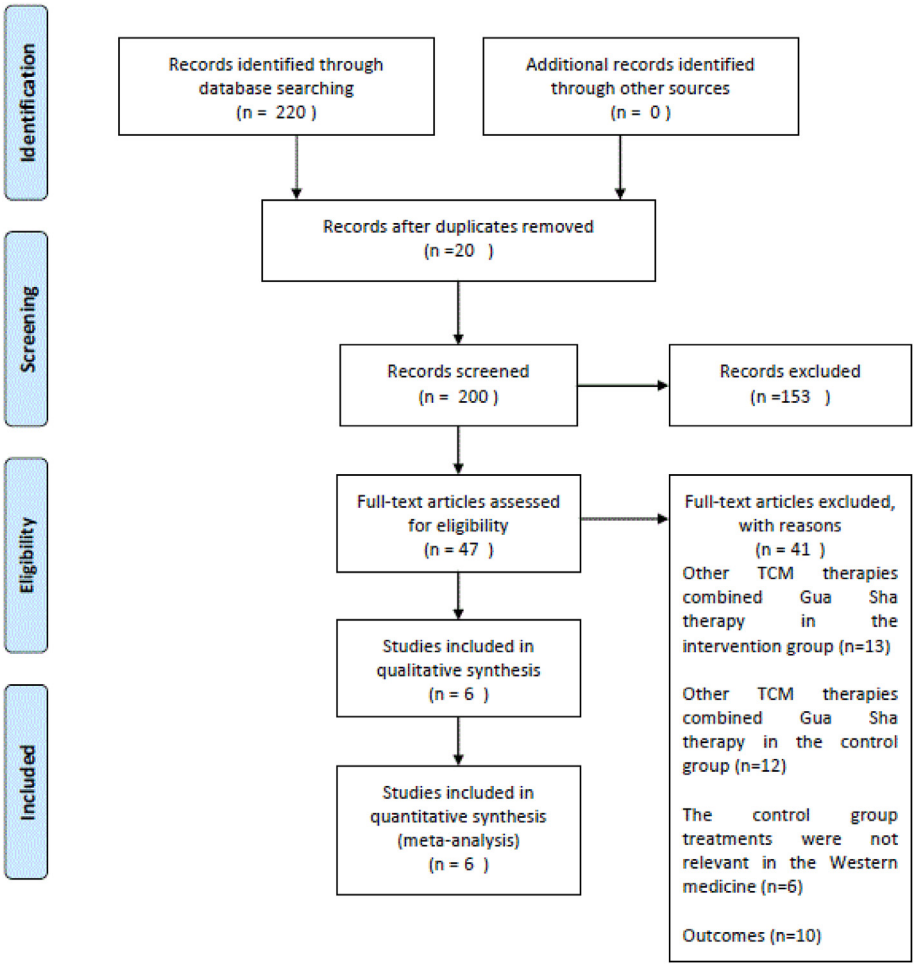

Fig. 1. Flowchart presenting the trial selection process.

Table 1
Summary of the randomized controls trials of Gua Sha therapy for PMS.

