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Effects of low-intensity pulsed ultrasound on knee osteoarthritis: A systematic review and meta-analysis of randomized controlled trials

Haoqian Chen[1,2], Zheng Wang[3], Xinan Zhang[3], and Mingli Sun[3]

Abstract

Objective: To systemically review the effects of low-intensity pulsed ultrasound (LIPUS) on pain relief and functional recovery in patients with knee osteoarthritis (KOA).

Data sources: PubMed, Web of Science, Cochrane Library, Physiotherapy Evidence Database (PEDro), and China National Knowledge Infrastructure (CNKI) were used from inception to 18 March 2022.

Review Methods: Meta-analysis was performed to evaluate pain and function recovery between control and LIPUS groups. Standardized mean difference (SMD) or mean difference (MD) and 95% confidence interval (CI) were calculated, and data were combined using the fixed or random-effect model.

Results: Thirteen studies involving 807 patients with KOA were included. Patients' outcomes treated by LIPUS were improved significantly, including Visual analog scale (VAS) score (MD = −0.95, 95% CI: −1.43 to −0.48, $P < 0.001$), Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) score (MD = −4.35, 95% CI: −8.30 to −0.40, $P = 0.0309$), Lysholm score (SMD = 1.59, 95% CI: 1.29 to 1.90, $P < 0.001$), Lequesne index (MD = −1.33, 95% CI: −1.69 to −0.96, $P < 0.001$), Range of motion (ROM) (MD = 2.43, 95% CI: 0.39 to 4.46, $P = 0.0197$) and 50 meter walking time (SMD = 1.48, 95% CI: 0.46 to 2.49, $P = 0.0044$). Subgroup analyses showed monotherapy of LIPUS produced a better effect on reducing VAS score ($P = 0.0213$), and the shorter therapeutic period (≤4 weeks) produced a more significant effect on raising the WOMAC score ($P = 0.0083$).

Conclusion: LIPUS was beneficial for pain relief and functional knee recovery and maybe as an alternative therapy in KOA rehabilitation.

[1]Graduate Students' Affairs Department, Shenyang Sport University, Shen-yang, China
[2]Sports Training College, Shenyang Sport University, Shen-yang, China
[3]College of Kinesiology, Shenyang Sport University, Shen-yang, China

Corresponding authors:
Mingli Sun, College of Kinesiology, Shenyang Sport University, No.36 Jinqiansong East Road, Sujiatun District, Shen-yang, Liaoning Province, 110102, China
Email: sun18940103126@163.com

Xinan Zhang, College of Kinesiology, Shenyang Sport University, No.36 Jinqiansong East Road, Sujiatun District, Shen-yang, Liaoning Province, 110102, China.
Email: zhangxa2725@163.com

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Introduction

Knee osteoarthritis (KOA) is a common degenerative knee joint disease, causing joint pain, stiffness, swelling, muscle weakness, loss of physical function, and even disability.[1] The number of KOA patients has increased with population aging, seriously affecting patients' quality of life and significantly burdens society.

Until now, medical therapy for KOA includes surgical therapies and nonsurgical therapies. Total knee arthroplasty is the definitive therapy for KOA. Before surgery, some nonsurgical therapies could relieve pain and promote functional recovery. Nonsurgical therapies include pharmacological and non-pharmacological approaches. Pharmacological approaches refer to analgesic drugs and supplements for promoting cartilage repair.[2–4] However, these drugs often have lower curative effects and some serious side effects. Exercise, weight loss, and physical factors are mainly non-pharmacological treatments, but exercise and weight loss have poor compliance.[5, 6] In recent years, physicians have paid increasing attention to physical factors therapies, including ultrasound, laser therapy, and electroanalgesia, to manage osteoarthritis.[7–12]low-intensity pulsed ultrasound (LIPUS), one kind of therapeutic ultrasound, has been approved to treat fresh fracture and nonunion for more than 20 years in the United States. In recent years, the effect of LIPUS on osteoarthritis has been discussed by various studies.[13] A systematic review published in 2018 and five randomized controlled trials showed that LIPUS played a beneficial role in pain relief and functional recovery and had no adverse effects on KOA patients. However, the number of trials is limited, with heterogeneity but no subgroup analysis.[14] Another systematic review published in 2019 only assessed the effect of LIPUS therapeutic ultrasound on the pain in patients with KOA.[15]

Fortunately, in recent years, high-quality randomized controlled trials have evaluated the impact of LIPUS on the treatment effect of KOA. Therefore, based on relevant studies, we designed and updated a meta-analysis to comprehensively analyze and determine the efficacy of LIPUS on KOA.

