



original research

The efficacy and safety of extracorporeal shockwave therapy in knee osteoarthritis: A systematic review and meta-analysis

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ABSTRACT

Background: Extracorporeal shockwave therapy (ESWT) has been widely applied for pain control in musculoskeletal disorders. Whether ESWT can improve pain relief and joint function for knee osteoarthritis remains controversial. Therefore, we designed a meta-analysis based on relevant studies to comprehensively analyze and determine the efficacy and safety of ESWT for knee osteoarthritis.

Methods: We identified relevant studies by an electronic search consisting of five English language databases: MEDLINE (1966 to July 2019), the Cochrane Central Register of Controlled Trials (2019 Issue 2), EMBASE (1980 to July 2019), and PubMed (1946 to July 2019). The methodological quality of randomized controlled trials (RCTs) was independently evaluated by two reviewers according to the criteria in the Cochrane Collaboration for Systematic Reviews. The quality of cohort and case-control studies was assessed by the Newcastle-Ottawa scale (NOS). We performed statistical analysis by the Stata software, version 15.

Results: Three RCTs and three cohort studies involving 589 patients were included. The present meta-analysis indicated that ESWT was associated a significant reduction of pain score at 4 weeks (WMD = -0.436 ; 95% CI = -0.604 to -0.269), 8 weeks (WMD = -0.234 ; 95% CI = -0.447 to -0.022) and 12 weeks (WMD = -0.239 ; 95% CI = -0.436 to -0.043). There were significant differences between the two groups in terms of the Western Ontario and McMaster Universities Osteoarthritis Index at 4 weeks (WMD = -3.107 ; 95% CI = -5.073 to -1.142), 8 weeks (WMD = -3.617 ; 95% CI = -5.760 to -1.475) and 12 weeks (WMD = -2.271 ; 95% CI = -3.875 to -0.667).

Conclusion: The ESWT was efficacious and safe for reducing pain and improving knee function in patients with knee osteoarthritis, without increasing the risk of adverse effects.

1. Introduction

Osteoarthritis (OA) is one of the leading causes of global disability and one of the most common degenerative conditions affecting knee joint, limiting its motion and necessitating surgical intervention [1,2]. The major clinical manifestations include joint pain, stiffness, swelling and muscle weakness. It is characterized by the degradation and erosion of articular cartilage, subchondral bone remodeling, and chronic joint and systemic inflammation [3,4]. The number of patients with knee OA has increased in tandem with population aging.

Although various interventions available, no effective treatment has been proven to inhibit the progression of knee OA development. Current treatments are mainly concentrated on the symptoms remission with the aim of pain relief and function recovery. Nonsurgical therapies include nonpharmacological and pharmacological approaches. Exercise and weight loss are the two recommended nonpharmacological

treatments but often with a poor compliance [5,6]. Pharmacological approaches for knee OA are focused on the administration of oral nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, glucosamine, and chondroitin [7–9]. However, the use of NSAIDs and analgesics is often accompanied with side effects. Intra-articular injection, as a minimally invasive therapy, is reported safe and effective for the treatment of knee OA, the short-term action limits the clinical application.

Extracorporeal shockwave therapy (ESWT) contains a sequence of single sound impulses characterized by a high-pressure peak and quick pressure rise in a short duration and it has been widely used for treating various musculoskeletal disorders [10]. It can inhibit the structural changes in subchondral bone, and subsequently suppress the degenerative changes in cartilage [11]. Noninvasive and a low complication rate makes it more interesting compared with other conservative and surgical treatments. Currently, the efficacy and safety of ESWT in

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reducing pain remains controversial in published clinical trials. Therefore, we designed a meta-analysis based on relevant studies to comprehensively analyze and determine the efficacy and safety of ESWT for knee OA.

2. Methods

The present review was conducted according to AMSTAR (Assessing the methodological quality of systematic reviews) guidelines [12] and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

2.1. Search strategy

We identified relevant studies by an electronic search consisting of five English language databases: MEDLINE (1966 to July 2019), the Cochrane Central Register of Controlled Trials (2019 Issue 2), EMBASE (1980 to July 2019), and PubMed (1946 to July 2019). The keywords and search strategy include: (extracorporeal shockwave) AND (osteoarthritis OR osteoarthrosis OR osteoarthrosis OR degenerative arthritis) AND knee. Besides, the reference lists of the relevant articles and reviews were evaluated to identify the potential eligible studies.

2.2. Inclusion and exclusion criteria

We included studies in accordance with the following criteria:

- (1) Patients: patients with knee OA who were diagnosed in clinical;
- (2) Experimental groups: low-dose ESWT;
- (3) Control groups: placebo treatment in an identical manner to the ESWT;
- (4) Outcomes: visual analog scale (VAS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Lequesne index, and adverse effects;
- (5) Study design: randomized controlled trials (RCTs) and retrospective studies.

Studies were excluded if they met the following criteria:

- (1) Non-human researches or trials on animals;
- (2) Articles belong to abstracts, letters, editorials, expert opinions, reviews, case reports or laboratory studies;
- (3) Studies without sufficient data for analysis. Two investigators independently reviewed the selected studies and any disagreement was resolved by discussion with the corresponding author.

2.3. Data extraction

The demographic characteristics extracted for systematic review were as follows: first author, year of publication, study design, sample size in each study, average age of patients, sex ratio, and follow-up. Pain score and joint function were chosen as the primary outcome in this meta-analysis. Secondary outcome measure was adverse effects. Any disagreement between the reviewers was resolved by discussion with the corresponding author. Extracted data were entered into a standardized Excel file and checked by a third investigator.

2.4. Quality assessment

The methodological quality of RCTs was independently evaluated by two reviewers according to the criteria in the Cochrane Collaboration for Systematic Reviews, which included the following key domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting. The quality of cohort and case-control studies was assessed by the Newcastle-Ottawa scale

(NOS). Disagreements between the authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. The grading of Recommendations Assessment, Development and Evaluation (GRADE) system approach was used to evaluate the quality of the evidence.

2.5. Synthesis of results

We performed statistical analysis by the Stata software, version 15 (StataCorp, College Station, TX, USA). Continuous variables were analyzed using the weighted mean difference (WMD), and dichotomous variables were analyzed using risk difference (RD). Heterogeneity was assessed using χ^2 test, and the I^2 statistic was applied to these summary data to describe the percentage of variation across studies. A value of I^2 more than 50% was considered high heterogeneity. A P value less than 0.05 was considered to indicate statistical significance. When $I^2 > 50\%$ and $P < 0.1$, it was considered to represent significant heterogeneity, then a random-effects model was used. In contrast, a fixed effect model was used. Sensitivity analysis was carried out using the leave one-out approach.

3. Results

3.1. Study selection and characteristics

There were 296 papers in the initial literature search. 214 articles were removed through duplicates checking. According to inclusion and exclusion criteria, four studies were excluded for non-human research and no control group. Finally, three RCTs [13–15] and three non-RCTs [16–18] were included in our study. The reference lists of all the studies were also reviewed. The flowchart process of screened and selected trials was presented in Fig. 1. Patients' characteristics were reported in Table 1. All six papers discussed the application of ESWT for treatment of knee OA. A total of 589 patients were included in the present study (290 in ESWT group, 299 in control group). The mean age of the participants ranged from 58 to 70 years. In addition, the follow-up of enrolled studies ranged from 12 to 24 weeks.

