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Warm needle acupuncture for osteoarthritis: A systematic review and meta-analysis

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ABSTRACT

Background: Warm needle acupuncture (WA) is considered a potential intervention in the treatment of osteoarthritis (OA).
Purpose: To systematically evaluate the clinical efficacy and safety of WA in the treatment of OA.
Study design: Systematic review and meta-analysis
Methods: Fourteen databases were searched from their inception until May 2022. Randomized controlled trials (RCTs) of WA for treating OA were identified. Study selection and data extraction were performed by two independent reviewers. The Cochrane risk of bias tool and the Grading of Recommendations Assessment, Development and Evaluation program were used to assess all included RCTs.
Results: A total of 66 RCTs met the inclusion criteria for this review. Most of the included studies had an unclear risk of bias, and the certainty of the evidence was very low. Twenty-four RCTs compared the effects of WA with those of oral drug therapies. Meta-analysis showed superior effects of WA for the total effective rate (risk ratio (RR): 1.22, 95% confidence interval (CI): 1.17 to 1.27, $I^2 = 26\%$, $p < 0.001$, 24 studies, $n = 2278$), pain, and function. Eight RCTs compared the effects of WA+drug therapy, and meta-analysis showed favorable effects for the total effective rate (RR: 1.27, 95% CI: 1.18 to 1.35, $I^2 = 0\%$, $p < 0.001$, 8 studies, $n = 646$). Eight RCTs compared the effects of WA and intra-articular sodium hyaluronate (IASH) injection on OA and found equivalent effects of WA on the symptoms of OA. Twenty-eight RCTs compared the effects of WA+IASH injection with those of IASH injection, and meta-analysis showed superior effects of WA+IASH in terms of the total effective rate (RR: 1.15, 95% CI: 1.11 to 1.19, $I^2 = 27.3\%$, $p < 0.001$, 25 studies, $n = 2208$), pain, and function. None of the RCTs reported serious adverse events.
Conclusions: WA may have some distinct advantages in the treatment of OA. However, well-designed RCTs with larger sample sizes are needed.

Abbreviations: AAOS, American Academy of Orthopaedic Surgeons; ACR, American College of Rheumatology; CI, confidence interval; COA, Chinese Orthopedic Association; CoE, certainty of evidence; HM, herbal medicine; HSS, hospital for special surgery; LKSS, Lysholm knee scoring scale; IASH, intra-articular sodium hyaluronate; MA, meta-analysis; MD, mean difference; n.r., not reported; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; QoL, quality of life; RCT, randomized controlled trial; RoB, risk of bias; SMD, standardized mean difference; SR, systematic review; TCM, traditional Chinese medicine; TCM-DTDS, TCM Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes; VAS, visual analog scale; WA, warm needle acupuncture; WM, Western medicine; WOMAC, Western Ontario and McMaster Universities Osteoarthritis index.

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Introduction

Osteoarthritis (OA) is one of the most common degenerative diseases caused by aging or excessive physical pressure (e.g., obesity, trauma, etc.) (Kim and Lee, 2011; Lee, 2002). Its main symptoms include joint pain, stiffness, decreased joint function, and impairment in activities of daily living, resulting from damage to the entire joint, articular cartilage, or subchondral bone (Kim, 2009).

Treatment focuses on controlling pain and improving joint function (depending on the condition of each patient) and includes exercise, weight control, sufficient rest, surgery, and drug therapy. Drug treatment focuses on addressing the effects of inflammation and providing pain relief, including by using nonsteroidal anti-inflammatory drugs (NSAIDs) and OA drugs (Hochberg et al., 2012). In particular, drug therapies have been found to be effective in relieving joint pain and improving joint function.

Patients are often dissatisfied with conventional medical approaches and turn to traditional medicine strategies, such as warm needle acupuncture (WA), to manage their symptoms (Lo et al., 2019). WA is a therapy that combines the efficacy of two approaches, acupuncture and moxibustion. After direct heat is applied to an inserted needle, moxa (Artemisia vulgaris) is added to the shaft of the inserted needle, which is then removed. The mechanism of WA is similar to that of heat therapy, in which a tissue is heated to promote metabolism, dilate blood vessels, and reduce the excitability of peripheral nerves (Lee et al., 2019; Yang et al., 2018). Recently, several studies have concluded that WA is more effective than conventional acupuncture in treating knee arthritis (Chen et al., 2019; Fan et al., 2020; Jiang and Zhang, 2019; Kong et al., 2019). WA is also reportedly more effective than drugs and is associated with a low recurrence rate (Lin et al., 2009).

Ten previous systematic reviews (SRs) (Chen et al., 2019; Fan et al., 2020; Feng et al., 2019; Guo and Chen, 2018;Jiang and Zhang, 2019; Kong et al., 2019; Lu, 2015; Luo et al., 2019; Zhang et al., 2019; Zhao et al., 2010) on OA treatment with WA concluded that the intervention group, treated by WA, experienced better resolution of symptoms than the control group, treated by Western medicine (WM). However, while WA is effective in alleviating symptoms, the quality of the related literature is very low, and the use of such therapy has not been clearly described and assessed/evaluated systematically.

The purpose of this review was to investigate the efficacy and safety of WA alone or WA combined with WM in treating patients with OA and to determine whether WA is effective in alleviating joint pain and improving function.

Methods

Study registration

The protocol for this SR was registered with PROSPERO (registration number: CRD42017079189) and published (Jun et al., 2016). The findings are reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist (Page et al., 2021).

Data source

Fourteen databases were searched from their inception to May 2022. These included English language databases, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). We also searched seven Korean medical databases (OASIS, Korean Traditional Knowledge Portal, Korean Studies Information Service System, Research Information Sharing Service, Korea Med, Korean Medical Database, and DBpia) and four Chinese databases, namely, China National Knowledge Infrastructure (CNKI), SinoMed, Wanfang, and VIP. We used the following search terms: “warm acupuncture” and “osteoarthritis”. We used database-specific filters for RCTs to develop the search strategy with no language restrictions. Details of the search terms are shown in Supplementary 1.

Study selection

Types of studies

All randomized controlled trials (RCTs) and quasi-RCTs of WA alone or combined with WM were included. Case studies, qualitative studies, uncontrolled trials, and reviews were excluded, as they were not controlled studies and failed to provide detailed information.

Types of participants

We included male and female patients of any age diagnosed with OA regardless of the disease duration.

Types of interventions

The intervention groups included WA alone and WA combined with WM. Any type of WA was included. However, studies that combined WA with traditional medicine, such as acupuncture alone, herbal medicine (HM), or moxibustion alone, were excluded.

The control groups included patients treated with WM. Patients treated with alternative medicine in combination with WA were excluded.

Types of outcome measurements

The included studies had to report at least one of the primary outcomes detailed below.

Primary outcomes

1) Total effective rate: (recovery + marked improvement + improvement)/total number of cases × 100% (Chen, 1994; Zheng, 2002)

2) Pain intensity measured with the following scales

- Visual analog scale (VAS)

- Western Ontario and Mcmaster Universities Osteoarthritis Index (WOMAC) for pain

3) Function measured with the following scales

- Hospital for special surgery (HSS) scale

- Lysholm knee scoring scale (LKSS)

- WOMAC for function

Secondary outcomes

1) Quality of life (QoL)

2) Adverse events (AEs)

Data extraction and risk of bias (RoB)

Two authors extracted data from the studies that met the inclusion criteria using EndNote 20 software. The selection process is summarized in a PRISMA flow diagram (website: https://prisma-statement.org). The following items were extracted: first author; year; age of participants; sample size; diagnostic criteria; intervention group; control group; outcome; results; and AEs.

Two authors assessed bias in each included study using the Cochrane RoB tool (Higgins and Green, 2011a). The items were divided into seven areas: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting; and 7) other bias. The RoB of each aspect was assessed and classified into three levels (low, high, and unclear), which are represented by the letters ‘L’, ‘H’, and ‘U’ (Higgins and Green, 2011a). Disagreements were resolved by

discussion between the two authors. In addition, the certainty of evidence (CoE) and the strength of recommendations were assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (Liu, 2022). The factors considered for judgment were as follows: study design; RoB; sample size; inconsistency; indirectness; impression; and published bias. The level of evidence assessed was classified as high, moderate, low, or very low. The summary of findings table (SOF table) was prepared as a summary of the CoE for each of the major findings obtained through the SR using Review Manager 5.4 and GRADEpro (htttps://gradepro.org/).

Data synthesis

Statistical analyses were performed using STATA/SE v.17.0 (StataCorp LLC, College Station, TX, USA). For dichotomous data, the treatment effect is presented as the risk ratio (RR) with 95% confidence interval (CI). For continuous data of the same scales, the treatment effect is presented as the mean difference (MD) with 95% CI. When different scales were used, the standardized mean difference (SMD) with 95% CI was provided. The random-effects model was used because of the clinical heterogeneity, and the prediction interval for estimating true effect values was calculated. The Chi-square and Higgins I^2 tests were used to assess heterogeneity (Higgins and Green, 2011b). Albatross plots were also generated to visualize the effects of direction on outcomes. An albatross plot showing the effects of direction and size range by p value and the given sample size was generated for each included study. When possible, publication bias was assessed using a funnel plot.

Results

Description of included trials

A total of 3890 citations were retrieved. Finally, 66 RCTs were included (Table 1 and Table 2). The flowchart of the literature selection process is shown in Fig. 1.

All included RCTs were conducted in China and published in journals or as dissertations. The studies were conducted from 2006 to 2021. In all included studies, the total number of study subjects was 6231, including 3263 patients in the intervention group and 2968 in the control group. The average age of the study participants was 60 years. In the control group, an anti-pyretic analgesic (acetaminophen), NSAIDs (celecoxib, diclofenac, ibuprofen, nabumetone, and loxoprofen sodium) and a derivative of hyaluronic acid (sodium hyaluronate) were used.

The acupuncture points used in the intervention group differed; there were 26 in total. The most commonly used acupuncture points for OA were SP10, EX-LE4, ST36, GB34, ST34, ST35, EX-LE5, EX-LE2, Ashipoint, and SP9 (Supplementary 2 and 3).

RoB

Twenty-seven RCTs used randomization methods and had a low RoB. Nine RCTs (He et al., 2018; Hu et al., 2016; Liang and Li, 2016; Ma et al., 2013; Ren and Li, 2012; Tu et al., 2016; Wang and Li, 2010; Zhang et al., 2019b; Zheng, 2008) were determined to have a high RoB because the order was assigned according to the treatment or treatment number. Three RCTs (Ding et al., 2009; Liu et al., 2014; Zhang, 2014) used the closed-envelope method and were determined to have a low RoB. Thirty-four RCTs did not report allocation concealment. All RCTs had a high RoB because neither the participants nor the researchers were blinded to the outcome assessments. One RCT (Liang and Li, 2016) had a high RoB due to the use of a per-protocol analysis. In all other RCTs, an intention-to-treat analysis was performed, and the RoB was judged to be low. For selective reporting, none of the RCTs had published protocols. One RCT (He et al., 2018) was judged to have a high RoB because the description of the basic content was missing, and the results could therefore be unreliable.