Methods

This meta-analysis met the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[16] The International Open Science Framework Registry Link is https://doi.org/10.17605/OSF.IO/FHSD9. The scientific research funding project from the Department of Education of Liaoning Province (LJKZ1048) supported this work.

Electronic literature searches were conducted on PubMed, Web of Science, Cochrane Library, Physiotherapy Evidence Database (PEDro), and China National Knowledge Infrastructure (CNKI) from their inception to 18 March 2022. We searched the keywords "Low-Intensity Pulsed Ultrasound," "Knee Osteoarthritis," and corresponding retrieved terms of Medical Subject Headings (MeSH). Each keyword and corresponding Medical Subject Headings term were combined with OR operator and two keywords with AND operator. The language was restricted to English and Chinese. We also screened the reference lists of the papers identified in database searches. The search strategy for each database was shown in Appendix 1.

The inclusion criteria based on the PICOS framework[17] (population, intervention, comparison, outcome, and study) are as follows: (1) Randomized controlled trials; (2) At least one group in the study using LIPUS as an intervention; (3) Outcomes reflecting efficacy (including symptoms, outcome measures); (4) Papers in English and Chinese; (5) Randomized controlled trials

studies at a high methodological quality (Jadad score > 3)[18]; (6) Studies with follow-up.

The following were the exclusion criteria: (1) Experimental studies (for example, animal studies); (2) A cohort study, case-control, or cross-sectional study; review articles, or conference abstracts; (3) Studies whose full text is not available or studies with no data available; and (4) randomized controlled trials studies at a low methodological quality (Jadad score $\leq$ 3).[18]

Following a systematic search, the retrieved articles were screened by two independent reviewers (HQC and ZW) for eligibility based on the inclusion criteria described below to determine whether the article title and abstract met the criteria. After excluding articles that did not meet the criteria, those likely to meet the criteria were read in detail and assessed in detail for final inclusion.

Two reviewers (HQC and ZW) independently extracted the data. The following data were extracted from the included articles: First author and year of publication; Characteristics of the subject (country or region, age, and gender of the participants); Intervention and Comparison group; LIPUS treatment parameters; Grading criteria for knee osteoarthritis; Outcome measurements; and Follow-up.

According to the Cochrane Collaboration, two reviewers (HQC and ZW) independently assessed the risk of the bias of the included studies.[19] The assessment involved six items (selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias). The associated risks were divided into unclear, low, and high. Any differences or discrepancies that exist were discussed or resolved by a third reviewer (MLS). Moreover, these have been agreed upon by researchers before.

Data from the included studies were analyzed using The R Programming Language × 64 4.0.5 software (R Development Core Team, Vienna, Austria).[20,21] The package (University of Freiburg, Germany) commands of "meta" and " metacont" called under R software were used to calculate the overall effect size, the forest plot is represented by "forest," and the publication bias is represented by "funnel" and "metabias".[22–24] For continuous outcomes with different scoring units or a big difference in the mean between different studies, each outcome metric's estimated effect size was pooled using a standardized mean difference (SMD) with a 95% CI. Continuous results had the same score, and the unit estimated effect size used the mean difference (MD) with a 95% CI to summarize each outcome indicator. I^2 test was used to evaluate the statistical heterogeneity, and the low heterogeneity $I^2 \leq 25\%$; Moderate heterogeneity $25\% < I^2 < 50\%$; significant heterogeneity $50\% < I^2 < 75\%$; High heterogeneity $I^2 \geq 75\%$.[25] When $I^2 < 50\%$, $P > 0.1$, the fixed-effect model was used for the summary mean difference evaluation of 95% CI, on the contrary, the random effect model was used.[26,27]

In addition, subgroup analysis and sensitivity analysis were performed to identify potential determinants of efficacy and heterogeneity,respectively. Furthermore, the potential publication bias was tested using Egger's test.[28] $P < 0.05$ was considered statistically significant.