3.2. Risk of bias

The risk of bias of RCTs was independently evaluated by two reviewers according to the Cochrane Collaboration for Systematic Reviews. All RCTs reported the detailed methods of random sequence generation and allocation concealments. The participants and personnel were blinded in two RCTs. Only one study attempted to blind the assessor. In addition, full details of withdrawals and dropouts were described in all studies. The risk of bias item for each included study was displayed in Fig. 2. The methodological quality assessment following the NOS for non-RCTs were presented in Table 2.

3.3. Pain score at 4 weeks

All the trials included in our study compare the pain score at 4 weeks between ESWT groups and control groups. There was no significant heterogeneity ($I^2 = 0\%$, $P = 0.441$) and a fixed-effect model was adopted. The present meta-analysis demonstrated that ESWT was associated a significant reduction of pain score at 4 weeks (WMD = -0.436 ; 95% CI = -0.604 to -0.269 ; $P < 0.001$, Fig. 3).

3.4. Pain score at 8 weeks

Four studies reported the pain score at 8 weeks after treatment. Pooled analyses were performed by using a fixed-effect model as there was no heterogeneity ($I^2 = 0\%$, $P = 0.663$). The results showed that there was significant difference between the ESWT groups and control groups in terms of pain score at 8 weeks (WMD = -0.234 ; 95%

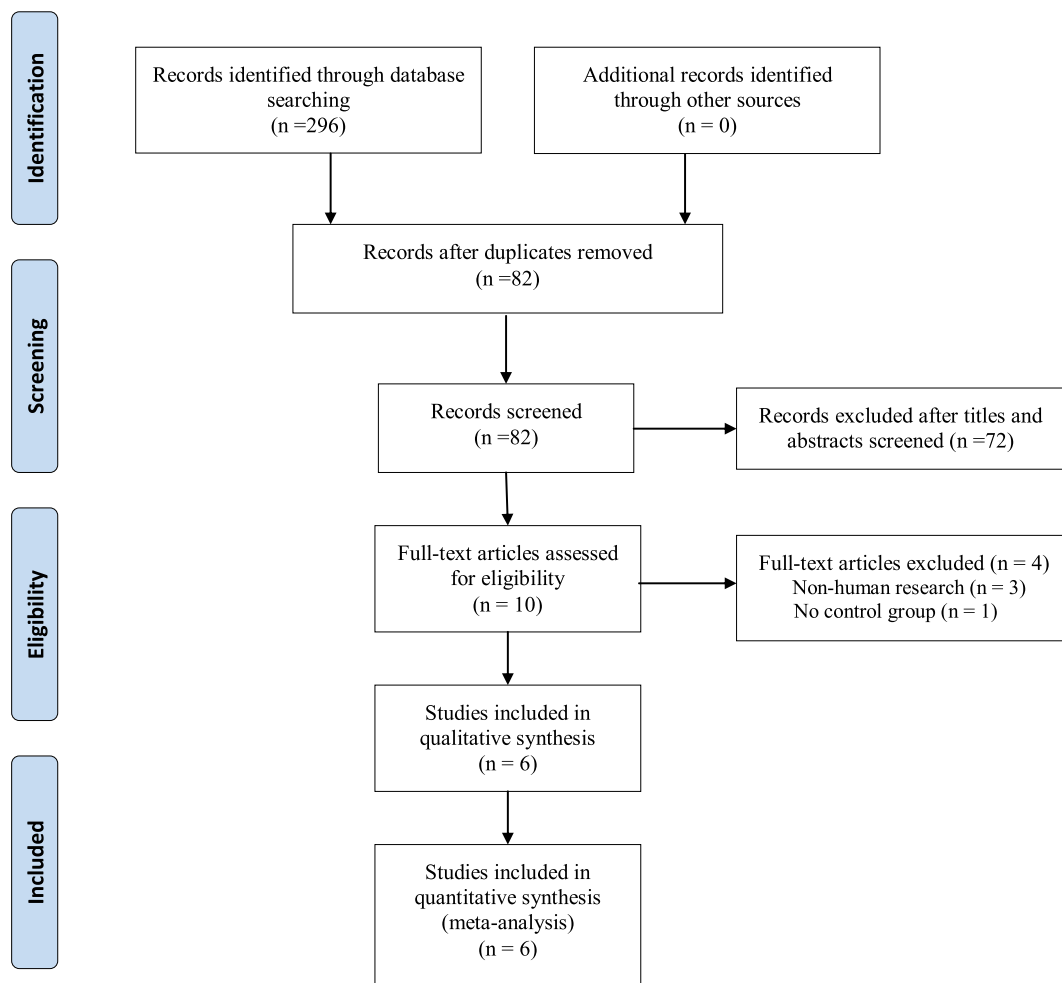


Fig. 1. Flow diagram of the included studies.

CI = -0.447 to -0.022 ; $P = 0.031$, Fig. 4).

3.5. Pain score at 12 weeks

A total of five studies reported the pain score at 12 weeks. No significant difference was found and a fixed-effect model was used ($I^2 = 0\%$, $P = 0.676$). The present meta-analysis indicated that ESWT demonstrated significantly lower pain score at 12 weeks compared with the controls (WMD = -0.239 ; 95% CI = -0.436 to -0.043 ; $P = 0.017$, Fig. 5).

3.6. WOMAC score at 4 weeks

WOMAC score at 4 weeks were collected from five studies, involving 529 knees. Pooled results indicated there was significant difference between groups (WMD = -3.107 ; 95% CI = -5.073 to -1.142 ; $P = 0.002$, Fig. 6). A fixed-effect model was applied ($I^2 = 0\%$, $P = 0.745$).

3.7. WOMAC score at 8 weeks

Four trials involving 466 participants reported the WOMAC score at 8 weeks. Compared with control, ESWT was associated with an improved WOMAC score at 4 weeks (WMD = -3.617 ; 95% CI = -5.760 to -1.475 ; $P = 0.001$, Fig. 7). No statistical heterogeneity was observed across trials ($I^2 = 0\%$, $P = 0.678$).

3.8. WOMAC score at 12 weeks

Five studies reported the outcome of WOMAC score at 12 weeks. There was no significant heterogeneity and a fixed-effect model was adopted ($I^2 = 0\%$, $P = 0.835$). Our study demonstrated that ESWT demonstrated significantly lower WOMAC score at 12 weeks compared with the controls (WMD = -2.271 ; 95% CI = -3.875 to -0.667 ; $P = 0.006$, Fig. 8).

3.9. Lequesne index

Three studies showed the Lequesne index after treatment. There was significant heterogeneity among studies and a random-effect model was adopted. No significant difference was found between the two groups (WMD = -1.335 ; 95% CI = -3.621 to 0.951 ; $P = 0.252$, Fig. 9).