Study (author/ year)	Sample size	Duration of Treatment	Intervention group (regimen)	Control group (regimen)	Main outcomes	Intergroup differences
Chen (2015) [33]	60	4 weeks	(A) Gua Sha therapy (1 session = 20 min, 1 time/week, total 4 weeks, n = 30), plus (B).	(B) Routine Care based on North American Menopause Society guidelines. HRT, Estradiol valerate was used according to doctors' prescription n = 30	KMI Score	MD, −4.85 [-6.26,-3.44], P < 0.01
Feng (2014) [34]	64	4 weeks	(A) Gua Sha therapy (1 session = 15 min, 2 times/week, total 4 weeks, n = 32), plus (B).	(B) Routine Care based on North American Menopause Society guidelines. HRT, Estradiol valerate was used according to doctors' prescription, n = 32	Serum level of FSH, LH and E_2	FSH: MD, −4.09 [-11.36,3.18], NS LH: MD, −2.97 [-11.19, 5.25], NS E_2: MD, −0.38 [1.06, 17.12], NS
Hu (2015) [35]	72	8 weeks	(A) Gua Sha therapy (1 session = 20 min, 2 times/week, total 8 weeks, n = 36), plus (B).	(B) Routine Care based on North American Menopause Society guidelines. HRT, Estradiol valerate was used according to doctors' prescription, n = 36	KMI Score	MD, 0.21 [-1.82, 2.24], NS
Meng (2016) [36]	70	4 weeks	(A) Gua Sha therapy (1 session = 15–20 min, 1 time/ week, total 4 weeks, n = 35), plus (B).	(B) Routine Care based on North American Menopause Society guidelines. HRT, Estradiol valerate was used according to doctors' prescription, n = 35	KMI Score MENQOL Scale	MD, −4.51 [-6.51,-2.51], P < 0.01 MD, −4.88 [-7.27, −2.49], P < 0.01;
Wang (2015) [37]	86	4 weeks	(A) Gua Sha therapy (1 session = 15–20 min, 1 time/ week, total 4 weeks, n = 35), plus (B).	(B) Routine Care based on North American Menopause Society guidelines. HRT, Estradiol valerate was used according to doctors' prescription, n = 35	KMI Score Serum level of FSH, LH and E_2	MD, −6.80 [-8.43,-5.17], P < 0.01 FSH: MD, −5.42 [-12.09, 1.25], NS LH: MD, −4.82 [-10.04, 0.40], NS E_2:MD, −7.35 [-13.69, −0.74], P = 0.03
Zhang (2016) [38]	86	4 weeks	(A) Gua Sha therapy (1 session = 15 min, once daily, total 4 weeks, n = 43), plus (B).	(B) Routine Care based on North American Menopause Society guidelines. HRT, Estradiol valerate was used according to doctors' prescription, n = 43	KMI Score MENQOL Scale Serum level of FSH, LH and E_2	MD, −5.65 [-8.00,-3.30], P < 0.01 MD, −8.84 [-18.08,0.40], NS FSH: MD, −5.42 [-12.09, 1.25], NS LH: MD, −4.82 [-10.04, 0.40], NS E_2:MD, −7.35 [-13.69, −0.74], P = 0.03

E2: Estrogen; FSH: Follicle-Stimulating Hormone; HRT: Hormone Replacement Therapy; KMI: Kupperman Menopausal Index; LH: Luteinizing Hormone; MD mean difference; MENQOL: Menopause-Specific Quality of Life; NS not significant; PMS: Perimenopausal Syndrome.

Table 2
Summary of the treatment points and other information related to the treatments.

Study (author/ year)	Types of cupping therapy	Treatment points	Acupoints' rational theory	Adverse events
Chen (2015) [33]	Manual Gua Sha therapy	Scrapping from BL11 to BL18 on Taiyang Bladder Meridian of Foot	TCM theory: Invigorate the blood and regulate Qi	None related to Gua Sha therapy
Feng (2014) [34]	Manual Gua Sha therapy	Scrapping on Du Meridian and Taiyang Bladder Meridian of Foot	TCM theory: Invigorate the blood and regulate Qi	None related to Gua Sha therapy
Hu (2015) [35]	Manual Gua Sha therapy	Scrapping on Du Meridian and Taiyang Bladder Meridian of Foot	TCM theory: Invigorate the blood and regulate Qi	None related to Gua Sha therapy
Meng (2016) [36]	Manual Gua Sha therapy	Scrapping on Taiyang Bladder Meridian of Foot, Shaoyin Heart Meridian of Hand, Shaoyin Kidney Meridian of Foot	TCM theory: Invigorate the blood and regulate Qi	n.r.
Wang (2015) [37]	Manual Gua Sha therapy	Scrapping on Du Meridian and Taiyang Bladder Meridian of Foot	TCM theory: warm meridians, relieve pain and regulate Qi	None related to Gua Sha therapy
Zhang (2016) [38]	Manual Gua Sha therapy	Scrapping on Du Meridian and Taiyang Bladder Meridian of Foot	TCM theory: Invigorate the blood and regulate Qi	None related to Gua Sha therapy

TCM traditional Chinese medicine; n.r. not reported.