Result

The flow diagram of the article screening process is shown in Figure 1. The search strategy proposed retrieved 213 documents. After the whole selection process, 37 articles were included in the systematic review, of which 13 studies with 807 subjects were included in the meta-analysis for statistical comparison.[29–41] The characteristics of the included studies are shown in Table 1.

Three studies in the intervention group used LIPUS as monotherapy regarding the interventions.[31,32,35] And ten studies used it as a combination therapy.[29,30,33,34,36–41] The outcome indicators of the included studies were: the Visual analog scale score, the Western Ontario and McMaster Universities Osteoarthritis Index score, the Lysholm score, the Lequesne index, Range of motion, 20 meters and 50 meters walking time. The follow-up period ranged from 2 weeks to 1 year. The overall bias of the included studies is shown in Figure 2.

Twelve studies with 783 participants reported the effects of different interventions on the Visual analog scale score outcome. As shown in Figure 3.[29–31,33–41] The synthesized data indicated that the intervention group had significantly

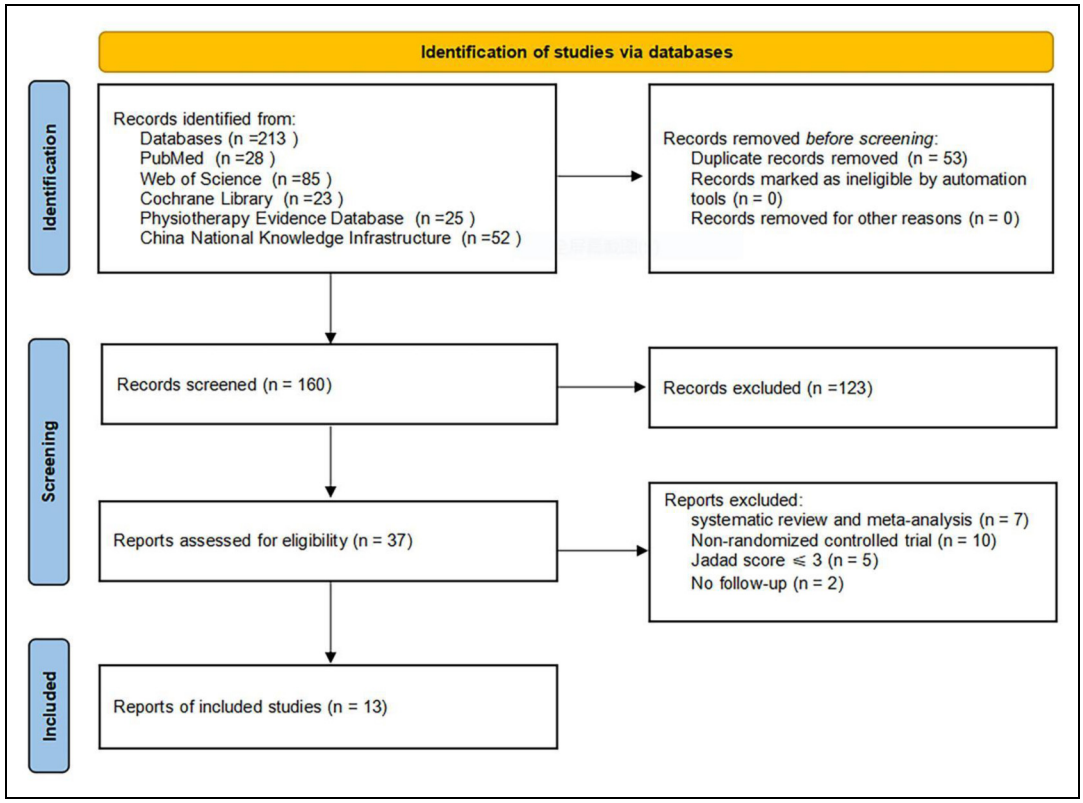

Figure 1. Flowchart for the selection of included trials.