3.10. Adverse effects

Five articles reported the adverse effects after ESWT, including reddening of skin and swelling. There was no significant heterogeneity and a fixed effect model was applied ($I^2 = 0\%$, $P = 0.488$). The present meta-analysis revealed that the application of ESWT did not increase the risk of adverse effects (RD = 0.008 , 95% CI: 0.014 to 0.029 , $P = 0.488$, Fig. 10).

3.11. Sensitivity analysis

Sensitivity analysis was performed by excluding one trial at a time

Table 1
Characteristics of the included RCTs.

Study	Year	Design	Sample size		Age	Gender (Male)		Intervention	Follow up	
			ESWT Control	ESWT Control		ESWT Control	ESWT Control			
Zhao et al.	2013	RCT	34	36	60	62	14	11	ESWT: Shockwaves of 4000 pulses in total were applied at 0.25 mJ/mm ² and a frequency of 6 Hz/s. Control: shockwave at 0 mJ/mm ² to the same area in the same manner.	12 weeks
Chen et al.	2014	RCT	30	30	62	64	12	13	ESWT: an impulse energy flux density of 0.03–0.4 mJ/mm ² (scaling from 1 to 20), a frequency of 1–8Hz and a pressure range of 11–82 MPa, 2000 impulses. Control: No Shockwaves therapy.	24 weeks
Imamura et al.	2017	Non-RCT	52	53	70	72	0	0	ESWT: 2000 impulses per session, positive energy flux density 0.10–0.16 mJ/mm ² . Impulses were applied at a frequency of 8 Hz. Control: placebo treatment in an identical manner to the ESWT treatments	12 weeks
Li et al.	2018	Non-RCT	60	45	60	59	38	27	ESWT: 3000 pulses of 0.11 mJ/mm ² at a frequency of 15Hz by using the Pain Treatment System of Radial Shockwave Device. Control: laser therapy.	12 weeks
Xu et al.	2019	Non-RCT	82	104	59	58	35	43	ESWT: 4000 pulses are applied at 2.0 bar, 0.25mJ/mm ² , and the frequency of 8 Hz/s. Control: oral administration of nonsteroidal anti-inflammatory drugs	24 weeks
Zhong et al.	2019	RCT	32	31	63	63	11	12	ESWT: 2000 pulses of 8 Hz frequency at 2.5 bars. Control: same physical therapist with the same ESWT protocol, but the air pressure was set at 0.2 bar.	12 weeks

RCT: randomized controlled trial, ESWT: extracorporeal shockwave therapy.

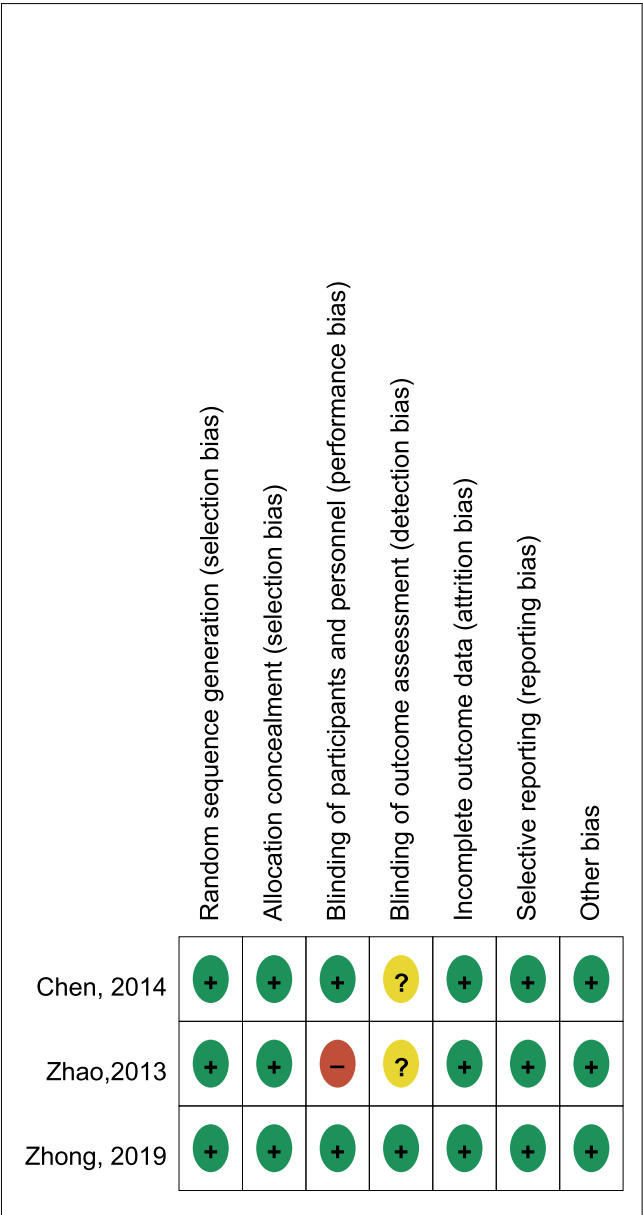


Fig. 2. Risk of bias summary of randomized controlled trials.

and recalculating the pooled WMD for the remaining trials, which showed that none of the studies affected the results (Fig. 11).

3.12. Quality of the evidence and recommendation strengths

Pain score and WOMAC score were assessed using the GRADE system. The overall evidence quality was low (Table 3). This finding may lower the confidence in any recommendations.

4. Discussion

This is the first meta-analysis to evaluate the efficacy and safety of ESWT for pain control in knee OA. The most interesting finding of the meta-analysis is that ESWT is associated a significant reduction of pain score at 4 weeks, 8 weeks and 12 weeks. There are significant differences between the two groups in terms of the Western Ontario and McMaster Universities Osteoarthritis Index at 4 weeks 8 weeks and 12 weeks.

Knee OA is the most common chronic degenerative joint disorder in

Table 2

Risk of bias was assessed using the Newcastle–Ottawa Scale. A higher overall score indicates a lower risk of bias; a score of 5 or less (out of 9) corresponds to a high risk of bias.