3.3.2. Serum level of FSH, LH, and E_2

In three RCTs (involving 236 patients) [35,38,39], serum levels of FSH, LH, and E_2 were used as outcomes for improvement of perimenopausal syndrome after treatment. Study participants in the Gua Sha therapy plus Western medicine therapy group showed significantly greater improvements in serum levels of FSH [MD = −5.00, 95% CI (−9.60, −0.40), $p = 0.03$], LH [MD = −4.00, 95% CI (−7.67, −0.33), $p = 0.03$], and E_2 [MD = −6.60, 95% CI (−12.32, −0.88), $p = 0.02$] when compared to participants who received Western medicine therapy, with low heterogeneity ($Chi^2 = 0.12$, $p = 0.94$, $I^2 = 0\%$ in FSH; $Chi^2 = 0.19$ $p = 0.91$, $I^2 = 0\%$ in LH; $Chi^2 = 0.93$, $p = 0.63$, $I^2 = 0\%$ in E_2) (Fig. 5).

3.3.3. MENQOL scale

Two RCTs (involving 156 patients) [37,39] were identified using the outcome measurement of MENQOL scale. Pooled results

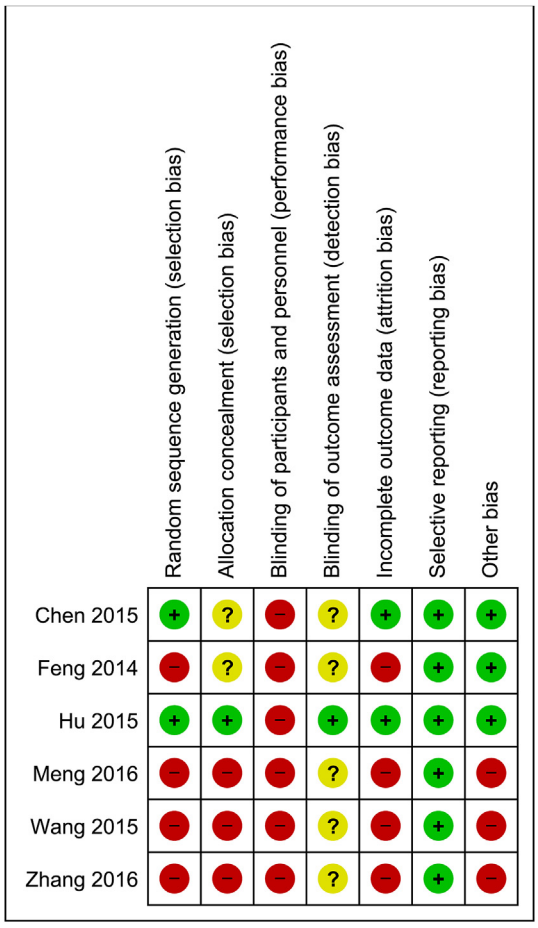

Fig. 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

displayed favorable significant effects of Gua Sha therapy combined with Western medicine therapy on the MENQOL scale when compared with the Western medicine therapy alone [MD = −5.13, 95% CI (−7.45, −2.81), $p < 0.01$] with low heterogeneity ($Chi^2 = 0.66$, $p = 0.42$, $I^2 = 0\%$) (Fig. 6).

3.4. Sensitivity analysis

According to the KMI index forest plot, a high heterogeneity ($Chi^2 = 29.57$ $p < 0.01$, $I^2 = 86\%$) existed using this measurement. To explore this issue, RCT quality and the sample size of study participants may be heterogeneous factors. Two of the included RCTs [33,36] had less than 70 study participants, whereas the remaining three RCTs [35,37,38] contained over 70 study participants. However, the results of the meta-analysis showed a statistically significant beneficial effects in both groups ([MD = −4.74, 95% CI (−5.89, −3.58), $p < 0.01$] and [MD = −4.24, 95% CI (−5.34, −3.15), $p < 0.01$]). Moreover, in terms of RCT quality, one of our included RCTs [35] was of the highest quality trial, one was of moderate quality [33], and the other four were all of poor quality [36–38]. The results of meta-analysis showed statistically significant beneficial effects in low quality groups ([MD = −5.83, 95% CI (−6.95, −4.72), $p < 0.01$] and moderate quality groups [MD = −4.85, 95% CI (−6.26, −3.44), p < 0.01]). These positive results were not found in the highest quality trial [35] ([MD = 0.21, 95% CI (−1.82, 2.24), $p > 0.05$]).