alleviated pain as compared with a comparison group (MD = −0.95, 95% CI: −1.43 to −0.48, $P < 0.001$), and a random-effect model was used because of a substantial heterogeneity for this synthesized outcome ($I^2 = 86.6\%$). For the subgroups of trials with therapeutic periods of ≤ 4 weeks and > 4 weeks, no differences in pain relief were found when comparing the effect between them ($P = 0.6443$), and all subgroups show heterogeneity ($I^2 > 50\%$). The comparison between subgroups in the therapeutic protocol showed that LIPUS monotherapy produced a more significant effect on pain relief (MD = −1.96, 95% CI: −2.79 to −1.14, $P = 0.0213$), and all subgroups show heterogeneity ($I^2 > 60\%$). In the subgroup analysis for the duration time of every therapy, no significant differences in pain relief were found between groups ($P = 0.7619$). The longer duration time (≥20 min) shows high heterogeneity ($I^2 = 92.9\%$), while the shorter duration time (< 20 min) shows moderate significant heterogeneity ($I^2 = 49.8\%$). Subgroup analysis is shown in Table 2.

Six studies with 341 participants reported the effects of different interventions on the Western Ontario and McMaster Universities Osteoarthritis Index score, as shown in Figure 4A.[31,32,36,37,40,41] The synthesized data indicated that the intervention group had significantly promoted the functional recovery as compared with a comparison group (MD = −4.35, 95% CI: −8.30 to −0.40, $P = 0.0309$), and a random-effect model was used because of a substantial heterogeneity for this synthesized outcome ($I^2 = 56.5\%$). The comparison between subgroups of trials with therapeutic periods of ≤4 weeks and > 4 weeks showed that the shorter therapeutic period (≤4 weeks) produced a more significant effect on reducing the Western Ontario and McMaster Universities Osteoarthritis Index score ($P = 0.0083$).

Table 1. Characteristics of eligible randomized controlled trials included in the meta-analysis.

First author-Year	Characteristics of subject	Intervention group (I) Comparison group (C)	LIPUS parameter	Treatment duration	Joint Kellgren and Lawrence class rating	Outcome measurements	Follow-up
Huang[29] -2005	Taiwan, China Age: 40-77 years M/F: 113/27	(I) LIPUS + Isokinetic exercises n = 35 (C) Isokinetic exercises n = 35	1MHZ,2.5W/cm^2	5 min/ 3 times a week 8 weeks	Knee (Altman grade II)	①②⑩⑬⑯	1 year
Huang[30] -2005	Taiwan, China Age: 42-72 years M/F: 20/100	(I) LIPUS + Isokinetic exercises n = 30 (C) Isokinetic exercises n = 30	1MHZ, 2.5W/cm^2	5 min/ 3 times a week 8 weeks	Knee (Altman grade II)	①②⑩⑬⑯	1 year
Tascioglu[31] -2010	Turkey Age: 54-70 years M/F: 25/56	(I) LIPUS n = 28 (C) Sham LIPUS + Placebo n = 27	1MHZ, 2W/cm^2	5 min/ 5 times a week 2 weeks	Knee, 2-3	①④⑮	2 weeks
Loyola[32] -2012	Canada Age:≥45 years M/F: 21/27	(I) LIPUS n = 13 (C) Sham LIPUS n = 14	1MHZ, 0.2W/cm^2 112.5J/cm^2	3 times a week, 8 weeks	Knee (OARSI-Medical JSN, grade 1 or 2)	④⑭	2 months
Li[33] -2013	China Age: 39-72 years M/F: 32/76	(I) LIPUS + Sodium hyaluronate n = 30 (C) Sodium hyaluronate n = 30	1MHZ	35 min/ the first week 20 min/the next 4 weeks 3 times a week 8 weeks	Knee, 1-3	①②	5 weeks
Cakir[34] -2014	Turkey Age: 40-80	(I) LIPUS + Self-discipline n = 20	1MHZ, 1W/cm^2	12 min/ 5 times a week 2 weeks	Knee, 2-3	①④⑮	6 months

(Continued)

Table 1. (Continued)