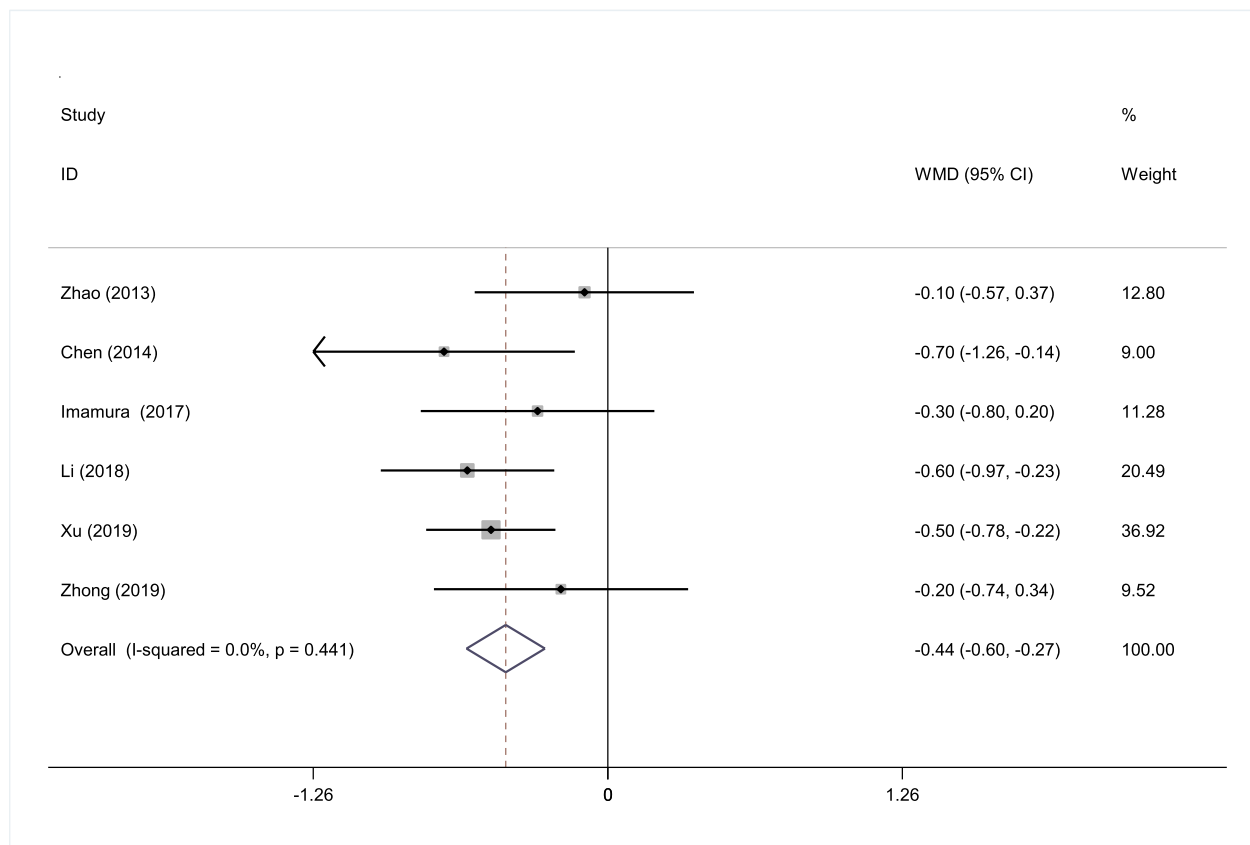
Study	Selection					Outcome			Total score
	Exposed cohort	No exposed cohort	Ascertainment of exposed	Outcome of interest	Comparability	Assessment of outcome	Length of follow up	Adequacy of follow-up	
Imamura et al.	*	*	*	*	*	*	*	–	7
Li et al.	*	*	*	*	*	*	*	*	8
Xu et al.	*	*	*	*	*	*	*	*	8

the clinical, which causes arthritic symptoms, such as joint pain, stiffness, limitations in movement and loss of functions. Worldwide estimates are that 9.6% of men and 18.0% of women aged over 60 years have symptomatic OA [19]. Conservative treatment is the first choice for early-stage OA including peri-articular injection of agents (non-steroidal anti-inflammatory drugs, glucocorticoids, glucosamine, hyaluronic acid), traditional Chinese medicine physiotherapy and the use of braces and orthotics. Previous studies have indicated that the use of drugs was associated with adverse events, including infection, erythra, gastric ulcer and even accelerating the degenerative process [20]. However, a majority of patients develop into end-stage OA and total knee arthroplasty is an ultimate treatment to reduce pain and improve joint function. It is reported that more than 640,000 procedures performed annually, costing about \$10.2bn (£8.3bn, €9.6bn) [21]. Although surgical procedure is effective, it was not suitable for older patients with limiting comorbidities.

ESWT is a non-invasive method, which has been widely used for treating knee OA in recent years. Zhao et al. [14] first reported the application of ESWT in knee OA and demonstrated that ESWT was effective and safe in reducing pain and improving knee function. Cartilage damage is the essential pathological changes for the development

of degenerative knee joint disorder. ESWT appears to regulate the inflammatory process and to promote bone repair process, as well as neovascularization and tissue regeneration. Zhao et al. [22] reported that ESWT significantly reduced the NO level in the synovial cavity of knee joints and chondrocyte apoptosis of rabbits with OA, which revealed that ESWT may be used as an alternative treatment for knee OA. Kang et al. [23] indicated that ESWT is an effective, reliable, and noninvasive treatment in patients with painful bone marrow edema in osteoarthritis of the knee. It has the potential to shorten the natural course of this disease. However, whether ESWT was effective for pain management in patients with knee OA remains controversial due to the limited data. In our study, six studies with 589 patients reported the pain score. The combined data showed that ESWT was associated with a significant reduction of pain score within 12 weeks after treatment.

Functional recovery of knee joint is an important parameter to evaluate the efficacy of various treatments. Patients with knee OA suffered joint stiffness and resulting in impaired range of motion. The mechanisms of action of ESWT on OA are complex and may include inhibiting afferent pain-receptor function and be affected by cartilaginous and noncartilaginous structures in the joint, allowing the significant reduction of activity limitations [24]. Shockwave therapy has