Outcome measurements

WA vs. drug therapy

Total effective rate. Twenty-four RCTs (Chen et al., 2018a; Chen et al., 2018b; Ding et al., 2009; Han, 2021; Ji, 2016; Qiao, 2018; Qin, 2013; Qiu, 2013; Song, 2016; Su et al., 2020; Wang, 2016; Wu et al., 2013; Wu, 2006; Xu and Zeng, 2020; Xu and Wu, 2019; Xue, 2011; Xue et al., 2015; Yang et al., 2012; Yao, 2018; Zhang, 2017, 2016, 2014; Zheng, 2008; Zuo and Jiang, 2011) examined the effects of WA compared with several types of drug therapy. Most of them showed superior effects of WA, while the other six RCTs (Chen et al., 2018a; Ding et al., 2009; Su et al., 2020; Xu and Wu, 2019; Xue, 2011; Yao, 2018) reported equivalent effects. Meta-analysis showed favorable effects of WA on the total effective rate (RR: 1.22, 95% CI: 1.17 to 1.27 [prediction interval, 95% CI: 1.08 to 1.37], $I^2 = 26\%$, $p < 0.001$, 24 studies, 2278 participants, low CoE, Fig. 3A) and the prediction interval (RR: 1.22, 95% CI: 1.08 to 1.37). Subgroup analysis showed superior effects of WA on the total effective rate compared with celecoxib (RR: 1.27, 95% CI: 1.14 to 1.42, $I^2 = 0\%$, $p < 0.001$, 3 studies, 230 participants), diclofenac (RR: 1.20, 95% CI: 1.13 to 1.27, $I^2 = 25.6\%$, $p < 0.001$, 11 studies, 1132 participants), and ibuprofen (RR: 1.20, 95% CI: 1.10 to 1.31, $I^2 = 46.1\%$, $p < 0.001$, 8 studies, 740 participants).

Pain

Ten RCTs (Chen et al., 2018a; Chen et al., 2018b; Ding et al., 2009; Han, 2021; Su et al., 2020; Xue et al., 2015; Xu and Zeng, 2020; Yang et al., 2012; Yao, 2018; Zhang, 2014) compared the effects of WA with those of drug therapy on pain. Seven RCTs (Chen et al., 2018b; Han, 2021; Su et al., 2020; Xu and Zeng, 2020; Yang et al., 2012; Yao, 2018; Zhang, 2014) showed superior effects of WA, while three RCTs (Chen et al., 2018a; Ding et al., 2009; Xue et al., 2015) reported equivalent effects. Meta-analysis showed favorable effects of drug therapy (SMD: −2.65, 95% CI: −3.92 to −1.38 [prediction interval, 95% CI: −7.54, 2.25], $I^2 = 98\%$, $p = 0.01$, 10 studies, 874 participants, very low CoE, Fig. 3B). Subgroup analysis showed superior effects of WA on pain compared with diclofenac (SMD: −1.22, 95% CI: −2.18 to −0.27, $I^2 = 90.7\%$, $p = 0.02$, 3 studies, 230 participants) and ibuprofen (SMD: −3.52, 95% CI: −5.90 to −1.12, $I^2 = 98.7\%$, $p = 0.05$, 5 studies, 464 participants) but not celecoxib.

Function

Twelve RCTs (Chao, 2018; Chen et al., 2018a; Chen et al., 2018b; Ding et al., 2009; Han, 2021; Ji, 2016; Su et al., 2020; Wang, 2016; Xu and Zeng, 2020; Xu and Wu, 2019; Yao, 2018; Zhang, 2014; Zheng, 2008) assessed the effects of WA on function. Eleven RCTs showed superior effects of WA, while one RCT (Ding et al., 2009) reported equivalent effects. Meta-analysis showed favorable effects of WA on function (SMD: −1.79, 95% CI: −2.31 to −1.26 [prediction interval, 95% CI: −3.91, 0.31], $I^2 = 93.6\%$, $p < 0.001$, 13 studies, 1354 participants, very low CoE, Fig. 3C). Subgroup analysis showed superior effects of WA on function compared with diclofenac (SMD: −2.20, 95% CI: −3.10 to −1.30, $I^2 = 96\%$, $p < 0.001$, 6 studies, 686 participants) and ibuprofen (SMD: −1.44, 95% CI: −1.95 to −0.92, $I^2 = 86.1\%$, $p < 0.001$, 7 studies, 668 participants).

QoL

Three RCTs (Ding et al., 2009; Qiao, 2018; Wang, 2016) reported superior effects of WA on QoL, and meta-analysis also showed superior effects of WA compared with drug therapy (SMD: 2.64, 95% CI: 2.34 to 2.93, $I^2 = 0\%$, $p < 0.00001$, 2 studies, 336 participants) (Qiao, 2018; Wang, 2016).

Table1
Summary of randomized clinical studies of warm needle acupuncture for osteoarthritis compared with oral drug therapy.

First author (year)	Sample size (M/F) Age (Mean)	Diagnostic criteria	Intervention group	Control group	Main outcomes	Main results	Adverse event
Zhang (2016)	80 (47/33) A: 60.2; B: 58.5	ACR	(A) WA (n.r., total 2 session, 1 session [once daily, 28 times], $n = 40$)	(B) Drug (Acetaminophen 5 mg, three times a day for 8 weeks, $n = 40$)	Total effective rate	RR 1.52 [1.14, 2.04], $p = 0.005$	n.r.
Zuo (2011)	50 (23/27) n.r.	ACR	(A) WA (n.r., total 2 session, 1 session [three times weekly, 10 times], $n = 25$)	(B) Drug (Celecoxib 0.2 g, once daily for 6 weeks, $n = 25$)	Total effective rate	RR 1.33 [1.03, 1.72], $p = 0.03$	n.r.
Xue (2015)	60 (27/33) A:64.7; B:65	ACR	(A) WA (30 min, 1 session [three times weekly, 12 times], $n = 30$)	(B) Drug (Celecoxib 0.2 g, once daily for 4 weeks, $n = 30$)	1) Total effective rate 2) Pain (VAS)	1) RR 1.33 [0.14, 1.72], $p = 0.03$ 2) MD −0.48 [−1.38, 0.42], NS	n.r.
Yang (2012)	120 (34/86) A:57.6; B:56.4	ACR	(A) WA (n.r., once weekly, total 4 times, $n = 60$)	(B) Drug (Celecoxib 0.2 g, once daily for 4 weeks, $n = 60$)	1) Total effective rate 2) Pain (VAS)	1) RR 1.23 [1.07, 1.42], $p = 0.003$ 2) MD −2.00 [−2.13, −1.87], $p < 0.00001$	Pain at needle insertion area (A:2); mild burn (A:2); stomach discomfort (B:7); face flushing and extremities edema (B:1); skin itchiness (B:1)
Wu (2006)	114 (38/76) A:61; B:60	ACR	(A) WA (n.r., total 2 session, 1 session [once daily, 10 times], $n = 60$)	(B) Drug (Diclofenac 75 mg, once daily for 3 weeks, $n = 54$)	Total effective rate	RR 1.67 [1.27, 2.20], $p = 0.0003$	n.r.
Wu (2013)	60 (25/35) 45.7	ACR	(A) WA (n.r., total 2 session, 1 session [once daily, 10 times], $n = 30$)	(B) Drug (Diclofenac 75 mg, once daily for 3 weeks, $n = 30$)	Total effective rate	RR 1.27 [1.01, 1.61], $p = 0.05$	n.r.
Song (2016)	100 (n.r.) n.r.	ACR	(A) WA (n.r., total 2 session, [1 session, once daily, 10 times], $n = 50$)	(B) Drug (Diclofenac 75 mg, once daily for 3 weeks, $n = 50$)	Total effective rate	RR 1.31 [1.08, 1.60], $p = 0.007$	n.r.
Zhang (2017)	112 (61/51) A:61.2; B:60.9	ACR	(A) WA (n.r., once daily, 30 times, $n = 56$)	(B) Drug (Diclofenac 100 mg, once daily for 4 weeks, $n = 56$)	Total effective rate	RR 1.15 [1.00, 1.32], $p = 0.04$	n.r.
Xue (2011)	60 (27/33) 50	ACR TCM-DTDS AAOS	(A) WA (n.r., total 3 session, 1 session [once daily, 10 times], $n = 30$)	(B) Drug (Diclofenac 75 mg, once daily for 4 weeks, $n = 30$)	Total effective rate	RR 1.07 [0.94, 1.23], NS	n.r.
Zhang (2014)	80 (29/51) A:46.4; B:45.1	ACR	(A) WA (n.r., total 2 session, 1 session [once daily, 10 times], $n = 40$)	(B) Drug (Diclofenac 75 mg, once daily for 3 weeks, $n = 40$)	1) Total effective rate 2) Pain (WOMAC) 3) Function (WOMAC)	1) RR 1.31 [1.07, 1.61], $p = 0.009$ 2) MD −13.05 [−15.81, −10.29], $p < 0.001$ 3) MD −14.02 [−15.95, −12.09], $p < 0.001$	n.r.
Su (2020)	90 (48/42) A:59.4; B:58.6	COA	(A) WA (n.r., total 2 session, 1 session [once daily, 10 times], $n = 45$)	(B) Drug (Diclofenac 100 mg, once daily for 3 weeks, $n = 45$)	1) Total effective rate 2) Pain (WOMAC) 3) Function (WOMAC)	1) RR 1.17 [0.98, 1.40], NS 2) MD −1.49 [−1.97, −1.01], $p < 0.001$ 3) MD −3.79 [−6.26, 1.32], $p = 0.003$	n.r.
Chen et al., 2018a	60 (29/41) A:57.5; B:58.9	COA TCM-DTDS	(A) WA (n.r. total 2 session, 1 session [once daily, 12 times], $n = 30$)	(B) Drug (Diclofenac 75 mg, once daily for 4 weeks, $n = 30$)	1) Total effective rate 2) Pain (WOMAC) 3) Function (WOMAC)	1) RR 1.23 [0.96, 1.57], NS 2) MD −0.47 [−1.22, 0.28], NS 3) MD −5.03 [−6.19, −3.87], $p < 0.001$	None
Wang (2016)	112 (61/51) A:61.2; B:60.9	ACR	(A) WA (n.r., once daily, 30 times, $n = 56$)	(B) Drug (Diclofenac 100 mg, once daily for 4 weeks, $n = 56$)	1) Total effective rate 2) Function (HSS) 3) QoL (SF-36)	1) RR 1.15 [1.00, 1.32], $p = 0.04$ 2) MD −13.60 [−15.35, −11.85], $p < 0.001$ 3) MD 9.80 [8.34, 11.26], $p < 0.001$	n.r.
Qiao (2018)	224 (122/102) A:61; B:60	TCM-DTDS	(A) WA (n.r., once daily, 30 times, $n = 112$)	(B) Drug (Diclofenac n.r., once daily for 4weeks, $n = 112$)	1) Total effective rate 2) Function	1) RR 1.26 [1.12, 1.42], $p < 0.001$ 2) MD −15.60	n.r.