3.5. Adverse events

Of the six included trials, five RCTs [33–35,37,38] assessed adverse events, whereas one [36] did not. Several common adverse outcomes, such as mild vaginal bleeding, weight increase, nausea, and vomiting were reported from HRT in Gua Sha combined with Western medical therapies [33–35,37,38]. Moreover, none of the six included RCTs reported any AEs induced by Gua Sha therapy.

4. Discussion

In the current meta-analysis, 6 RCTs were identified, covering a total of 438 participants that involved comparison of Gua Sha therapy combined with Western medicine therapy with Western medicine therapy alone for the treatment of perimenopausal syndrome. Overall, the combined use of Gua Sha therapy and Western medicine therapy was superior to Western medicine therapy alone in terms of KMI Score, serum levels of FSH, LH, and E_2, and MENQOL. Nevertheless, given the high risk of bias of the included trials, the results should be carefully interpreted.

4.1. Comparison with the past narrative review

Previously, Peng et al. [27] summarized current evidence to evaluate the effect of TCM on perimenopausal syndrome. In that narrative review, the author only included one RCT to test the effect of Gua Sha therapy on perimenopausal syndrome. Their findings were somewhat consistent with the results presented in the current study in that Gua Sha therapy has a beneficial effect on improving serum levels of FSH, LH, and E_2 in patients with perimenopausal syndrome. However, in the previous study, the author only employed several laboratory examinations and AEs, and other

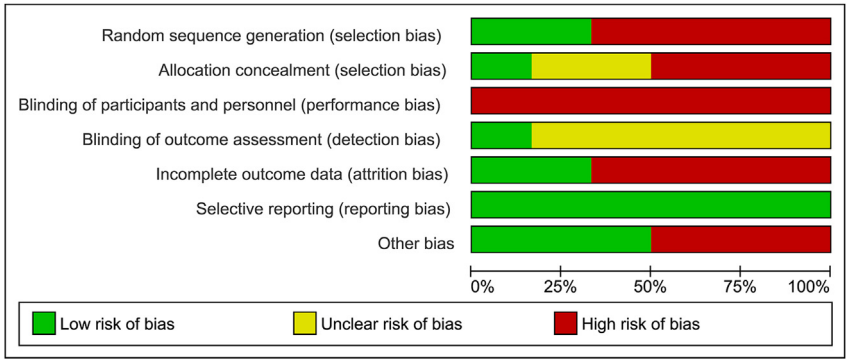

Fig. 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

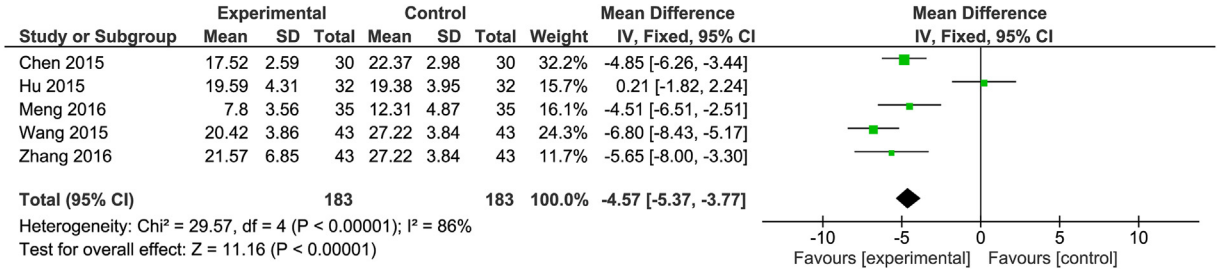

Fig. 4. Western medicine vs. Western medicine Plus Gua Sha therapy on the KMI Score.