**Fig. 3.** Forest plot of pain score at 4 weeks.

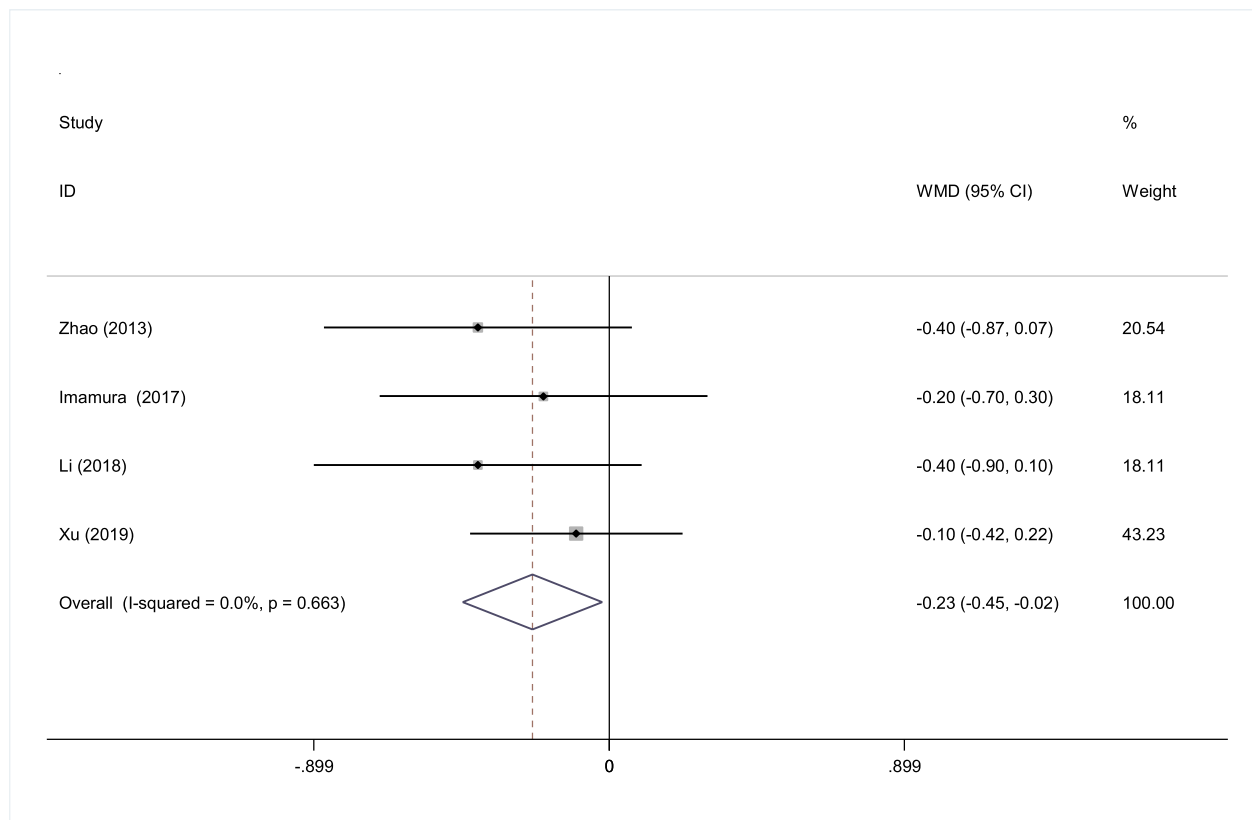


Fig. 4. Forest plot of pain score at 8 weeks.

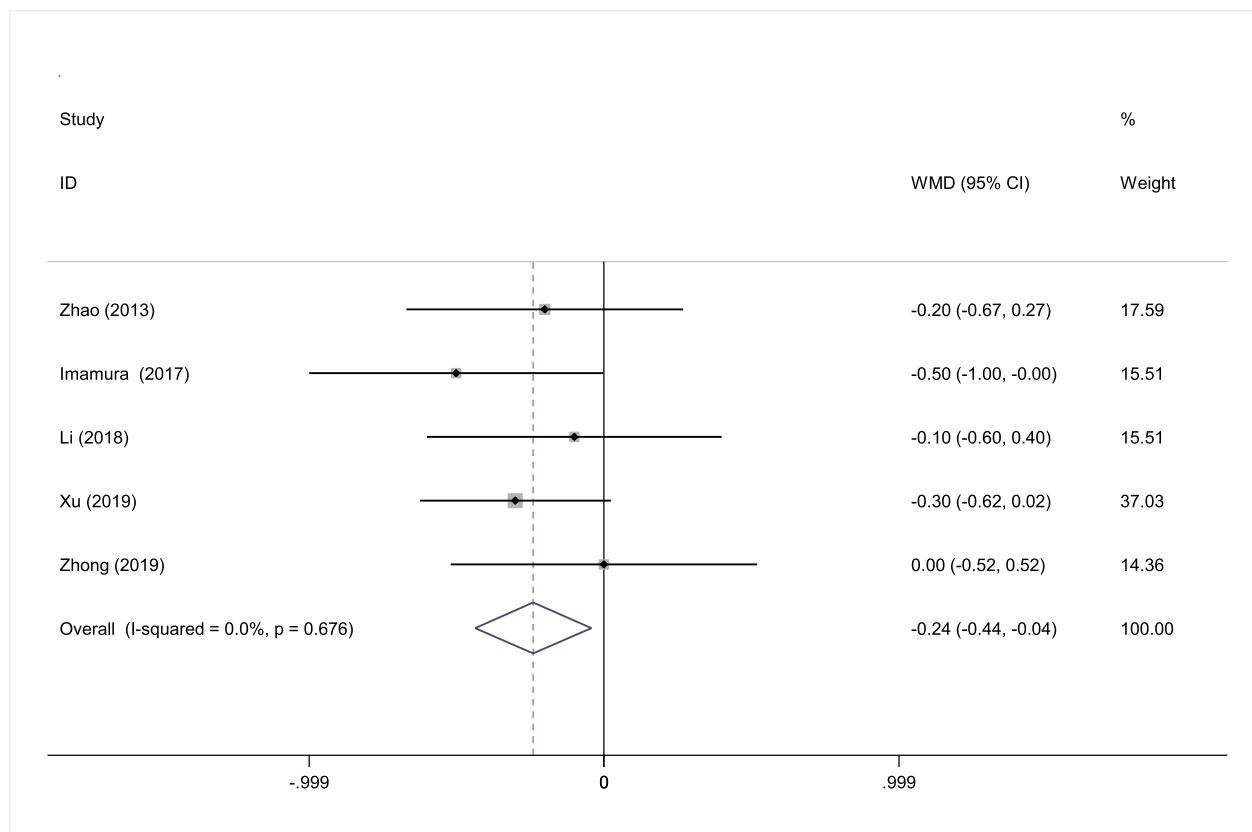


Fig. 5. Forest plot of pain score at 12 weeks.