First author-Year	Characteristics of subject	Intervention group (I) Comparison group (C)	LIPUS parameter	Treatment duration	Joint Kellgren and Lawrence class rating	Outcome measurements	Follow-up
	years M/F: 13/47	(C) Sham LIPUS + Self-discipline n = 20					
Yildiz[35] -2015	Turkey Age: 40-65 years M/F: 15/75	(I) LIPUS n = 30 (C) Sham LIPUS + Placebo n = 30	1MHZ, 1.5W/cm^2	5 min/ 5 times a week 2 weeks	Knee, 2-3	①②⑩	2 months
Gao[36] -2016	China Age: 25-45 years M/F: 32/76	(I) LIPUS + NSAID (a) n = 20 (C) NSAID (a) n = 20	3MHZ, 40mW/cm^2	20 min/ 6 times a week 6 weeks	Knee (ICRS, grades I-II)	①③④⑪	6 weeks
Jia[37] -2016	China Age:≥40 years M/F: 30/76	(I) LIPUS + NSAID (b) n = 53 (C) NSAID (b) n = 53	0.6 MHZ, 120mW/cm^2 a pulse repetition frequency 300HZ	20 min/ 1 time a day 10 times in 2 weeks	Knee, 2-3	①②④⑤⑩⑬	12 weeks
Cheng[38] -2019	China Age: 43-71 years M/F: 45/56	LIPUS + NSAID (b) n = 52 (C) NSAID (b) n = 52	3MHZ, 40mW/cm^2 0.6MHZ,30mW/cm^2	40 min, 4 weeks	unclear	①③⑥⑦⑧	4 weeks
Luo[39] -2019	China Age:≥40 years M/F: 25/50	(I) LIPUS + NSAID (b) n = 36 (C) NSAID (b) n = 39	3MHZ,40mW/cm^2 0.6MHZ,30mW/cm^2	40 min, 8 weeks	Knee, 1-3	①②③	8 weeks
Kim[40] -2019	Korea Age: 25-45 years M/F: 32/76	(I) LIPUS + TENs n = 19 (C) TENs n = 19	1MHZ, 0.1W/cm^2	20 min,≤3 times a day, >10 times a week, 8 weeks	Knee, 1-4	①④⑤⑫	1 month

(Continued)

Table 1. (Continued)

First author-Year	Characteristics of subject	Intervention group (I) Comparison group (C)	LIPUS parameter	Treatment duration	Joint Kellgren and Lawrence class rating	Outcome measurements	Follow-up
Karakas[41] -2020	Turkey Age:≥40 years M/F: 12/63	(I) LIPUS + Self-discipline n = 36 (C) Sham LIPUS + Self-discipline n = 36	1MHZ, 1W/cm^2	10 min, 3 times a week 8 weeks	Knee, 2-3	①④⑨	12 weeks

LIPUS: low-intensity pulsed ultrasound, TENs: Transcutaneous Electrical Nerve Stimulation, (I): Intervention group, (c): Comparison group, M: male, F: female, NSAID: non-steroidal anti-inflammatory drug, NSAID (a): Celecoxib capsules NSAID (b): Diclofenac sodium sustained-release tablets, n: participants, OARSI: Osteoarthritis Research Society International, JSN: joint space narrowing, ICRS: International cartilage repair society.
①Visual analog scale (VAS) ②Lequesne index ③Lysholm score ④Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score ⑤short form 36 item general health questionnaire (SF-36) ⑥Activity of daily living (ADL) ⑦Noyes articular cartilage defects ⑧score evaluation of clinical symptoms ⑨Timed up and go test (TUG) ⑩Range of motion (ROM) ⑪Magnetic Resonance Imaging (MRI) T2 weighted image ⑫Femoral articular cartilage (FAC) thickness⑬50 meters walking time ⑭6 min walk test⑮20 meters walking time ⑯muscle peak torques during knee flexion (MPT).