(*continued on next page*)

Table1 (*continued*)

					(HSS) 3) QoL (SF-36)	[−16.83, −14.37], $p <$ 0.001 3) MD 11.10 [10.04, 12.16], $p <$ 0.001	
Xu (2019)	120 (41/79) A:59.7; B:57.7	COA	(A) WA (n.r., total 2 session, 1session [once daily, 10 times], $n = 60$)	(B) Drug (Diclofenac 75 mg, once daily for 3 weeks, $n = 60$)	1) Total effective rate 2) Function (HSS)	1) RR 1.08 [0.94, 1.24], NS 2) MD −5.98 [−7.88, −4.08], $p < 0.001$	n.r.
Qiu (2013)	74 (32/42) A:55.5; B:56.6	ACR	(A) WA (30 min, total 3 session, 1 session [once daily, 10 times], $n = 36$)	(B) Drug (Ibuprofen n.r., 2 weeks, $n = 38$)	Total effective rate	RR 1.28 [1.04, 1.57], $p < 0.02$	None
Qin (2013)	120 (59/61) 69.4	ACR	(A) WA (40 min, total 2 session, 1 session [once daily, 5 times], $n = 40$)	(B) Drug (Ibuprofen 0.3 g, twice daily for 2 weeks, $n = 40$)	Total effective rate	RR 1.59 [1.17, 2.16], $p = 0.003$	Stomach discomfort (B:6)
Chen (2018b)	140 (74/66) A:57.9; B:58.2	CGND-TCM	(A) WA (n.r., total, 3 session, 1 session [once daily, 10 times], $n = 70$)	(B) Drug (Ibuprofen 0.3 g, twice daily for 4 weeks, $n = 70$)	1) Total effective rate 2) Pain (VAS) 3) Pain (WOMAC) 4) Function (WOMAC)	1) RR 1.26 [1.10, 1.46], $p = 0.001$ 2) MD −1.52 [−1.82, −1.22], $p < 0.001$ 3) MD −1.13 [−1.17, −1.09], $p < 0.001$ 4) MD −0.96 [−1.18, −0.74], $p < 0.001$	None
Yao (2018)	80 (23/37) A:61.2; B:62.4	ACR	(A) WA (40 min, total 2 session, 1 session [once daily, 5 times], $n = 40$)	(B) Drug (Ibuprofen 0.3 g, twice daily for 2 weeks, $n = 40$)	1) Total effective rate 2) Pain (VAS) 3) Function (LKSS)	1) RR 1.09 [0.95, 1.25], NS 2) MD −1.51 [−2.00, −1.02], $p < 0.001$ 3) MD −8.11 [−10.86, −5.36], $p <$ 0.001	n.r.
Han (2021)	74 (n.r.) A:58.9; B:58.9	COA	(A) WA (20 min, n.r., 30 times, $n = 37$)	(B) Drug (Ibuprofen n.r., twice daily for 4 weeks, $n = 37$)	1) Total effective rate 2) Pain (WOMAC) 3) Function (WOMAC)	1) RR 1.20 [1.02, 1.41], $p = 0.03$ 2) MD −8.40 [−12.46, −4.34], $p <$ 0.001 3) MD −10.92 [−14.97, −6.87], $p <$ 0.001	n.r.
Ding (2009)	90 (25/65) A:59.4; B:52.0	ACR	(A) WA (40 min, total 2 session, 1 session [once daily, 5 times], $n = 30$)	(B) Drug (Ibuprofen 0.3 g, twice daily for 2 weeks, $n = 30$)	1) Total effective rate 2) Pain (WOMAC) 3) Function (WOMAC) 4) QoL (SF-36)	1) RR 0.96 [0.80, 1.16], NS 2) MD −1.28 [−6.87, 4.31], NS 3) MD −2.11 [−7.10, 2.88], NS] 4) n.r. total	Stomach discomfort (B:3)
Xu (2020)	110 (57/53) A:53.8; B:53.9	COA	(A) WA (30 min, total 3 session, 1 session [once daily, 10 times], $n = 55$)	(B) Drug (Ibuprofen 0.3 g, twice daily for 4 weeks, $n = 55$)	1) Total effective rate 2) Pain (n.r.) 3) Function (HSS)	1) RR 1.21 [1.04, 1.41], $p = 0.02$ 2) MD −1.06 [−1.13, −0.99], $p < 0.001$ 3) MD −14.75 [−18.66, −10.84], $p <$ 0.001	n.r.
Zheng (2008)	122 (48/74) A:60.2; B:60.3	ACR	(A) WA (n.r., total 2 session, 1 session [once daily, 10 times], $n = 90$)	(B) Drug (Ibuprofen n.r., twice daily for 3 weeks, $n = 32$)	1) Total treatment effect 2) Function (LKSS)	1) RR 1.12 [0.98, 1.28], NS 2) MD −19.90 [−23.35, −16.45], $p <$ 0.001	n.r.
Chao (2018)	82 (33/49) A:70.6; B:69.3	ACR	(A) WA (15 min, once daily, 21 times, $n = 41$)	(B) Drug (Ibuprofen 0.2 g, three times a day for 3 weeks, $n = 41$)	Function (LKSS)	MD −14.68 [−17.27, −12.09], $p <$ 0.001	n.r.

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Table1 (*continued*)

Ji (2016)	96 (41/56) A:41.6; B:42.4	ACR	(A) WA (n.r., total 3 session, 1 session [once daily, 10 times], $n = 48$)	(B) Drug (Nabumetone 1 g, once daily for 6 weeks, $n = 48$)	Total effective rate	RR 1.28 [1.07, 1.52], $p = 0.006$	n.r.
Lin (2020)	80 (38/42) A:56.1; B:57.2	TCM-DTDS COA	(A) WA (n.r. total 2 session, 1 session [three times weekly, 3 times], $n = 40$), plus B	(B) Drug (Celecoxib 0.2 g, once daily for 2 weeks, $n = 40$)	1) Total effective rate 2) Pain (VAS) 3) Pain (WOMAC) 4) Function (WOMAC)	1) RR 1.48 [1.10, 1.99], $p = 0.01$ 2) MD −0.91 [−0.97, −0.85], $p < 0.001$ 3) MD −0.72 [−0.84, −0.60], $p < 0.001$ 4) MD −5.98 [−6.62, −5.34], $p < 0.001$	Abnormal blood routine (A:2; B:1); abnormal liver function (B:1); abnormal kidney function (A:1, B:1); gastrointestinal reaction (A:2; B:1)
Shu (2021)	60 (39/21) A:62.5; B:64.5	COA	(A) WA (30 min, total 4 session, 1 session [once daily, 7 times], $n = 30$), plus B	(B) Drug (Diclofenac 75 mg, once daily for 4 weeks, $n = 30$)	1) Total effective rate 2) Function (HSS)	1)RR 1.27 [1.01, 1.99], $p = 0.05$ 2) MD −9.07 [−15.40, −2.74], $p = 0.005$	n.r.
Yu (2016a)	40 (24/16) 66.8	COA	(A) WA (n.r., total 2 session, 1 session [two times weekly, 4 times], $n = 20$), plus (B)	(B) Drug (Ibuprofen 0.3 g, twice daily for 2 weeks, $n = 20$)	Total effective rate	RR 1.29 [0.93, 1.77], NS	n.r.
Dang (2019)	78 (22/56) A:57.5; B:57.6	TCM-DTDS COA	(A) WA (30 min, total 2 session, 1 session [once daily, 7 times], $n = 39$), plus B	(B) Drug (Ibuprofen 0.3 g, twice daily for 2 weeks, $n = 39$)	Total effective rate	RR 1.23 [1.04, 1.45], $p = 0.02$	None
Guo (2019)	88 (51/37) A:50.4; B:50.4	AAOS	(A) WA (40 min, total 2 session, 1 session [once daily, 5 times], $n = 44$) plus B	(B) Drug (Ibuprofen n.r., twice daily for 2 weeks, $n = 44$)	1) Total effective rate 2) Pain	1) RR 1.45 [1.16, 1.81], $p = 0.001$ 2) MD −4.80 [−5.01, −4.39], $p < 0.001$	n.r.
Zheng (2016)	76(34/42) A: 65.8; B: 66.5	COA	(A) WA (40 min, total 8 session, 1 session [once daily, 5 times], $n = 38$), plus B	(B) Drug (Ibuprofen 0.3 g, twice daily for 8 weeks, $n = 38$)	1) Total effective rate 2) QoL (SF-36)	1) RR 1.16 [0.98, 1.37], NS 2) MD 12.21 [9.88, 14.54], $p < 0.001$	n.r.
Zhang (2019b)	112 (39/73) A: 58; B:59	COA	(A) WA (n.r., total 2 session, 1 session [once daily, 12 times], $n = 56$), plus B	(B) Drug (Loxoprofen Sodium 60 mg, three times daily for 4 weeks, $n = 56$)	1) Total effective rate 2) Function (LKSS)	1) RR 1.26 [1.08, 1.46], $p = 0.003$ 2) MD −16.79 [−20.43, −13.15], $p < 0.001$	n.r.
Hou (2020)	112 (39/73) A: 57.7; B:58.7	TCM-DTDS COA	(A) WA (n.r. total 2 session, 1 session [once daily, 12 times], $n = 56$), plus B	(B) Drug (Loxoprofen Sodium 60 mg, three times daily for 4 weeks, $n = 56$)	1) Total effective rate 2) Function (LKSS)	1) RR 1.26 [1.08, 1.46], $p = 0.003$ 2) MD 16.79 [6.34, 27.24], $p = 0.002$	n.r.

AAOS: AAOS-CPG on treatment of osteoarthritis of the knee; ACR: The American College of Rheumatology; CGND-TCM: The clinical guideline of New Drug for TCM; COA: Chinese Orthopedic Association-Guideline for diagnosis and treatment of osteoarthritis; HM: herbal medicine; HSS: score of hospital for special surgery; LKSS: Lysholm scoring system; MD: mean difference; n.r.: not reported; NS: not significant; QoL: quality of life; RR: risk ratio; TCM: traditional Chinese medicine; TCM-DTDS: TCM criteria of diagnosis and therapeutic effect of diseases and diseases and syndromes; VAS: visual analogue scale; WA: warm needle acupuncture; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

WA + drug therapy vs. drug therapy

Total effective rate

Eight RCTs (Dang, 2019; Guo and Ding, 2019; Hou et al., 2020; Lin and Ye, 2020; Shu, 2021; Yu and Lin, 2016b; Zhang et al., 2019b; Zheng, 2016) assessed the total effective rate of WA+drug therapy compared with drug therapy. Six RCTs showed positive effects, while two RCTs (Yu and Lin, 2016b; Zhang et al., 2019b) reported equivalent effects. Meta-analysis showed favorable effects of WA+drug therapy (RR: 1.27, 95% CI: 1.18 to 1.35 [prediction interval, 95% CI: 1.18 to 1.35], $I^2 = 0\%$, $p < 0.001$, 8 studies, 646 participants, low CoE, Fig. 4A). Subgroup analysis showed superior effects of WA+drug therapy on the total effective rate compared with ibuprofen (RR: 1.25, 95% CI: 1.13 to 1.38, $I^2 = 0\%$, $p < 0.001$, 4 studies, 239 participants) and loxoprofen sodium (RR: 1.26, 95% CI: 1.13 to 1.40, $I^2 = 0\%$, $p < 0.001$, 2 studies, 224 participants).

Pain

Two RCTs (Guo and Ding, 2019; Lin and Ye, 2020) showed a reduction in pain by WA combined with drug therapy (SMD: −5.85, 95% CI: −7.84 to −3.85, $I^2 = 87\%$, $p < 0.001$, 2 studies, 168 participants).

Function

Four RCTs (Hou et al., 2020; Lin and Ye, 2020; Shu, 2021; Zhang et al., 2019b) evaluated the effects of WA+drug therapy on joint function compared with drug therapy. Three RCTs reported superior effects of WA+drug therapy compared with drug therapy alone, while the other RCT (Hou et al., 2020) failed to do so. Meta-analysis showed no difference between the two groups in joint function (SMD: −1.45, 95% CI: −3.11 to 0.22 [prediction interval, 95% CI: −9.52 to 6.63], $I^2 = 97.8\%$, $p < 0.001$, 4 studies, 364 participants, very low CoE, Fig. 4B).

WA vs. intra-articular sodium hyaluronate (IASH) injection

Total effective rate

Five RCTs (Liang and Li, 2016; Liu et al., 2014; Ren and Li, 2012; Wang and Su, 2019a; Wang and Li, 2010) assessed the effects of WA on the total effective rate compared with IASH injection therapy. All included RCTs showed equivalent effects of WA on the total effective rate compared with IASH injection (RR: 0.99, 95% CI: 0.91 to 1.09 [prediction interval, 95% CI: 0.86 to 1.15], I^2 =0%, $p = 0.87$, 5 studies, 465 participants, very low CoE, Fig. 5A).

Pain

Eight RCTs (Hu et al., 2016; Liang and Li, 2016; Liu et al., 2014; Ren and Li, 2012; Tu et al., 2016; Wang and Su, 2019a; Wang and Li, 2010; Zhang and Jiao, 2019a) compared the effects of WA with IASH injection on pain. Four RCTs showed positive effects (Hu et al., 2016; Tu et al., 2016; Wang and Li, 2010; Zhang and Jiao, 2019a), while four RCTs (Liang and Li, 2016; Liu et al., 2014; Ren and Li, 2012; Wang and Su, 2019a) reported equivalent effects. Meta-analysis failed to show a significant difference between the two groups (SMD: −0.01, 95% CI: −0.57 to 0.55 [prediction interval, 95% CI: −2.03 to 2.01], $I^2 = 92.6\%$, $p = 0.99$, 8 studies, 726 participants, very low CoE, Fig. 5B).