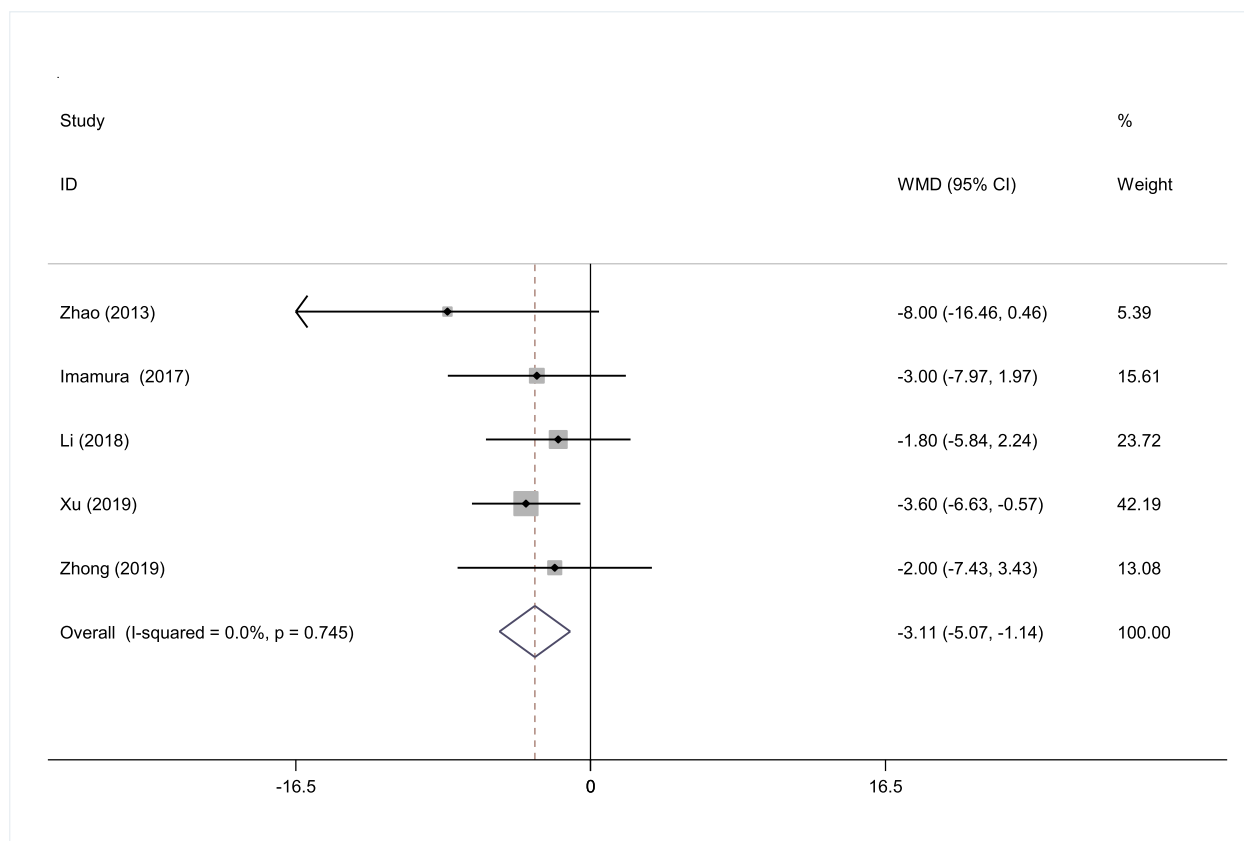


Fig. 6. Forest plot of WOMAC score at 4 weeks.

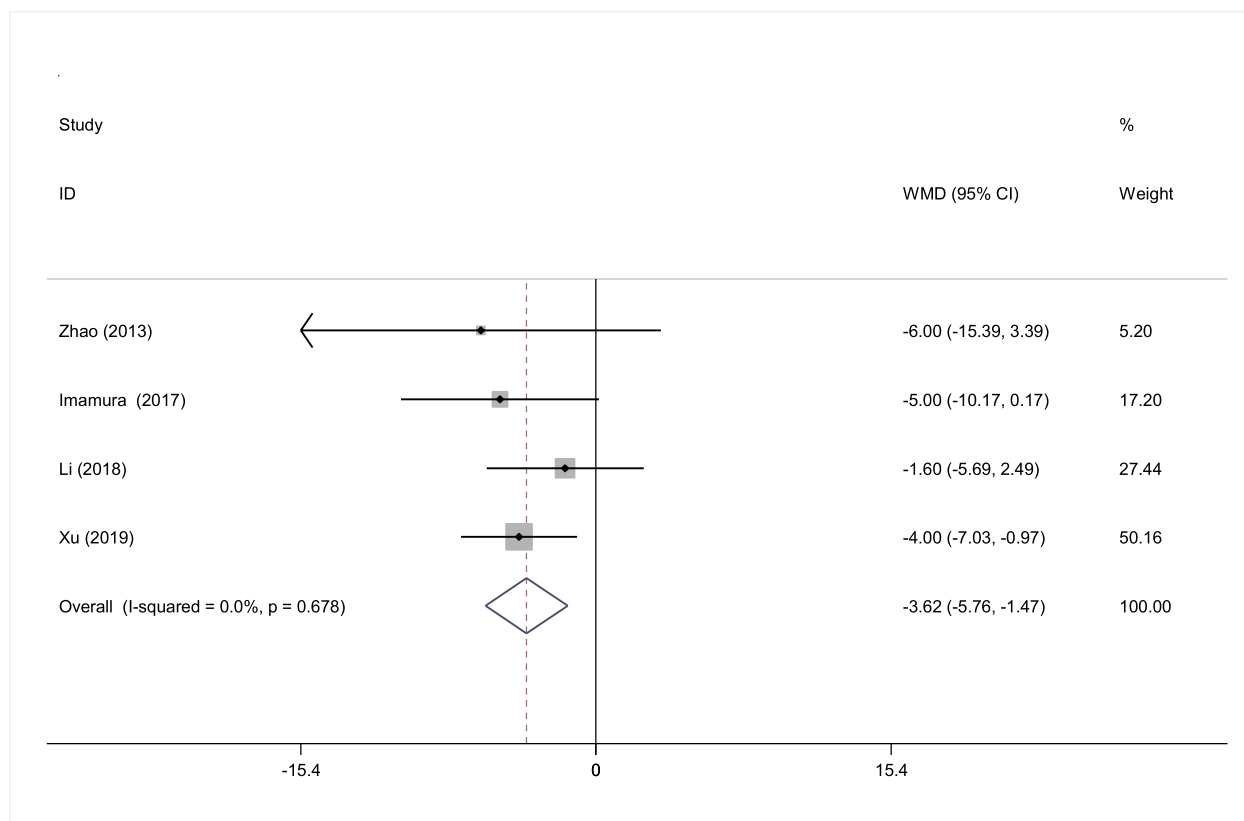


Fig. 7. Forest plot of WOMAC score at 8 weeks.