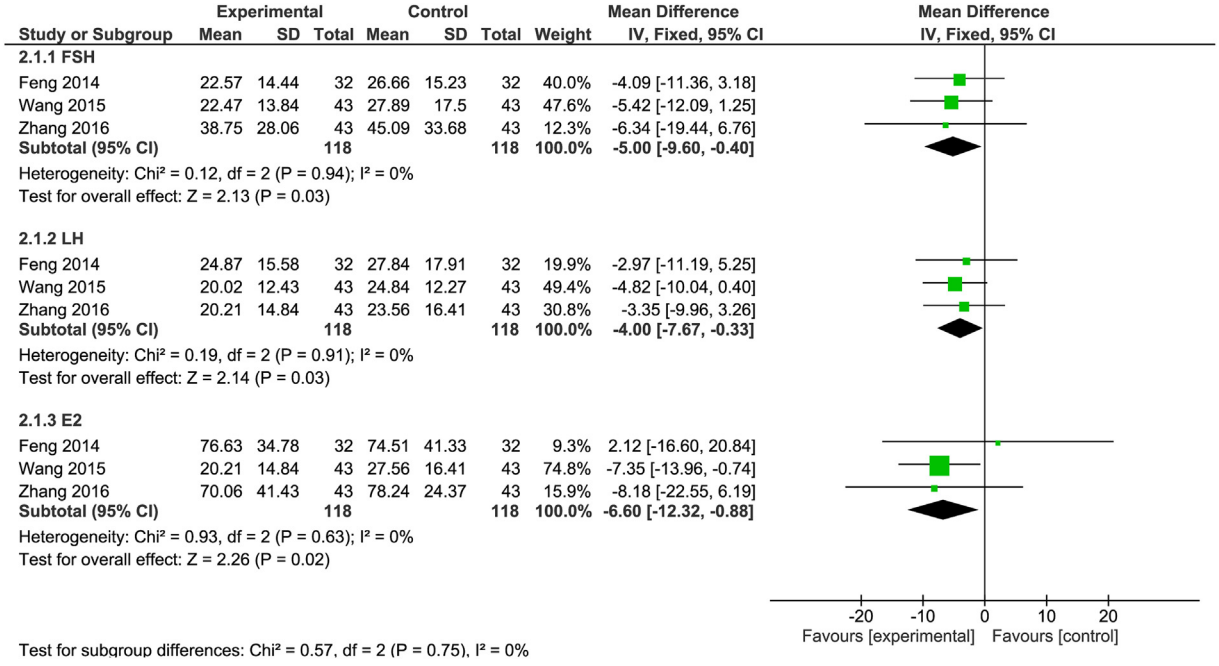

Fig. 5. Western medicine vs. Western medicine Plus Gua Sha therapy on serum levels of FSH, LH and E2.

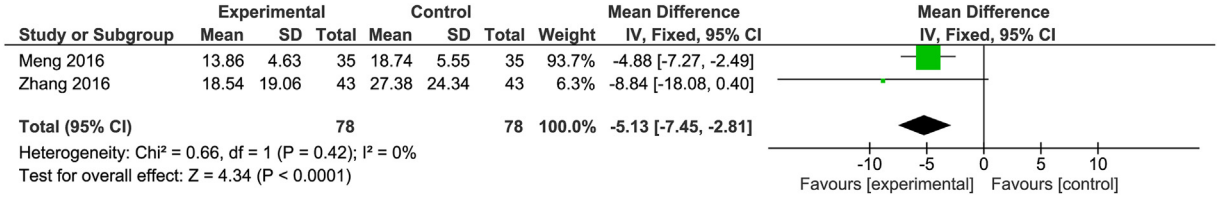

Fig. 6. Western medicine vs. Western medicine Plus Gua Sha therapy on MENQOL Scale.

important outcomes, such as quality of life were not assessed. The previous narrative review is now outdated. Compared with the study performed by Peng et al. [27], several new RCTs were published in China since 2014 and were included and analyzed in the current study. Therefore, it is of utmost importance to periodically update a meta-analysis as new RCTs are published.

4.2. External and internal validity

In 2014, an online survey on TCM diagnosis, treatment, prognosis, and decision-making in perimenopausal syndrome treatment was established [40]. Participants replied that women with perimenopausal syndrome (5.1 ± 2.8) were treated with a multimodal treatment method consisting of Chinese herbal medicine, acupuncture, and Gua Sha. In Gua Sha therapy, participants replied that pressured unidirectional stroking was repeatedly applied on the lubricated skin surface at the back or spine region lubricated using a smooth-edged tool. Using this Gua Sha method, it was commonly reported in that the survey was found to be consistent with the procedures of Gua Sha in our included RCTs. Moreover, most respondents who were surveyed in that study agreed that Du Meridian and Taiyang Bladder Meridian of Foot were chosen as the stroke lines for patients with perimenopausal syndrome. In the RCTs that were included in our study, Du Meridian and Taiyang Bladder Meridian of Foot were applied for perimenopausal syndrome in all included trials. Thus, the use of these meridians in our study was consistent with the data presented in the previously published online survey. In addition, most respondents surveyed