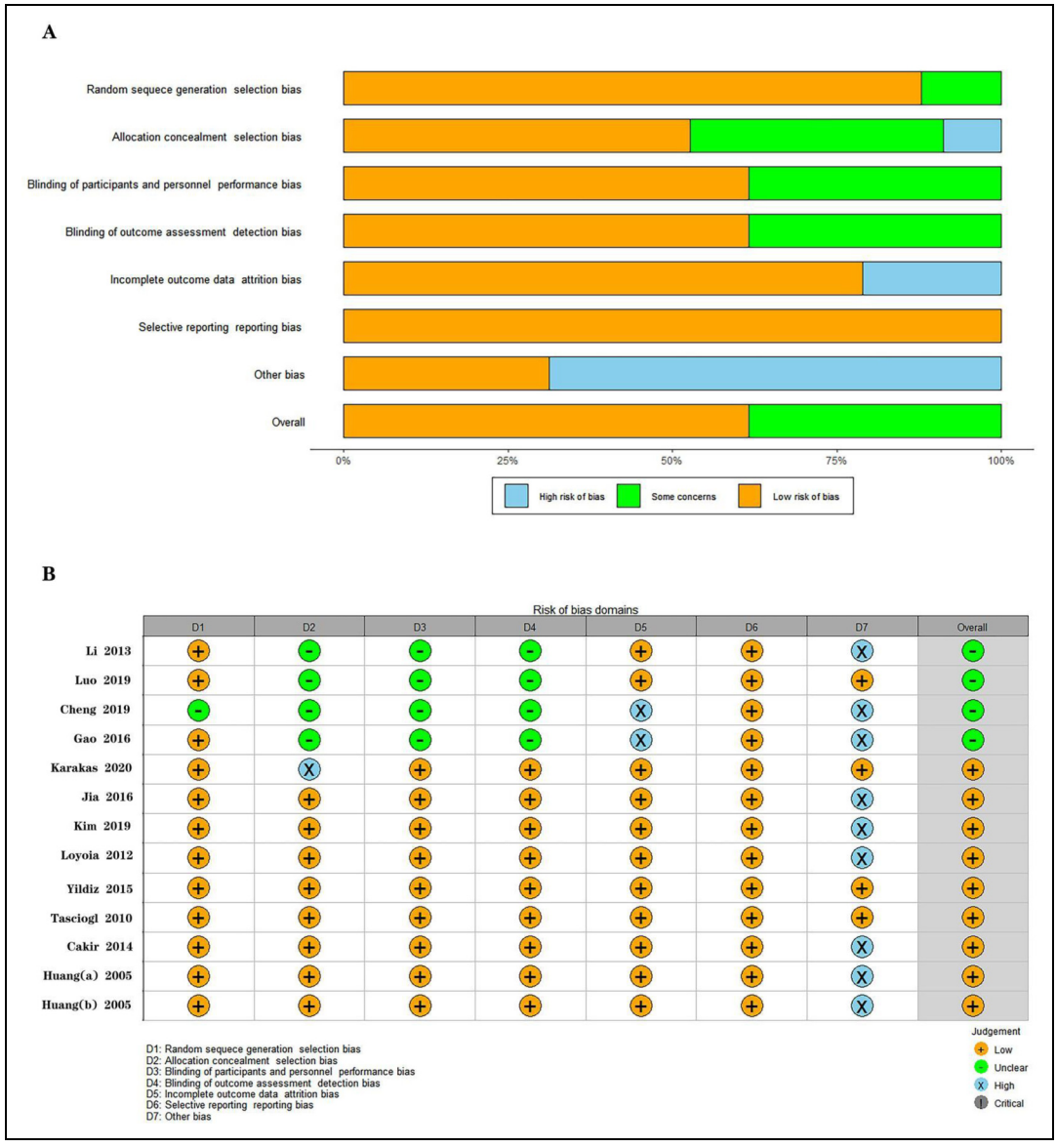

Figure 2. Risk of bias for the included randomized controlled trials. A.Risk of bias graph, B.Risk of bias summary.

The longer therapeutic periods (> 4 weeks) show no heterogeneity ($I^2 = 0.0\%$), and the shorter therapeutic periods (≤4 weeks) show moderate heterogeneity ($I^2 = 34.2\%$). In a subgroup analysis, there was no significant difference between the effects of LIPUS monotherapy, LIPUS combined with pharmacotherapy, and LIPUS combined with non-pharmacological treatment on the Western Ontario and McMaster Universities Osteoarthritis Index scores ($P = 0.1948$). There was heterogeneity in the LIPUS monotherapy regimens and LIPUS combined with pharmacological treatment ($I^2 > 25\%$). However, there is moderate heterogeneity in the regimen of LIPUS combined with non-pharmacological