Function

Six RCTs (Liang and Li, 2016; Liu et al., 2014; Ren and Li, 2012; Wang and Su, 2019a; Wang and Li, 2010; Zhang and Jiao, 2019a) tested the effects of WA on function compared with IASH injection. Two RCTs showed favorable effects of WA (Liu et al., 2014; Zhang and Jiao, 2019a), while four RCTs (Liang and Li, 2016; Ren and Li, 2012; Wang and Su, 2019a; Wang and Li, 2010) showed equivalent effects with IASH injection. Meta-analysis showed no significant difference between the two groups (SMD: −0.60, 95% CI: −1.59 to 0.39 [prediction interval, 95% CI: −4.25 to 3.06], $I^2 = 96.6\%$, $p = 0.25$, 6 studies, 547 participants, very low CoE, Fig. 5C).

WA + iash injection vs. iash injection

Total effective rate

Twenty-five RCTs (Chen et al., 2017; Gao, 2017; Han and Zhang, 2016; Han, 2019; Jiang, 2014; Li et al., 2018; Liang and Li, 2016; Liang, 2018; Liang and Liang, 2012; Liu et al., 2014; Ma and Zhao, 2020; Ma et al., 2021, 2013; Ou et al., 2018; Ren and Li, 2012; Teng and Li, 2020; Wang and Su, 2019a; Wang and Li, 2010; Wang, 2018; Wu, 2018; Yu, 2016a; Zhang and Wang, 2011; Zhang et al., 2018, 2011; Zhou, 2020; Zuo, 2015) assessed the effects of WA+IASH injection on the total treatment effect compared with IASH injection. Fourteen RCTs showed positive effects of WA+IASH injection (Chen et al., 2017; Han and Zhang, 2016; Han, 2019; Jiang, 2014; Liang and Li, 2016; Liu et al., 2014; Ma et al., 2021; Ren and Li, 2012; Wang and Su, 2019a; Wang and Li, 2010; Wang, 2018; Wu, 2018; Zhou, 2020; Zuo, 2015), while eleven RCTs (Gao, 2017; Li et al., 2018; Liang, 2018; Liang and Liang, 2012; Ma and Zhao, 2020; Ma et al., 2013; Ou et al., 2018; Teng and Li, 2020; Yu, 2016a; Zhang et al., 2018; Zhang and Wang, 2011) failed to do so. Meta-analysis showed favorable effects of WA+IASH injection on the total effective rate (RR: 1.15, 95% CI: 1.11 to 1.19 [prediction interval, 95% CI: 1.04 to 1.27], $I^2 = 27.3\%$, $p < 0.001$, 25 studies, 2208 participants, very low CoE, Fig. 6A).

Pain

Nineteen RCTs (Chen et al., 2017; Han, 2019; He et al., 2018; Jiang, 2014; Liang and Li, 2016; Liang, 2018; Liu et al., 2014; Ma and Zhao, 2020; Ma et al., 2021; Ma, 2016; Ou et al., 2018; Ren and Li, 2012; Shi and Li, 2016; Teng and Li, 2020; Wang and Su, 2019a; Wang and Li, 2010; Wu, 2018; Yu, 2016a; Zhang et al., 2018) tested the effects of WA+IASH injection on pain. Seventeen RCTs showed positive effects of WA+IASH injection (Chen et al., 2017; Han, 2019; He et al., 2018; Jiang, 2014; Liang and Li, 2016; Liang, 2018; Ma and Zhao, 2020; Ma et al., 2021; Ma, 2016; Ou et al., 2018; Ren and Li, 2012; Teng and Li, 2020; Wang and Su, 2019a; Wang and Li, 2010; Wu, 2018; Zhang et al., 2018), while three RCTs (Liu et al., 2014; Shi and Li, 2016; Yu, 2016a) failed to do so. Meta-analysis showed favorable effects of WA+IASH injection on pain (SMD: −1.68, 95% CI: −2.07 to −1.29 [prediction interval, 95% CI: −3.56 to 0.19], $I^2 = 92\%$, $p < 0.001$, 19 studies, 1789 participants, very low CoE, Fig. 6B).

Function

Twenty-two RCTs (Chen et al., 2017; Gao, 2017; Han and Zhang, 2016; Han, 2019; He et al., 2018; Jiang, 2014; Liang and Li, 2016; Liang, 2018; Liu et al., 2014; Ma and Zhao, 2020; Ma et al., 2021; Ma, 2016; Ou et al., 2018; Ren and Li, 2012; Shi and Li, 2016; Wang and Su, 2019a; Wang and Li, 2010; Wu, 2018; Yu, 2016a; Zhang et al., 2018; Zuo, 2015) assessed the effects of WA+IASH injection on function. Seventeen RCTs showed positive effects of WA+IASH injection, while three RCTs (Liu et al., 2014; Shi and Li, 2016; Zhang et al., 2018) reported equivalent effects. Meta-analysis showed favorable effects of WA+IASH injection on function (SMD: −1.40, 95% CI: −1.72 to −1.08 [prediction interval, 95% CI: −2.96 to 0.16], $I^2 = 96.6\%$, $p < 0.001$, 22 studies, 2012 participants, very low CoE, Fig. 6C).

Other studies

Two RCTs (Gao, 2017; Ma, 2016) compared the effects of WA+IASH injection on QoL, and both studies showed favorable effects of WA+IASH injection.

AEs

Eleven RCTs (Chen et al., 2018a; Chen et al., 2018b; Dang, 2019; Ding et al., 2009; Lin and Ye, 2020; Ou et al., 2018; Qin, 2013; Qiu, 2013; Teng and Li, 2020; Wei, 2013; Yang et al., 2012) reported AEs. Among them, six (Chen et al., 2018aChen et al., 2018b; Dang, 2019; Ou et al., 2018; Qin, 2013; Wei, 2013) reported no AEs. Patients in the control group reported stomach discomfort, facial flushing, extremity edema, pruritus in the skin of the arms and chest, abnormal liver and kidney function, and gastrointestinal reactions. Patients in the WA group reported mild burns and pain around the area of needle insertion. Patients in the WA combination therapy group reported abnormal routine blood parameters, abnormal kidney function, gastrointestinal reactions, scalding, and skin allergies. The details of the symptoms are shown in Table 1.

Albatross plot and publication bias

For the total effective rate, the points were scattered across the contour lines (Fig. 7A). All the points were clustered on the positive association side of the plot, indicating that ginseng is favorable for the management of OA by WA. For the continuous outcomes, including pain, function and QoL, most points were scattered and accumulated on the right side of the plot, with many points clustered around the null line, failing to show specific effects of WA on these outcomes (Fig. 7B).

Funnel plots were asymmetrical for the RR for the total effective rate and SMD of pain and function, presenting potential publication bias (Supplement 6 A to F). IA: intra-articular; RR: risk ratio; QoL: quality of life; SMD: standard mean difference; WA: warm needle acupuncture.

CoE

The CoE was assessed using GRADEpro, and a summary of the

Table 2
Summary of randomized clinical studies of warm needle acupuncture for osteoarthritis compared with intra-articular sodium hyaluronate injection.

First author (year)	Sample size (M/F) Age (Mean)	Diagnostic criteria	Intervention group	Control group	Main outcomes	Main results	Adverse event
Hu (2016)	90 (40/50) A:55; B:56	COA	(A) WA (30 min, total 4 session, 1 session [once daily, 7 times], $n = 45$)	(B) IASH injection (2 ml, once a week for 4 weeks, $n = 45$)	Pain (VAS)	MD −0.90 [−1.46, −0.34], $p = 0.002$	n.r.
Tu (2016)	89 (40/49) A:55.3; B: 56.1	COA	(A) WA (30 min, total 4 session, 1 session [once daily, 7 times], $n = 44$)	(B) IASH injection (2 ml, once a week for 4 weeks, $n = 45$)	Pain (VAS)	MD −0.87 [−1.43, −0.31], $p < 0.002$	n.r.
Zhang (2019a)	82 (37/45) A:55.3; B:55.3	COA	(A) WA (30 min, total 4 session, 1 session [once daily, 6 times], $n = 41$)	(B) IASH injection (2 ml, once a week for 4 weeks, $n = 41$)	1) Pain (VAS) 2) Function (HSS)	1) MD −0.83 [−1.30, −0.36], $p < 0.001$ 2) MD −13.50 [−16.41, −10.59], $p < 0.001$	n.r.
Liu (2014)	186 (90/96) A:58; B:58; C:60	ACR	(A) WA (n.r., total 5 session, 1 session [once daily, 5 times], $n = 62$) (B) WA (n.r., total 5 session, 1 session [once daily, 5 times], $n = 62$), plus B	(C) IASH injection (2 ml, once a week for 5 weeks, $n = 62$)	1) Total effective rate 2) Pain (VAS) 3) Pain (WOMAC) 4) Function (WOMAC)	1) A vs. C: RR 0.98 [0.83, 1.16], NS; B vs. C: RR 1.16 [1.02, 1.32], $p = 0.03$ 2) A vs. C: 0.14 [−0.65, 0.93], NS; B vs. C: MD −0.42 [−0.78, −0.07], $p = 0.02$ 3) A vs. C: MD −0.93 [−1.70, −0.16], $p = 0.02$; B vs. C: MD −0.11 [−1.36, 1.14], NS 4) A vs.C: MD 7.49 [4.19, 10.79], $p < 0.001$; B vs. C: MD 0.79 [−2.48, 4.06], NS	n.r.
Wang (2010)	120 (38/82) A:44.5; B:45.3; C:46.3	ACR TCM-DTDS	(A) WA (n.r., total 5 session, 1 session [once daily, 5 times], $n = 40$) (B) WA (n.r., total 5 session, 1 session [once daily, 5 times], $n = 40$), plus B	(C) IASH injection (2 ml, once a week for 5 weeks, $n = 40$)	1) Total effective rate 2) Pain (VAS) 3) Function (LKSS)	1) A vs. C: RR 1.07 [0.84, 1.35], NS; B vs. C: RR 1.27 [1.04, 1.54], $p = 0.02$ 2) A vs. C: MD 0.55 [0.19, 0.90], $p = 0.003$; B vs. C: MD −1.58 [−2.27, −0.89], $p < 0.001$ 3) A vs. C: MD 3.60 [0.33, 6.87], $p = 0.03$; B vs. C: MD −29.90 [−33.33, −26.47], $p < 0.001$	n.r.
Ren (2012)	150 (73/77) 59.2	ACR TCM-DTDS CGND-TCM	(A) WA (n.r., total 3 session, 1 session [once daily, 10 times], $n = 50$) (B) WA (n.r., total 3 session, 1 session [once daily, 10 times], $n = 50$), plus B	(C) IASH injection (2 ml, once a week for 3 weeks, $n = 50$)	1) Total effective rate 2) Pain (VAS) 3) Function (LKSS)	1) A vs. C: RR 0.95 [0.77, 1.17], NS; B vs. C: RR 1.18 [1.01, 1.37], $p = 0.04$ 2) A vs. C: MD 0.16 [−0.24, 0.56], NS; B vs. C: MD −0.9 [−1.29, −0.51], $p < 0.001$ 3) A vs. C: MD 4.90 [1.51, 8.29], $p < 0.01$; B vs. C: MD −15.10 [−18.86, −11.34], $p < 0.001$	n.r.
Wang (2019a)	150 (87/63) A:59.2; B:58.7; C:57.1	COA	(A) WA (n.r., total 3 session, 1 session [once daily, 5 times], $n = 50$ (B) WA (n.r., total 3 session, 1 session [once daily, 5 times], $n = 50$, plus B	(C) IASH injection (2.5 ml, once a week for 3 weeks, $n = 50$)	1) Total effective rate 2) Pain (VAS) 3) Function (LKSS)	1) A vs. C: RR 1.02 [0.85, 1.24], NS; B vs. C: RR 1.18 [1.01, 1.37], $p = 0.04$ 2) A vs. C: MD −0.11 [−0.56,	n.r.