agreed that stroking was repeated until the Sha rash was raised on meridians with 15 min per treatment session. In addition, survey respondents all agreed that Gua Sha should be performed at least 1 time/week. In our study, the session length of the interventions across included studies ranged from 15 to 20 min, and Gua Sha was performed from 1 time/week to 2 times/week. Therefore, the treatment session length and frequency of Gua Sha was consistent with that of the previously published online survey. Furthermore, participants replied that (2.8 ± 1.3) weeks were required for 50% reduction in KMI Score, and (5.2 ± 2.7) weeks for 80% reduction in KMI Score. This 'dose' of Guasha fits well with what has been used in the reviewed trials. In our study, the duration of intervention ranged from 4 weeks to 8 weeks, and meta-analysis showed superior effects of Gua Sha therapy when compared with control therapy. Therefore, for external validity, Gua Sha may be a good treatment regimen for women with perimenopausal syndrome.

The survey respondents used Gua Sha as part of a multi-modal intervention. This was different from our included trials. To explore this issue, in 2015, the Endocrine Society issued a Clinical Practice Guideline (CPG) on identifying women who were candidates for treatment of perimenopausal syndrome and for selecting the best treatment option for each individual [41]. However, in that CPG, TCM was not recommended as an optional treatment approach for patients with perimenopausal syndrome due to the lack of high quality evidence. Hence, TCM was not a standard therapy that was given to the control group as in our study. In addition, according to the view of several evidence-based complementary and alternative Medicine experts, the inclusion criteria in the systematic review should give a more concrete picture on the role of the TCM technique [42]. Thus, by referring to the previously published paper [43], in our included criteria, studies were excluded if the control group treatments were not relevant to Western medicine therapy or other TCM therapies, such as acupuncture, moxibustion, massage, Chinese herbals, and Chinese patent medicine, were used as an adjunct treatment in conjunction with Western medicine therapy. In the future, when high quality single variable TCM intervention is performed, evidence-based multiple-variable TCM interventions can be applied for the treatment of perimenopausal syndrome.

We assessed the methodological quality of RCTs using the risk of bias assessment tool described in the Cochrane Handbook. Most included trials had an “unclear” or “high” risk of bias in the domains of allocation concealment, attrition bias, and blinding. RCTs with inadequate random sequence generation and inadequate allocation concealment may be subject to selection bias and are more likely to overestimate the results of the outcome measures [44,45]. Moreover, RCTs with inadequate, incomplete outcome data reporting may lead to attrition bias [46]. Furthermore, the lack of assessor blinding may result in detection bias [44].

4.3. Sensitivity analysis

Based on the funnel plot for the KMI measurement, the KMI measurement of sensitivity analysis, except for that of the RCT quality, was similar, without being significantly affected. Therefore, the quality of included RCTs may be the source of heterogeneity in KMI measurement. Thus, the results from the KMI measurement should be interpreted with caution given the heterogeneity of included trials.

4.4. Culture conflicts in Gua sha therapy

Transitory Sha petechiae and ecchymoses are therapeutic and intentional with Gua Sha therapy and resolve in 3–5 days. According to TCM principles, petechiae, and ecchymoses represented resolution of Qi and ‘blood stasis’. As East Asians migrated to the West, the appearance of Sha from Gua Sha therapy was misinterpreted as ‘dermabrasion’ and ‘burns’ by Western doctors and mistaken as signs of abuse/child abuse, then pseudo-abuse [16,17,20,28,47]. The literal translation of Gua sha therapy as ‘scraping’ has also been misleading as Gua Sha therapy does not represent ‘scraping’ of the skin as in dermabrasion. Dissemination of information regarding the therapeutic benefit of Gua Sha, the specific nature of the technique as press-stroking a lubricated area of body surface with a smooth-edged instrument, the intentional role of therapeutic petechiae and ecchymosis and their basis in science has contributed to an understanding of and respect for this TCM technique.