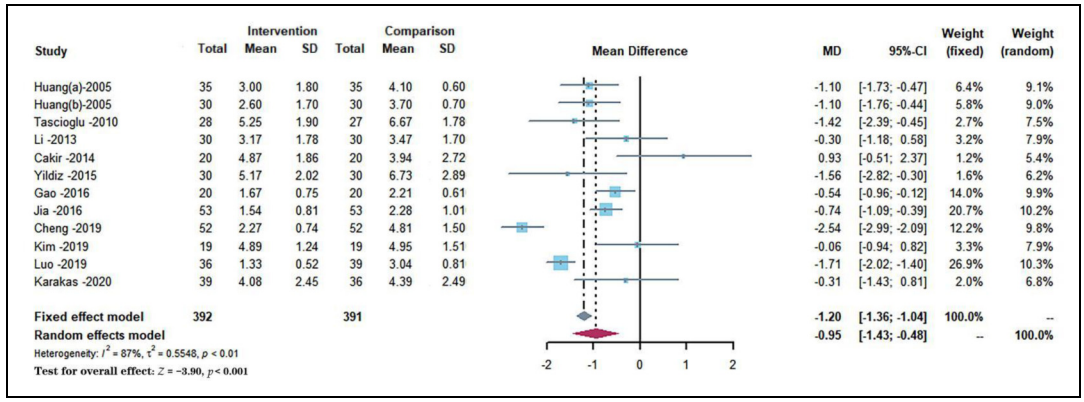

Figure 3. Forest plots demonstrated the effect of low-intensity pulsed ultrasound on pain relief evaluated by the Visual analog scale score.

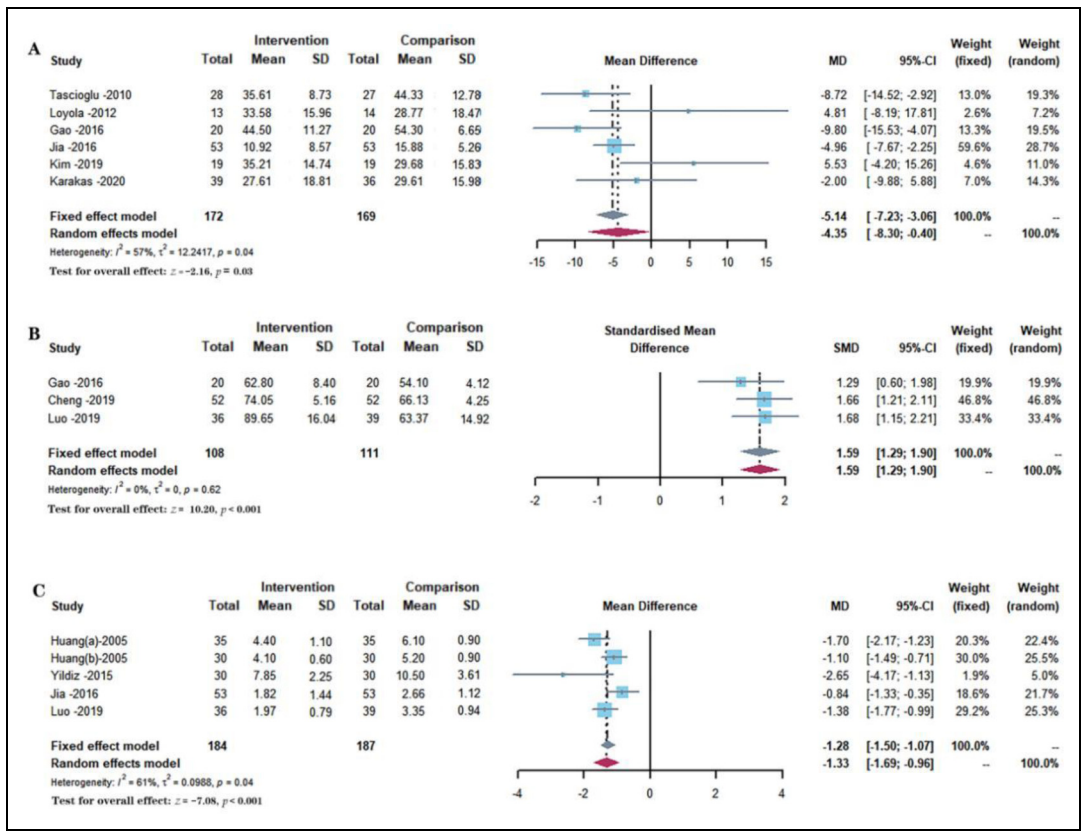

Figure 4. Forest plots demonstrated the effect of low-intensity pulsed ultrasound on functional recovery evaluated by several scores. A. Western Ontario and McMaster Universities Osteoarthritis Index score, B. Lysholm score, C. Lequesne index.

treatments ($I^2 = 28.1\%$). For the subgroups of the duration time of every therapy (≥20 min and < 20 min), no differences were found when comparing the effect ($P = 0.7266$). The longer duration time (≥20 min) showed significant heterogeneity ($I^2 = 72.1\%$), while the shorter duration time (< 20 min) showed moderate heterogeneity ($I^2 = 44.8\%$). Subgroup analysis is shown in Table 2.