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Table 2 (*continued*)

						0.34], NS; B vs. C: MD −2.11 [−2.48, −1.74], $p < 0.001$ 3) A vs. C: MD −0.25 [−3.24, 2.74], NS; B vs. C: MD −20.21 [−22.94, −17.48], $p < 0.001$	
Liang (2016)	96 (34/62) A:46; B:46.3; C: 46.7	ACR	(A) WA (n.r., total 3 session, 1 session [once daily, 5 times], $n = 32$) (B) WA (n.r., total 3 session, 1 session [once daily, 5 times], $n = 32$), plus B	(C) IASH injection (2.0 ml, once a week for 4~5 weeks, $n = 32$)	1) Total effective rate 2) Pain (WOMAC) 3) Function (WOMAC)	1) A vs. C: RR 0.95 [0.75, 1.21], NS; B vs C: RR 1.12 [0.98, 1.30], NS 2) A vs. C: MD 2.23 [1.58, 2.87], $p < 0.001$; B vs C: MD −1.16 [−1.52, −0.80], $p < 0.001$ 3) A vs. C: MD −0.25 [−0.75, 0.26], NS; B vs C: MD −9.00 [−14.43, −3.57], $p = 0.001$	n.r.
Liang (2012)	60 (15/45) A:55.3; B:56.1	ACR	(A) WA (10 min, once daily, 7 times, $n = 30$), plus B	(B) IASH injection (2.5 ml, once a week for 5 weeks, $n = 30$)	Total effective rate	RR 1.17 [0.95, 1.43], $p = 0.14$	n.r.
Ma (2013)	60 (27/33) A:57; B:55	ACR	(A) WA (30 min, total 4 session, 1 session [three times weekly, 3 times], $n = 30$), plus B	(B) IASH injection (2 ml, once a week for 5 weeks, $n = 30$)	Total effective rate	RR 1.00 [0.94, 1.07], $p = 1.00$	n.r.
Wang (2018)	100 (n.r.) n.r.	ACR	(A) WA (30 min, total 4 session, 1 session [once daily, 7 times], $n = 50$), plus B	(B) IASH injection (2 ml, once a week for 4 weeks, $n = 50$)	Total effective rate	RR 1.18 [1.01, 1.37], $p = 0.04$	n.r.
Zhou (2020)	82 (54/28) A:50.2; B:49.2	TCM-DTDS	(A) WA (30 min, total 4 session, 1 session [once daily, 7 times], $n = 41$), plus B	(B) IASH injection (2 ml, once a week for 4 weeks, $n = 41$)	Total effective rate	RR 1.26 [1.04, 1.52], $p = 0.02$	n.r.
Teng (2020)	136(52/84) A: 62.1; B: 58.5	COA	(A) WA (30 min, once weekly, 5 times, $n = 68$), plus B	(B) IASH injection (2.5 ml, once a week for 5 weeks, $n = 68$)	1) Total effective rate 2) Pain (VAS)	1) RR 1.05 [0.93, 1.19], NS; 2) MD −4.28 [−4.79, −3.77], $p < 0.00001$	Scald (A:2); skin allergies (A:1)
Jiang (2014)	69 (8/61) A:64.1; B:62.9	ACR	(A) WA (30 min, three times weekly, 15 times, $n = 34$), plus B	(B) IASH injection (2.5 ml, once a week for 5 weeks, $n = 35$)	1) Total effective rate 2) Pain (VAS) 3) Function (LKSS)	1) RR 1.17 [1.00, 1.38], NS 2) MD −2.29 [−2.97, −1.61], $p < 0.001$ 3) MD −16.19 [−22.36, −10.02], $p < 0.001$	n.r.
Chen (2017)	92 (52/40) A:58.5; B:59.2	COA CGND-TCM	(A) WA (n.r., total 3 session, 1 session [once daily, 8 times], $n = 46$, plus B	(B) IASH injection (2m, once a week for 4 weeks, $n = 46$)	1) Total effective rate 2) Pain (VAS) 3) Function (LKSS)	1) RR 1.22 [1.05, 1.41], $p = 0.010$ 2) MD −1.96 [−2.36, −1.56], $p < 0.001$ 3) MD –26.95 [−32.61, −21.29], $p < 0.001$	n.r.
Liang (2018)	100 (55/45) A:62.8; B: 62.4	COA	(A) WA (30 min, total 5 session, 1 session [three times weekly, 3 times], $n = 50$), plus B	(B) IASH injection (2.5 ml, once a week for 5 weeks, $n = 50$)	1) Total effective rate 2) Pain (VAS) 3) Function (LKSS)	1) RR 1.20 [1.03, 1.39], $p = 0.02$ 2) MD −1.75 [−2.18, −1.32], $p < 0.001$ 3) MD −15.64 [−20.50, −10.78], $p < 0.001$	n.r.
Han (2019)	90 (43/47) A:58.2; B:56.1	CGND-TCM	(A) WA (n.r., total 4 session, 1 session [once daily, 5 times], $n = 45$), plus B	(B) IASH injection (2 ml, once a week for 4 weeks, $n = 45$)	1) Total effective rate 2) Pain (VAS) 3) Function (LKSS)	1) RR 1.25 [1.01, 1.55], $p = 0.04$ 2) MD −0.47 [−0.69, −0.25], $p < 0.001$ 3) MD −5.38 [−8.26, −2.50], $p < 0.001$	n.r.

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Table 2 (*continued*)

Ma (2021)	118 (41/77) A:70.5; B:70.3	COA	(A) WA (n.r. total 3 session, 1 session [once daily, 10 times], $n = 59$), plus B	(B) IASH injection (2 ml, once a week for 5 weeks, $n = 59$)	1) Total effective rate 2) Pain (VAS) 3) Function (LKSS)	1) RR 1.35 [1.11, 1.64], $p = 0.002$ 2) MD −1.40 [−1.49, −1.31], $p < 0.001$ 3) MD −15.90 [−18.88, −12.92], $p < 0.001$	n.r.
Gao (2017)	80 (58/22) A:59.2; B:60.5	TCM-DTDS	(A) WA (15 min, once daily for 35 times, $n = 40$), plus B	(B) IASH injection (2.5 ml, once a week for 5 weeks, $n = 40$)	1) Total effective rate 2) Pain (VAS) 3) Function (LKSS) 4) QoL (n.r.)	1) RR 1.19 [0.99, 1.44], NS 2) MD −1.50 [−1.82, −1.18], $p < 0.001$ 3) MD −10.20 [−13.84, −6.56], $p < 0.001$ 4) MD 11.90 [9.44, 14.36], $p < 0.001$	n.r.
Ma (2020)	60 (36/24) A:64.7; B:63.5	COA	(A) WA (35 min, total 4 session, 1 session [once daily, 7 times], $n = 30$), plus B	(B) IASH injection (2 ml, once a week for 4 weeks, $n = 30$)	1) Total effective rate 2) Pain (VAS) 3) Function (HSS)	1) RR 1.27 [1.01, 1.61], $p = 0.05$ 2) MD −1.70 [−2.41, −0.99], $p < 0.001$ 3) MD −13.70 [−21.96, −6.44], $p < 0.001$	n.r.
Yu (2016b)	46 (21/25) n.r.	COA	(A) WA (30 min, once weekly, total 4 times, $n = 23$), plus B	(B) IASH injection (2 ml, once a week for 4 weeks, $n = 23$)	1) Total effective rate 2) Pain (VAS) 3) Pain (WOMAC) 4) Function (WOMAC)	1) RR 1.10 [0.92, 1.32], NS 2) MD −0.40 [−0.86, 0.06], NS 3) MD −1.81 [−2.58, −1.04], $p < 0.001$ 4) MD −5.84 [−9.05, −2.63], $p < 0.001$	
Zhang (2018)	62 (24/38) A:54.1; B:56.9	COA	(A) WA (30 min, once daily, 25 times, $n = 31$), plus B	(B) IASH injection (2 ml, once a week for 5 weeks, $n = 31$)	1) Total effective rate 2) Pain (WOMAC) 3) Function (WOMCA)	1) RR 1.07 [0.94, 1.22], NS 2) MD −1.17 [−1.81, −0.53], $p = 0.0003$ 3) MD −0.91 [−2.22, 0.40], NS	n.r.
Wu (2018)	76 (39/37) A:61.7; B:56.3	COA CGND-TCM	(A) WA (n.r., three times weekly, 12 times, $n = 38$), plus B	(B) IASH injection (2 ml, once a week for 4 weeks, $n = 38$)	1) Total effective rate 2) Pain (WOMAC) 3) Function (WOMAC)	1) RR 1.52 [1.16, 2.00], $p = 0.003$ 2) MD −6.30 [−7.74, −4.86], $p < 0.001$ 3) MD −18.89 [−23.67, −14.11], $p < 0.001$	n.r.
Ou (2018)	56 (25/31) A:57.4; B:58.2	ACR	(A) WA (20 min, total 5 session, 1 session [once daily, 5 times], $n = 28$), plus B	(B) IASH injection (2 ml, once a week for 5 weeks, $n = 28$)	1) Total effective rate 2) Pain (WOMAC) 3) Function (WOMAC)	1) RR 1.13 [0.92, 1.38], NS 2) MD −2.66 [−3.39, −1.93], $p < 0.001$ 3) MD −4.54 [−5.57, −3.51], $p < 0.001$	None
Li (2018)	48 (28/20) A: 63.5; B: 62.4	AAOS	(A) WA (30 min, total 4 session, 1 session [once daily, 7 times], $n = 24$), plus B	(B) IASH injection (2 ml, once a week for 4 weeks, $n = 24$)	1) Total effective rate 2) Pain	1) RR 1.15 [0.94, 1.40], NS 2) MD −2.14 [−2.69, −1.59], $p < 0.001$	n.r.
Zhang (2011)	179 (61/118) A:56.8; B:29.2	COA	(A) WA (20 min, total 5 session, 1 session [once daily, 5 times], $n = 90$), plus B	(B) IASH injection (2 ml, once a week for 5 weeks, $n = 89$)	1) Total effective rate 2) Function (LKSS)	1) RR 1.08 [0.99, 1.16], NS 2) MD −12.15 [−14.56, −9.74], $p < 0.001$	n.r.
Zuo (2015)	100 (44/56) A:48.3; B:49.5	ACR	(A) WA (30 min, total 2 session, 1 session [once daily, 7 times], $n = 50$), plus B	(B) IASH injection (2 ml, once a week for 4 weeks, $n = 50$)	1) Total effective rate 2) Function (LKSS)	1) RR 1.18 [1.00, 1.40], $p = 0.05$ 2) MD −13.43	n.r.