4.5. Placebo-control and safety of Gua sha therapy

In a previous study, patients assigned to the Gua Sha group may increase patient-TCM practitioner face-to-face time, and build a good doctor–patient relationship rather than patients in the control group. This may reduce the levels of anxiety in patients and improve therapeutic efficacy [48]. Thus, a placebo effect may be observed when TCM practitioners performed Gua Sha therapy for their patients [49]. However, setting up a proper placebo control of Gua Sha therapy is challenging as patients can see petechiae associated with Gua Sha [50,51]. The safety of Gua Sha therapy is another important issue that should be discussed. In this study, none of the included RCTs mentioned any information about the AEs, thereby suggesting that Gua Sha therapy may be a relatively safe treatment for perimenopausal syndrome. However, it is worth noting that reusing of Gua Sha instruments without a high-level disinfection (HLD) risks blood-borne pathogen exposure to other patients [52]. Thus, in order to avoid risk of transfer of blood-borne pathogens, Nielsen et al. offered relevant Safety Standards for Gua sha therapy [52,53]. In the future, details about the AEs associated with Gua Sha safety assessment should be included in the RCTs.

4.6. The mechanism of Gua sha therapy

The mechanism of action of Gua Sha therapy has been developing. Microcirculation perfusion of the treatment areas is shown to be significantly increased by Gua Sha therapy. In addition, Kwong et al. reported that the therapeutic petechiae following Gua Sha therapy and their resolution reflect a process called “ferroheme metabolism” stimulated the upregulation of heme oxygenase-1 (HO-1) [28]. HO-1 has anti-nociceptive, anti-inflammation and cell protective effects as well as immunomodulation effects [41,42,50]. Gua Sha has been shown to confer hepatoprotection, which is thought to be mediated by upregulation of HO-1 [28,29].

Taken together, it is hypothesized that the beneficial effects of Gua Sha's for perimenopausal syndrome may be attributed to an anti-nociceptive, anti-inflammatory, and immunoregulatory effect via upregulation of HO-1 expression [20].

5. Limitations and implications for further research

Although our data is promosing, our meta-analysis has several important limitations that should be addressed. First, all included RCTs were associated with a high risk of bias. In the future, to improve the quality of included trials, RCTs that involve Gua Sha therapy should be reported following the CONSORT statements [40,55]. Second, the number of studies included in our systematic review and meta-analysis were relatively small. In the future, when more RCTs are available in the literature, our systematic review will be updated. Third, the sample size of included studies was limited and therefore small sample size effects may be generated. Thus, in

the future, the sample size calculation should be considered in the included RCTs. Fourth, a potential risk of bias of this systematic review may originate from the databases that were used for our search. An increased number in potential trials that are published in the Korean or Japanese language may be identified if search databases were expanded. Fifth, because the number of pooled studies was small, it was not appropriate to formally test the asymmetry in the funnel plot. Finally, most included RCTs were conducted on Chinese populations, thereby limiting the results to this Asian population subset. Therefore, this may limit the ability to extrapolate results in this study. In the future, more large-scale, rigorously designed, multicenter, randomized, placebo-controlled, double-blind trials are warranted in Western countries.

6. Conclusions

Overall, as a potential low cost therapy, preliminary evidence supports the hypothesis that Gua Sha therapy effectively improves treatment efficacy in patients with perimenopausal syndrome. In the future, results from RCTs with increased rigorous standards must be employed to overcome the limitations of the current dataset, and to achieve more reliable conclusions.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A

Search strategies

MEDLINE

1. (Climacteric or menopause).tw.
2. (Postmenopause or perimenopause).tw.
3. Vasomotor.tw.
4. Exp Menopause, Premature/or exp Menopause/
5. Exp Climacteric/
6. Exp Perimenopause/
7. Exp Postmenopause/
8. Exp Hot Flashes/
9. (Hot flash or hot flush).tw.
10. or/1–9
11. Scraping
12. Gua Sha
13. Coining.tw.
14. Skin-scraping.tw.
15. Pressured-stroking.tw.
16. Cao gio
17. Kerok
18. Kerokan
19. Kos khyal
20. Ga-sal
21. Khoud lam
22. or/13–21
23. 10 and 22
24. Randomized controlled trial.pt.
25. Controlled clinical trial.pt.
26. Randomized controlled trials/
27. Random allocation.sh.
28. Double blind method.sh.
29. Single-blind method.sh.
30. or/24–29
31. Exp animals/not human/
32. 30 not 31
32. 32 and 23

Appendix B. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ctcp.2018.03.012.

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