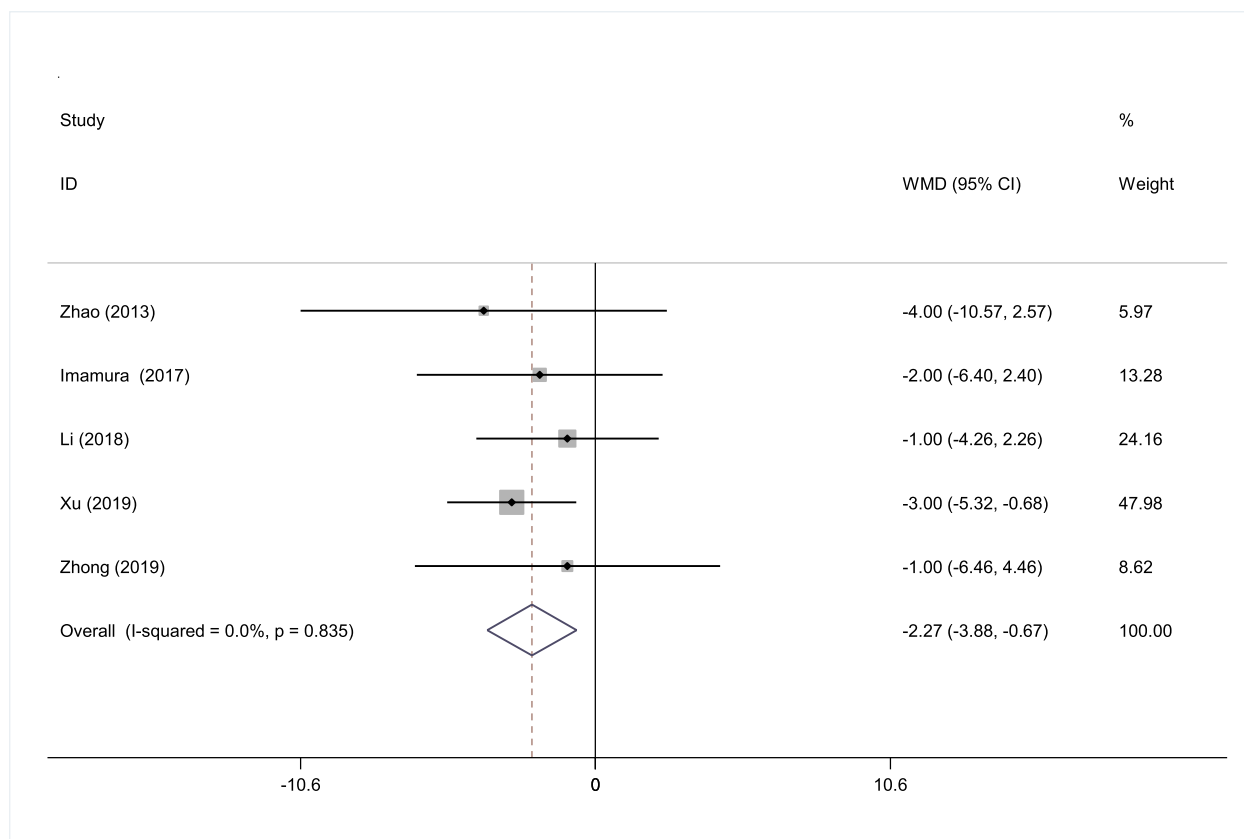


Fig. 8. Forest plot of WOMAC score at 12 weeks.

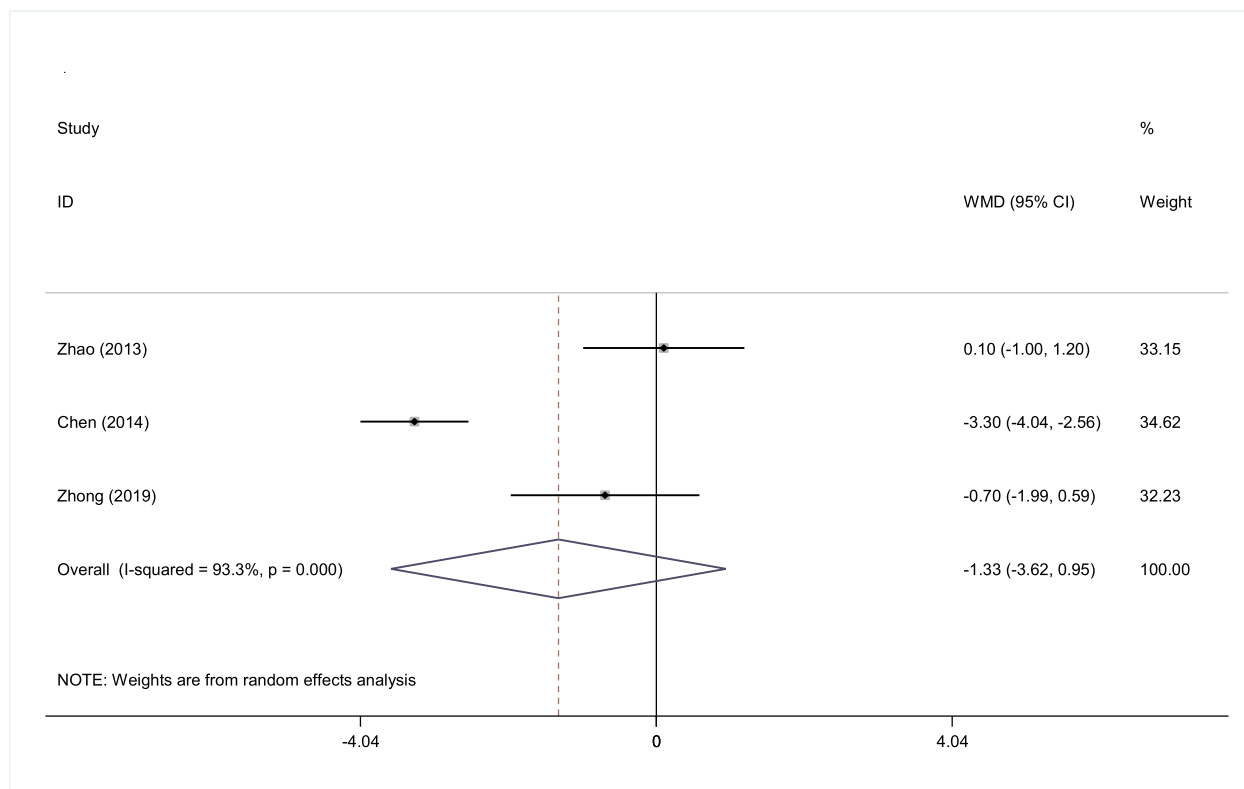


Fig. 9. Forest plot of Lequesne index.