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Table 2 (*continued*)

						[−17.24, −9.62], $p < 0.001$	
Han (2016)	128 (62/66) A:62.4; B:63	COA	(A) WA (30 min, n.r., $n = 64$), plus B	(B) IASH injection (2 ml, n.r., $n = 64$)	1) Total effective rate 2) Function (LKSS)	1) RR 1.13 [1.00, 1.27], $p = 0.04$ 2) MD −7.53 [−9.98, −5.08], $p < 0.001$	n.r.
He (2018)	158 (78/80) A:63.7; B:63.9	COA	(A) WA (30 min, total 5 session, 1 session [once daily, 5 times], $n = 79$), plus B	(B) IASH injection (2 ml, once a week for 5 weeks, $n = 79$)	1) Pain (VAS) 2) Function (LKSS)	1) MD −1.92 [−2.21, −1.63], -$p < 0.001$ 2) MD −30.62 [−35.13, −26.11], $p < 0.001$	n.r.
Shi (2016)	60 (n.r.) A:61.4; B: 60.4	COA	(A) WA (20 min, three times weekly, 15 times, $n = 30$), plus B	(B) IASH injection (2 ml, once a week for 5 weeks, $n = 30$)	1) Pain (WOMAC) 2) Function (WOMAC)	1) MD −0.19 [−1.91, 1.53], NS 2) MD −2.35 [−6.45, 1.75], NS	n.r.
Ma (2016)	72 (30/42) A:56.8; B:55.8	ACR	(A) WA (n.r., three times weekly, 15 times, $n = 36$), plus B	(B) IASH injection (2 ml, once a week for 5 weeks, $n = 36$)	1) Pain (WOMAC) 2) Function (WOMAC) 3) QoL (SF-36)	1) MD −6.12 [−7.63, −4.61], $p < 0.001$ 2) MD −14.11 [−18.88, −9.34], $p < 0.001$ 3) MD 0.23 [0.15, 0.31], $p < 0.001$	n.r.
Wang (2019b)	80 (45/35) A:61.4; B:61.3	COA	(A) WA (40 min, total 2 session, 1 session [once daily, 5 times], $n = 40$)	(B) IASH injection (2 ml, once a week, $n = 40$) + Drug (Diclofenac 100 mg, once daily for 8 weeks)	1) Total effective rate 2) Pain (VAS) 3) Function (LKSS)	1) RR 1.23 [1.01, 1.51], $p < 0.04$ 2) MD −1.88 [−1.97, −1.79], $p < 0.001$ 3) MD −8.88 [−9.66, −8.10], $p < 0.001$	n.r.
Wei (2013)	80 (47/33) A:63; B:61	CGND-TCM	(A) WA (40 min, total 3 session, 1 session [once daily, 10 times], $n = 40$) + IASH injection (2 ml, once weekly for 5 weeks)	(B) Drug (Ibuprofen 0.3 g, twice daily for 4 weeks, $n = 40$	Total effective rate	RR 1.37 [1.09, 1.73], $p = 0.008$	None

AAOS: AAOS-CPG on treatment of osteoarthritis of the knee; ACR: The American College of Rheumatology; CGND-TCM: The clinical guideline of New Drug for TCM; COA: Chinese Orthopedic Association-Guideline for diagnosis and treatment of osteoarthritis; HM: herbal medicine; HSS: score of hospital for special surgery; IASH: intra-articular sodium hyaluronate; LKSS: Lysholm scoring system; mos: months;MD: mean difference; n.r.: not reported; NS: not significant; QoL: quality of life; RR: risk ratio; TCM: traditional Chinese medicine; TCM-DTDS: TCM criteria of diagnosis and therapeutic effect of diseases and diseases and syndromes; VAS: visual analogue scale; WA: warm needle acupuncture; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

findings, including studies with low or very low CoE, is shown in Table 3.

Discussion

Summary of the main results

The main findings of the present study indicated that WA alone or in combination with drug therapy or IASH injection was superior to drug therapy or IASH injection in reducing pain and improving both the total effective rate and function. In all the studies included, it was determined that the randomization and allocation concealment as well as the blinding of participants and researchers were not properly implemented, which may have affected the results. Therefore, the overall RoB of the included studies was concerning, and the CoE was very low. The side effects of WA were mild or transient, with most being skin burns. WA therapy is safer than drug therapy and does not induce serious side effects, but the evidence of its safety is not sufficient since only three studies evaluated the safety of this treatment.

Overall completeness and applicability of the evidence

WA may be better than drug therapy or IASH injection in terms of improving OA symptoms; however, future SRs should be conducted on the safety of WA to confirm this. Furthermore, research on the standard distance between the acupuncture point and the skin surface should be conducted, and clinical research on treatment devices that can replace WA is also warranted.

Quality of the evidence

The biases of the studies included were rated as high or unclear. Most of the studies failed to report randomization methods and allocation concealment. It was determined that the performance biases were very high because the researchers and participants were not blinded properly, and no placebo-controlled groups were included. Furthermore, since not all studies had registered protocols, it was determined that the biases in the confirmation of the results and in the reporting were high. Insufficient concealment of the assignment of the orders and poor blinding of the participants and researchers led to a high RoB or ambiguity in the studies considered for the review, and thus the CoE was very low. Given the high RoB and the small sample sizes, the level of evidence was found to be very low. To improve the quality of the literature, future studies on this topic should use a double-blind design by developing a mimic heat source and a suitable random assignment method.

Potential biases in the review process

There are several limitations to this review. First, although our search was comprehensive, we may have overlooked studies published in the gray literature. The results of the funnel plots used to assess publication bias included possible publication bias. It is conceivable that several RCTs demonstrating negative findings remain unpublished; thus, the overall picture could be biased. Second, many studies lacked

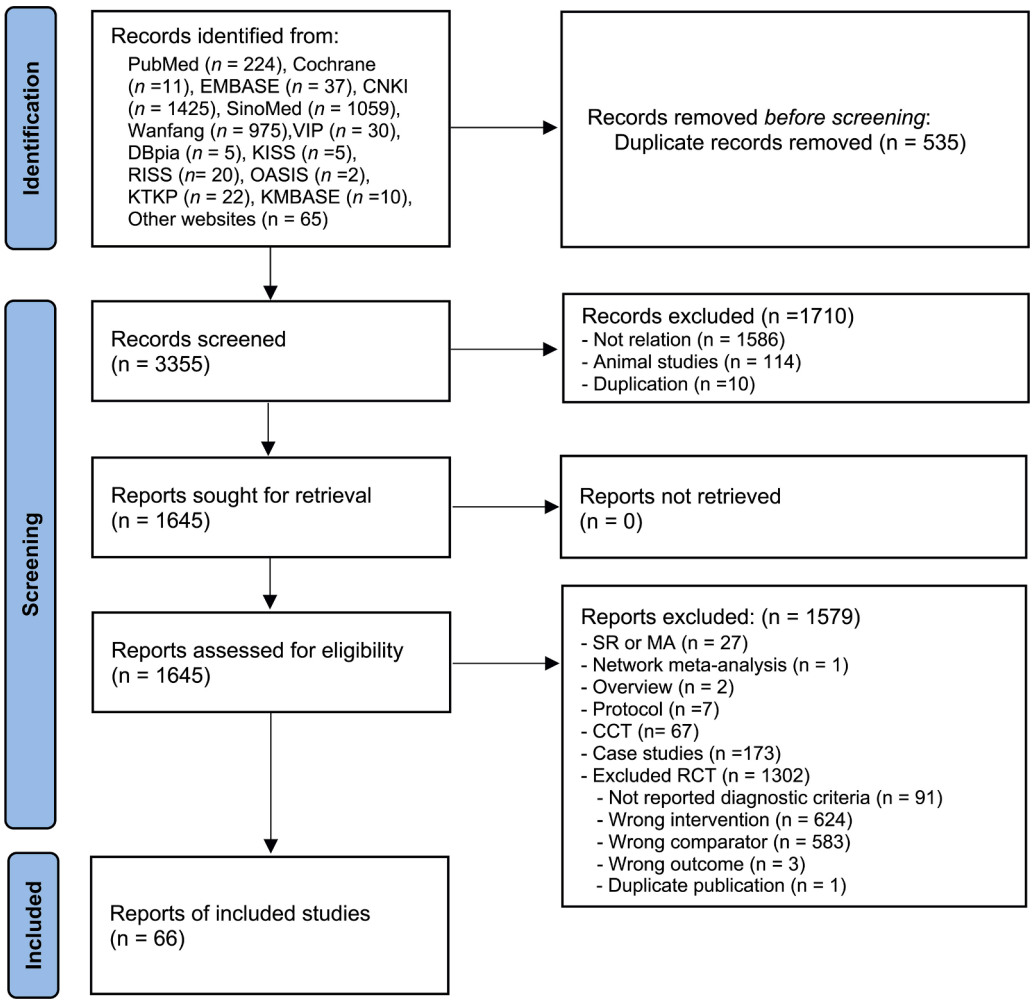

Fig. 1. Flowchart of the trial selection process. CCT: clinical controlled trial; MA: meta-analysis; RCT: randomized controlled trial; SR: systematic review.

detailed explanations of how randomization and allocation concealment were conducted. Our intention to contact the authors of the studies to obtain more information, such as the method of randomization, was thwarted by the frequent lack of author information in the majority of studies published in China. While we intended to include only RCTs or quasi-RCTs in this review, the lack of author contact information meant that we were unable to confirm whether all included trials were actually randomized. If studies were not properly randomized or allocation was not properly concealed, the study results included in this review could be biased. Most studies could not be properly double-blinded because of the nature of the acupuncture procedure. Third, reviewer subjectivity cannot be ruled out because the assessment was performed with a subjective assessment tool for OA. Because the outcome variables for pain and function are generated by a questionnaire and have complex effects that depend on the circumstances and conditions of the participants and researchers, it is necessary to assess outcomes that can be measured in an objective manner. Regarding the assessment indicators, a limitation is that the reliability of the assessment results may be low because the assessment indicators are frequently used and the subjectivity of the raters cannot be excluded. Fourth, there was substantial clinical heterogeneity in the included studies, including the WA method, type of drug therapies, and criteria used to assess clinical efficacy. Although we attempted to pool the results, the findings should be interpreted with caution. Several variables play a role in the efficacy of WA, such as the method, the material of the acupuncture needles, the distance between the end of the needle and the patient's skin, and the acupuncture point used. The method used in this study consisted of inserting acupuncture needles into acupuncture points and applying moxibustion in the form of a moxa stick. The temperature also varies depending on the material of the needles used for acupuncture treatment (Lee et al., 2019). According to one study, the temperature of gold and silver needles is almost twice that of stainless steel needles (Choi and Eom, 1992). In addition, the acupuncture points used were not identical in the studies included in this review. Because different acupuncture points were used in each study, it is difficult to conclude that WA treatments are effective in treating OA. Although different types of evaluation criteria were used for efficacy, they can be pooled because of the similarity of the evaluation criteria. However, there is also a possibility of bias in pooling the results. Fifth, the lack of detailed reporting may also have contributed to possible misclassification of studies and biased the effect estimates used in the current study. Other limitations include the small number and often suboptimal methodological quality of primary data. The included studies used different definitions for measuring outcomes. The use of the SMD may exaggerate the effects of WA on pain and function. Finally, the short duration of the included treatment trials and their limited reporting of AEs means that we do not have reliable information on the number or type of AEs that may be associated with the interventions.

Agreements and disagreements with other studies or reviews

In a previous SR of studies on this topic (Chen et al., 2019; Fan et al., 2020; Feng et al., 2019; Guo and Chen, 2018; Jiang and Zhang, 2019; Kong et al., 2019; Lu, 2015; Luo et al., 2019; Zhang et al., 2019; Zhao et al., 2010), the efficacy of WA was investigated when applied alone

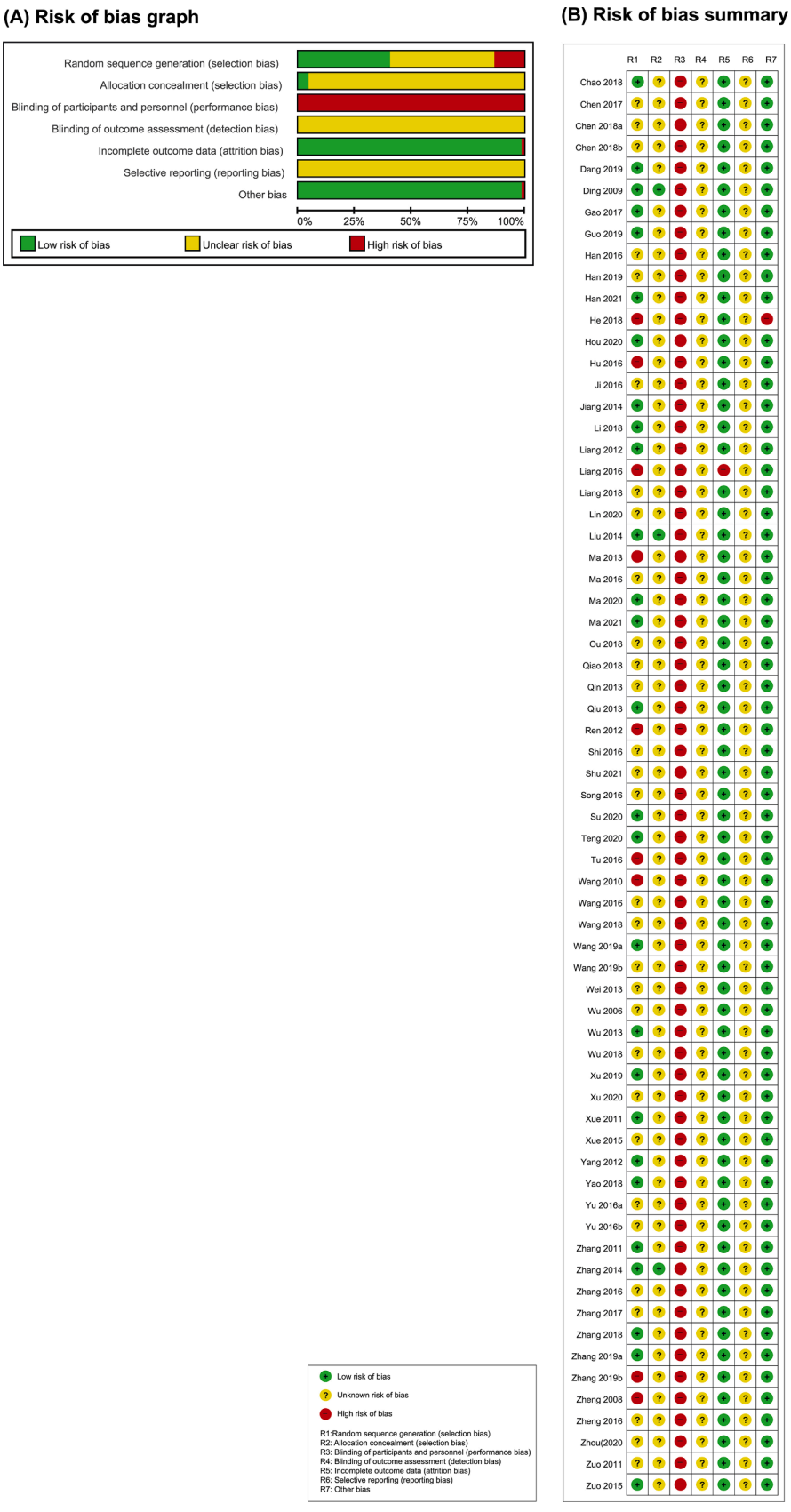

Fig. 2. (A) Risk of bias graph. (B) Risk of bias summary.

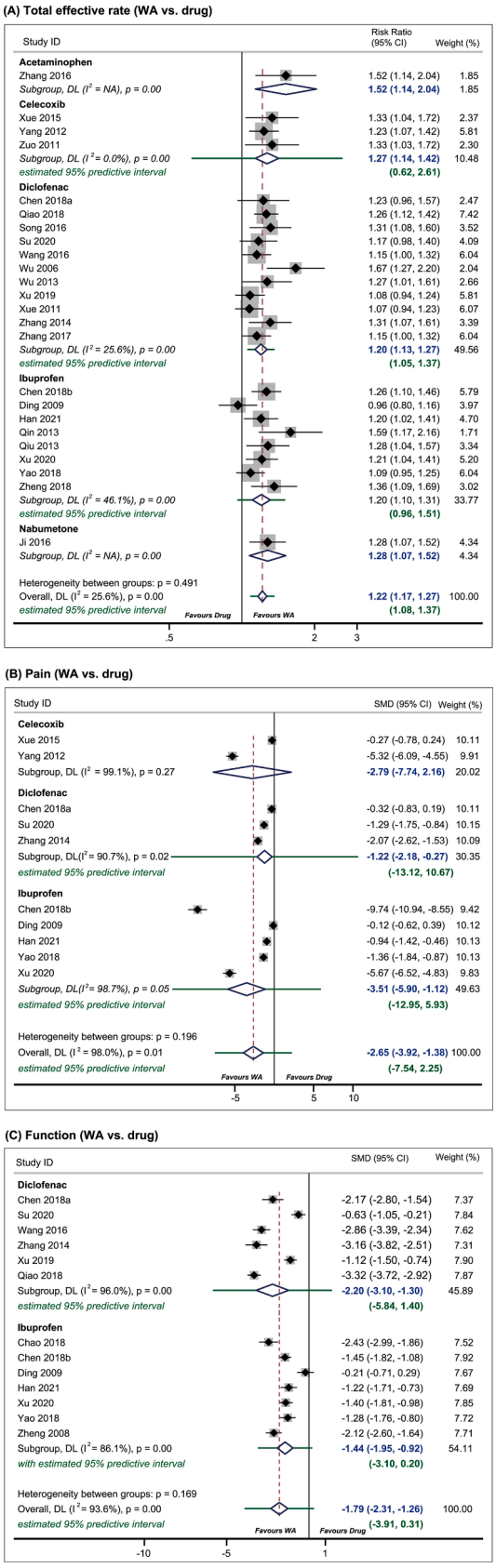

Fig. 3. Forest plot of outcomes of WA vs. drug therapy. (A) Total treatment effect. (B) Pain. (C) Function. SMD: standard mean difference; WA: warm needle acupuncture.

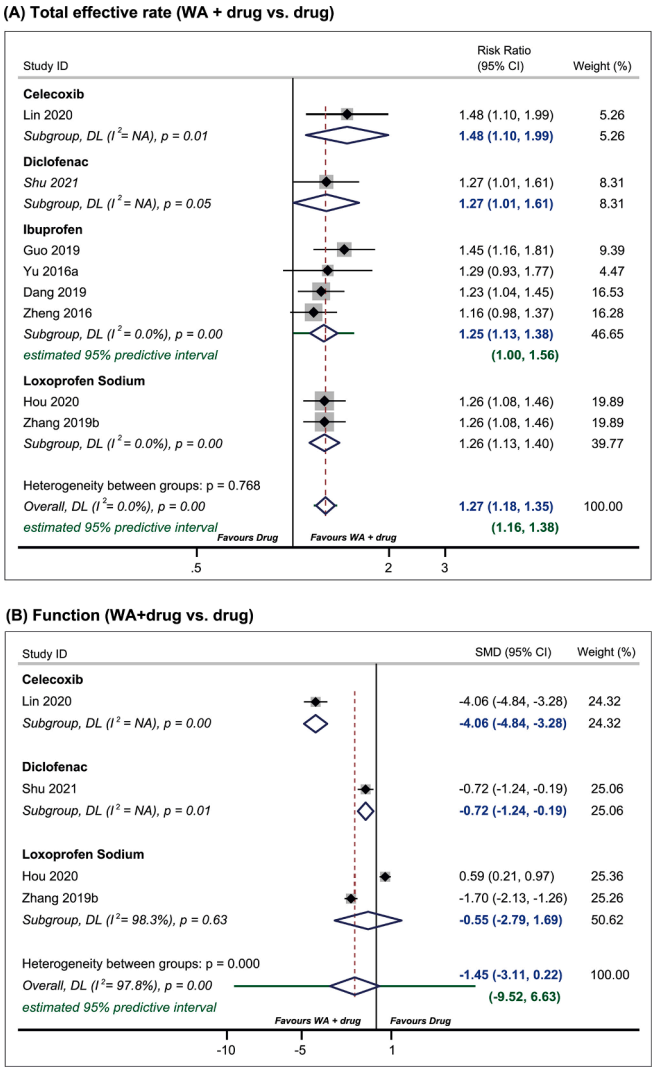

Fig. 4. Forest plot of outcomes of WA+drug therapy vs. drug therapy. (A) Total treatment effect. (B) Function. SMD: standard mean difference; WA: warm needle acupuncture.

and in combination with other treatments. All SRs conducted thus far have reported that both WA monotherapy and combination therapies show more significant therapeutic effects than control treatments (WM or conventional acupuncture or HM). However, the range of the literature search database was narrow, the quality of the literature was low, information on WA was missing, and the amount of literature considered for such reviews was quite small. Extensive research on the effects of WA monotherapy or combination therapies on OA should be conducted in a systematic and comprehensive manner through an extensive search of the literature and databases.

Implications for practice and research

WA was effective in reducing pain and improving joint function. However, the RoB was unclear in the review; thus, further verification is needed. Therefore, WA should be recommended with caution for patients with OA because its efficacy has not been confirmed.

A more rigorously designed large-sample RCT is required in the future because the level of evidence of the selected studies here was very low. For clear evidence, joint effort should be directed toward trying to comply with the CONSORT guidelines (Schulz et al., 2010) to improve the quality of RCTs related to WA therapies and ensure the veracity and reliability of the conclusions both domestically and internationally. In

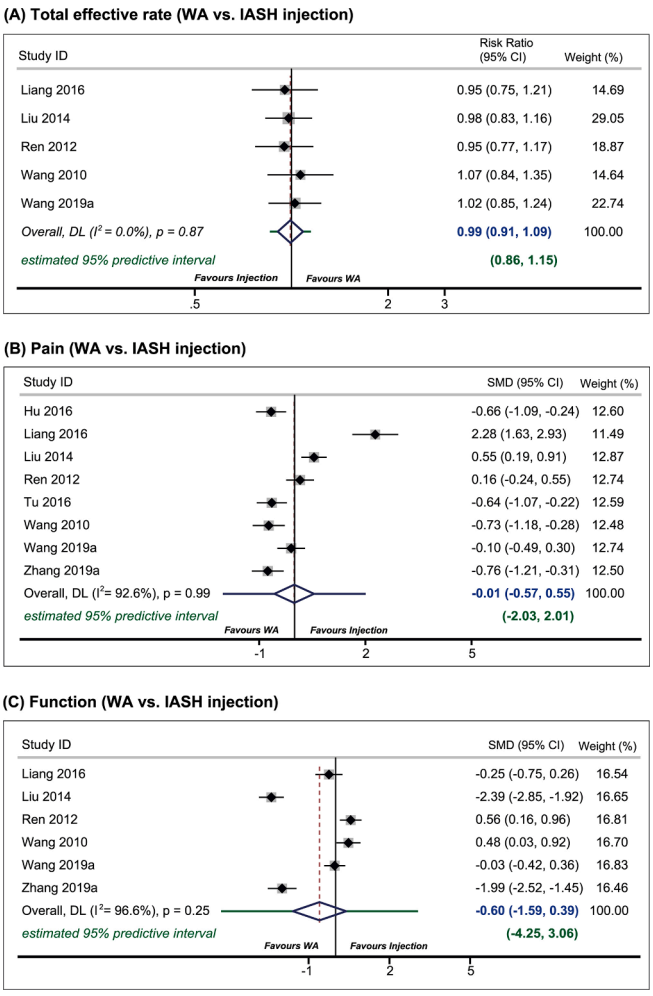

Fig. 5. Forest plot of outcomes of WA vs. IASH injection. (A) Total treatment effect. (B) Pain. (C) Function. IASH: Intra-articular sodium hyaluronate; SMD: standard mean difference; WA: warm needle acupuncture.

future studies, the WA method should be reported according to the STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) (MacPherson et al., 2010) and STandards for Reporting Interventions in Clinical Trials of Moxibustion (STRICTOM) (Cheng et al., 2013) guidelines. In addition, active clinical research using standardized acupoints is needed.

Conclusions

The evidence provided in this review suggests that WA may be more effective than drug therapy or IASH injection) in alleviating symptoms of OA. Furthermore, the results of this study could serve as a foundation for future clinical research enabling WA to be widely used as a preventive and therapeutic treatment for OA.