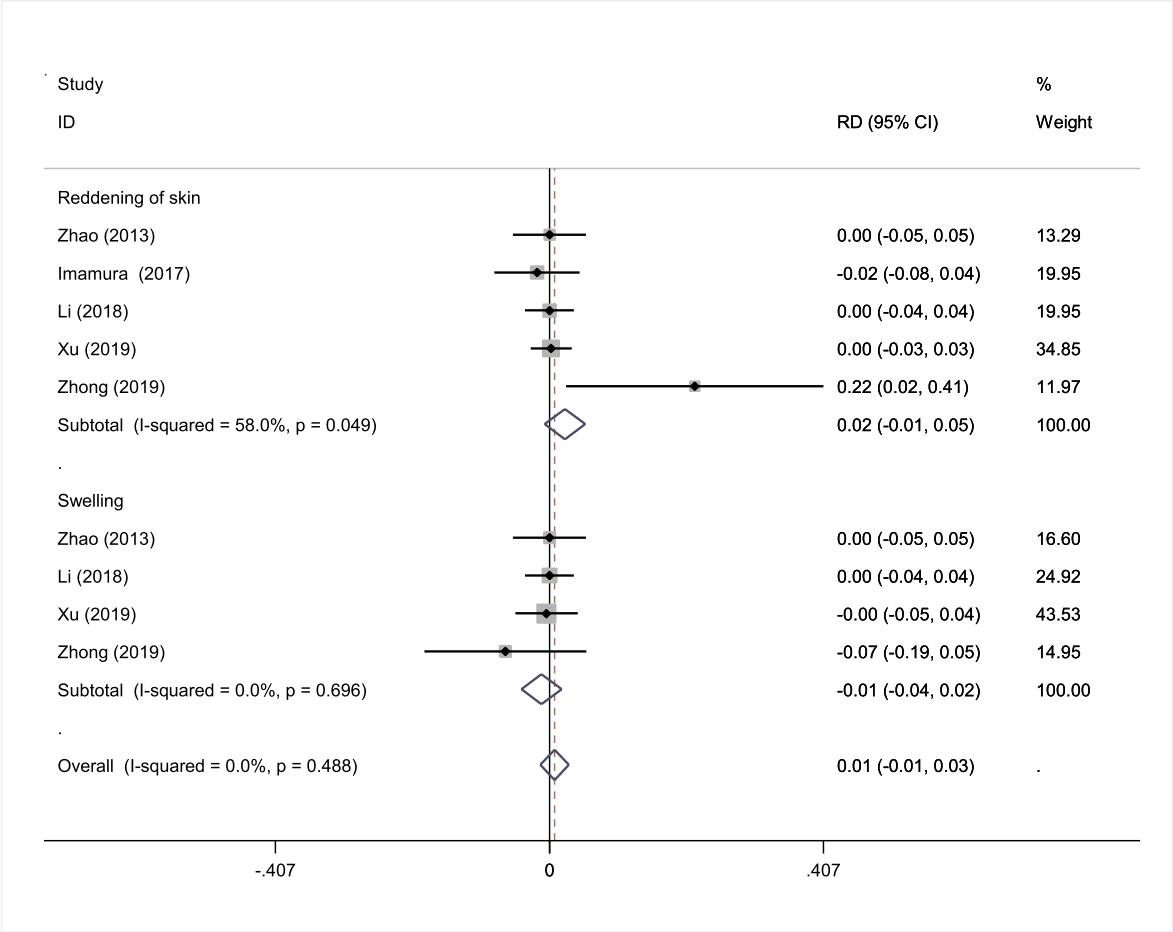


Fig. 10. Forest plot of adverse effects.

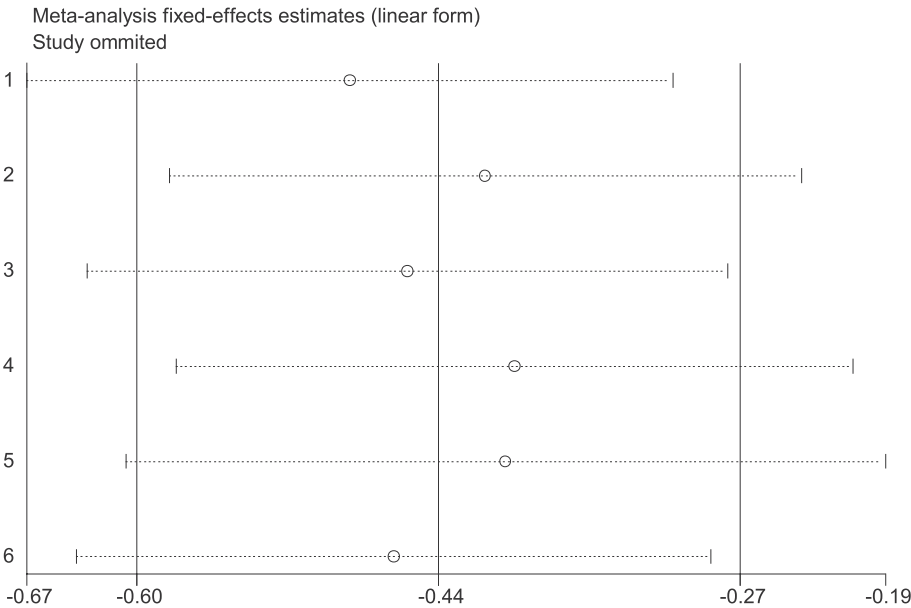


Fig. 11. Sensitivity analysis.

the mechanical effect and this may have increased the blood and lymph flow, which accelerates cartilage repair and subcartilage bone remodeling. These circulatory changes may also result in enhanced muscle function and increase active range of motion. Besides, anti-inflammation effects may further increase extensibility and flexibility,

leading to increased joint range of motion. Lizis et al. [25] reported that after the intervention the statistical significant between groups differences favoring the ESWT were found in the WOMAC with regard to physical function, extension and flexion of the affected knee respectively. Lee et al. [26] demonstrated that there was no significant

Table 3
The GRADE evidence quality for each outcome.

Quality assessment	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect	Quality	Importance
Outcomes						WMD/RD (95% CI)		
Pain score at 4 weeks	Serious	None serious	None serious	None serious	None	WMD = -0.436; 95% CI = -0.604 to -0.269	⊕○○○LOW	CRITICAL
Pain score at 8 weeks	Serious	None serious	None serious	None serious	None	WMD = -0.234; 95% CI = -0.447 to -0.022	⊕○○○LOW	CRITICAL
Pain score at 12 weeks	Serious	None serious	None serious	None serious	None	WMD = -0.239; 95% CI = -0.436 to -0.043	⊕○○○LOW	CRITICAL
WOMAC score at 4 weeks	Serious	None serious	None serious	None serious	None	WMD = -3.107; 95% CI = -5.073 to -1.142	⊕○○○LOW	CRITICAL
WOMAC score at 8 weeks	Serious	None serious	None serious	None serious	None	WMD = -3.617; 95% CI = -5.760 to -1.475	⊕○○○LOW	CRITICAL
WOMAC score at 12 weeks	Serious	None serious	None serious	None serious	None	WMD = -2.271; 95% CI = -3.875 to -0.667	⊕○○○LOW	CRITICAL
Lequesne index	Serious	None serious	None serious	None serious	None	WMD = -1.335; 95% CI = -3.621 to 0.951	⊕○○○LOW	IMPORTANT
Adverse effects	Serious	None serious	None serious	None serious	None	RD = 0.008; 95% CI = -0.014 to 0.029	⊕○○○LOW	IMPORTANT

difference between ESWT and intra-articular injections of hyaluronic acid regarding WOMAC score in patients with knee OA. In our study, five articles reported knee function using WOMAC score in this systematic review and meta-analysis, and pooled results showed that ESWT was associated with a significant improvement of knee function.

As is widely known, adverse effects is a major concern when evaluating the efficacy of ESWT. Therefore, the use of ESWT will hold less clinical value if there was a higher risk of adverse effects. Local reactions such as skin reddening and swelling are common. In our study, five articles reported the incidence of adverse effects after receiving ESWT. The present meta-analysis indicated that ESWT did not increase the risk of local reactions. In addition, other adverse events were also recorded in this study, all of them were mild and no further intervention was performed. Considering the small sample size of the included studies, the safety of ESWT should be further discussed.

Some limitations of this study should be noted [1]: The small sample size may have affected the significant difference between the two interventions [2]. There are few RCTs in the meta-analysis, and statistical tests might be insufficient [3]. Parameter of ESWT differs from each other and therapeutic effects may be affected [4]. Heterogeneity among the included studies was unavoidable by a variety of factors, such as age, gender, racial differences and analgesia methods [5]. Different bias including selection bias, language bias, bias in provision of data, and publication bias may have reduced the efficiency of the results.

5. Conclusion

The ESWT was efficacious and safe for reducing pain and improving knee function in patients with knee osteoarthritis, without increasing the risk of adverse effects.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

No Ethical Approval was given because this is a meta-analysis.

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This work was not supported by funding.

Author contribution

Huanzhi Ma: writing.
Wei Zhang: data collections.
Jun Shi: data analysis.
Dongsheng Zhou: figure and table edit.
Jian Wang: study design.

Trial registry number

Research registry.
Unique Identifying Number (UIN): reviewregistry713.
<https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/5d144e9b5ba22b000b7b377d/>

Guarantor

Jian Wang.

Data statement

The current data is extracted from published studies, so we think that all data is accurate.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijssu.2020.01.017>.

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