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CRediT authorship contribution statement

Ji Hee Jun: Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft. **Tae-Young Choi:** Validation,

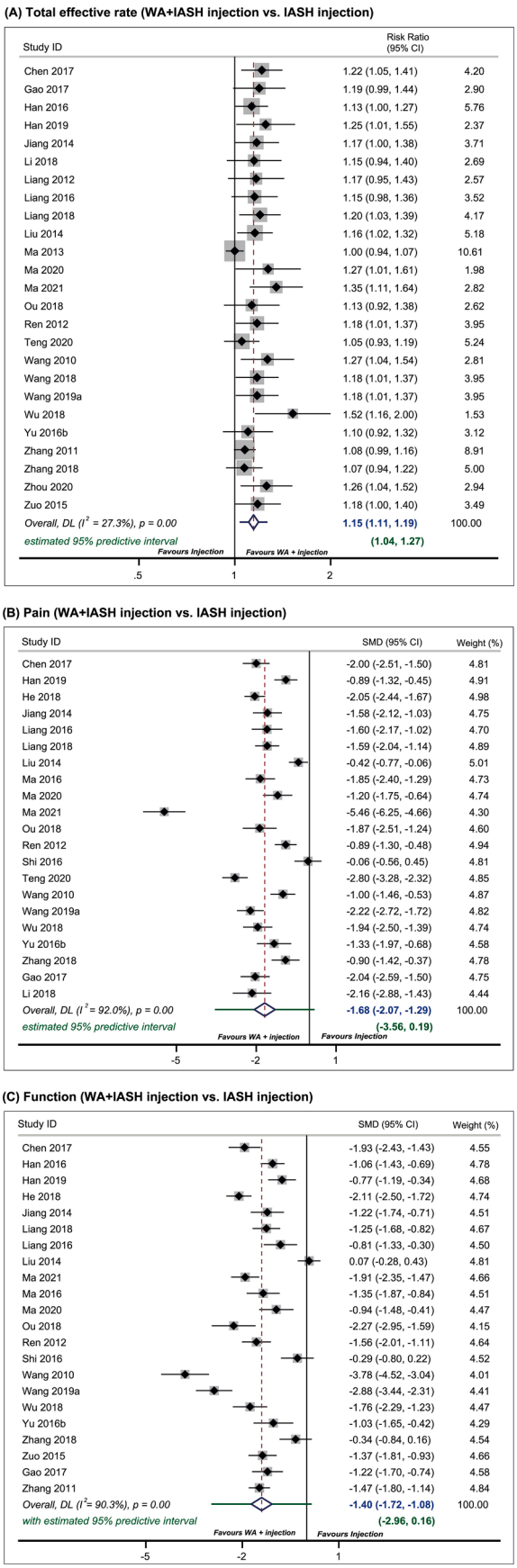
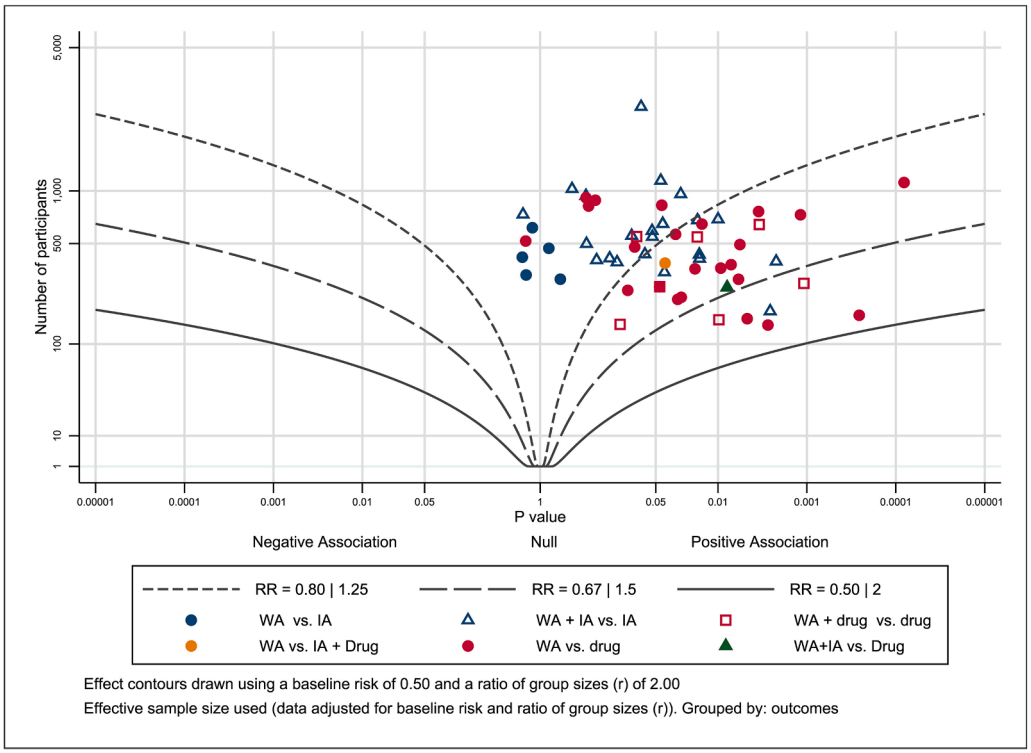


Fig. 6. Forest plot of outcomes of WA+IASH injection vs. IASH injection. (A) Total treatment effect. (B) Pain. (C) Function. IASH: Intra-articular sodium hyaluronate; SMD: standard mean difference; WA: warm needle acupuncture.

(A) Total treatment effect



(B) Continous outcomes

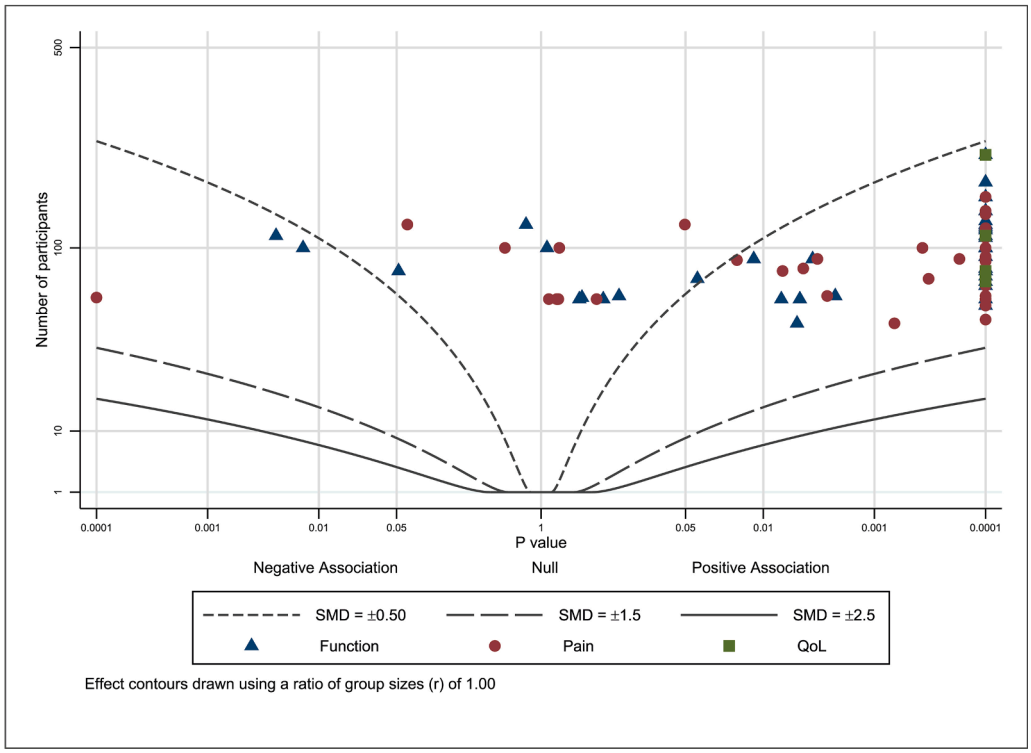


Fig. 7. Albatross plot of (A) total effective rate and (B) pain, function, and quality of life (QoL).

Table 3
Summary of findings

Patient or population: Osteoarthritis
Intervention: WA / WA + drug therapy / WA + IASH injection
Comparison: Drug therapy / IASH injection

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with placebo	Risk difference with GRADE
WA vs. drug therapy					
Total effective rate	2278 (24 RCTs)	⨁⨁◯◯ LOW [a]	RR 1.22 (1.17 to 1.27)	436 per 1000	166 more per 1000 (128 more to 203 more)
Pain	874 (10 RCTs)	⨁◯◯◯ VERY LOW [a,b]	-	-	SMD 2.65 SD lower (3.92 lower to 1.38 lower)
Function	1354 (13 RCTs)	⨁◯◯◯ VERY LOW [a,b]	-	-	SMD 1.79 lower (2.31 lower to 1.26 lower)
WA + drug therapy vs. drug therapy					
Total effective rate	646 (8 RCTs)	⨁⨁◯◯ LOW [a]	RR 1.27 (1.18 to 1.35)	731 per 1000	197 more per 1000 (132 more to 256 more)
Pain	168 (2 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	-	SMD 5.85 lower (7.84 lower to 3.85 lower)
Function	364 (4 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	-	-	SMD 1.45 lower (3.11 lower to 0.22 higher)
WA vs. IASH injection					
Total effective rate	465 (5 RCTs)	⨁◯◯◯ VERY LOW [a,c]	RR 0.99 (0.91 to 1.09)	803 per 1000	8 fewer per 1000 (72 fewer to 73 more)
Pain	726 (8 RCTs)	⨁◯◯◯ VERY LOW [a,b,e]	-	-	SMD 0.01 SD lower (0.57 lower to 0.55 higher)
Function	547 (6 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	-	-	SMD 0.6 lower (1.59 lower to 0.39 higher)
WA + IASH injection vs. IASH injection					
Total effective rate	2238 (25 RCTs)	⨁◯◯◯ VERY LOW [a,d]	RR 1.15 (1.11 to 1.19)	804 per 1000	611 more per 1000 (0 fewer to 1000 more)
Pain	1789 (19 RCTs)	⨁◯◯◯ VERY LOW [a,b]	-	-	SMD 1.68 lower (2.07 lower to 1.29 lower)
Function	2012 (22 RCTs)	⨁◯◯◯ VERY LOW [a,b]	-	-	SMD 1.40 lower (1.72 lower to 1.08 lower)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); CI: Confidence interval; IASH injection: intra-articular sodium hyaluronate injection; RCT: randomized controlled trial; RR: Risk ratio; SMD: Standardized mean difference; WA: warm needle acupuncture

GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect; Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations:

a. Downgrade by two level: Overall risk of bias is uncertain. Only four studies reported the simple randomization method, and the remaining studies did not provide relevant information. All studies reported a lack of allocation concealment and blinding. Other risk of bias domains was also concerning due to poor reporting. Therefore, the studies included were judged to have serious methodological limitations; b. Downgrade by two level: Heterogeneity across the studies is fairly high; c. It passes confidence interval 1; e. 95% confidence intervals included no effect; d. Downgrade by one level: Heterogeneity across the studies is fairly high;

Formal analysis, Writing – review & editing. **Nicola Robinson:** Conceptualization, Methodology, Writing – review & editing. **Ji-Yeun Park:** Validation, Data curation, Writing – review & editing. **Eun-Young Jun:** Validation, Data curation, Resources, Writing – review & editing. **Kyeong Han Kim:** Project administration, Validation, Writing – review & editing. **Hye Won Lee:** Methodology, Visualization, Formal analysis, Writing – review & editing. **Myeong Soo Lee:** Conceptualization, Formal analysis, Investigation, Writing – original draft. **Sunju Park:** Investigation, Resources, Writing – review & editing.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phymed.2022.154388.

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