Three studies with 219 participants reported the effects of different interventions on the Lysholm score, as shown in Figure 4B.[36,38,39] The synthesized data indicated that the intervention group had significantly promoted the functional recovery as compared with a comparison group (SMD = 1.59, 95% CI: 1.29 to 1.90, $P < 0.001$), and a fixed-effect model was used because of no heterogeneity for this synthesized outcome ($I^2 = 0\%$).

Five included studies with 371 participants reported the effects of different interventions on the Lequesne index, as shown in Figure 4C.[29,30,35,37,39] The synthesized data indicated that the intervention group had significantly promoted the functional recovery as compared with a comparison group (MD = −1.33, 95% CI: −1.69 to −0.96, $P < 0.001$), and a random-effect model was used because of a substantial heterogeneity for this synthesized outcome ($I^2 = 61.3\%$). No differences were found for the subgroups of the therapeutic periods (≤4 weeks and >4 weeks) when comparing their effect ($P = 0.8055$). A therapeutic period (≤4 weeks) showed high heterogeneity ($I^2 = 79.7\%$), but a therapeutic period (> 4 weeks) showed moderate heterogeneity ($I^2 = 46.6\%$). In the subgroup analysis for the Lequesne index, no significant differences were found among the different groups ($P > 0.05$). There was heterogeneity in the regimes of LIPUS combined with pharmacological therapy and LIPUS combined with non-pharmacological therapy ($I^2 > 60\%$). However, no data were available for subgroup analysis of LIPUS monotherapy treatment. For the comparison between subgroups in terms of duration time of every therapy, no significant differences were found when comparing the effect ($P = 0.3147$), and all subgroups show significant heterogeneity ($50\% < I^2 < 75\%$). Subgroup analysis is shown in Table 2.

Three included studies with 236 participants reported the effects of different interventions on the Range of motion, as shown in Figure 5A.[29, 30, 37] A fixed-effect model was used. The synthesized data indicated that knee range of motion significantly increased in the intervention group compared with a comparison group (MD = 2.43, 95% CI: 0.39 to 4.46, $P = 0.0197$).

Two included studies with 95 participants reported the effects of different interventions on the 20 meters walking time.[31, 34] And three included studies totaling 236 participants reported the effects of different interventions on 50 meters walking time, as shown in Figure 5 B-C.[29, 30, 37] A random-effect model was used, and the synthesized data indicated that 20 meters walking time were no significant increase in the intervention group compared with a comparison group (MD = −1.13, 95% CI: −5.23 to 2.98, $P = 0.5911$), while 50 meters walking time was a significant decrease in the intervention group compared with a comparison group (SMD = 1.48, 95% CI: 0.46 to 2.49, $P = 0.0044$).

The publication bias of primary outcomes (Visual analog scale score, Western Ontario and McMaster Universities Osteoarthritis Index score, and Lequesne index) was evaluated using funnel plots based on 13 studies. The results showed $P = 0.2324$ for Visual analog scale score, $P = 0.3877$ for Western Ontario and McMaster Universities Osteoarthritis Index score, and $P = 0.3670$ for Lequesne index by Egger's test, respectively, demonstrating that no publication bias was found for the primary outcomes of LIPUS therapy in patients with KOA .

Due to the high heterogeneity of the meta-analysis results, the sensitivity analysis was performed by deleting each study to determine the robustness. The statistical heterogeneity of this synthesized outcome decreased after removing one study from the 12 studies participating in the Visual analog scale score (MD = −0.81, 95% CI: −1.22 to −0.40, $I^2 = 77.3\%$).[38] After removing one of the six studies involved in the Western Ontario and McMaster Universities Osteoarthritis Index score, the statistical heterogeneity of this combined result showed a significant decrease in the Western Ontario and McMaster Universities Osteoarthritis

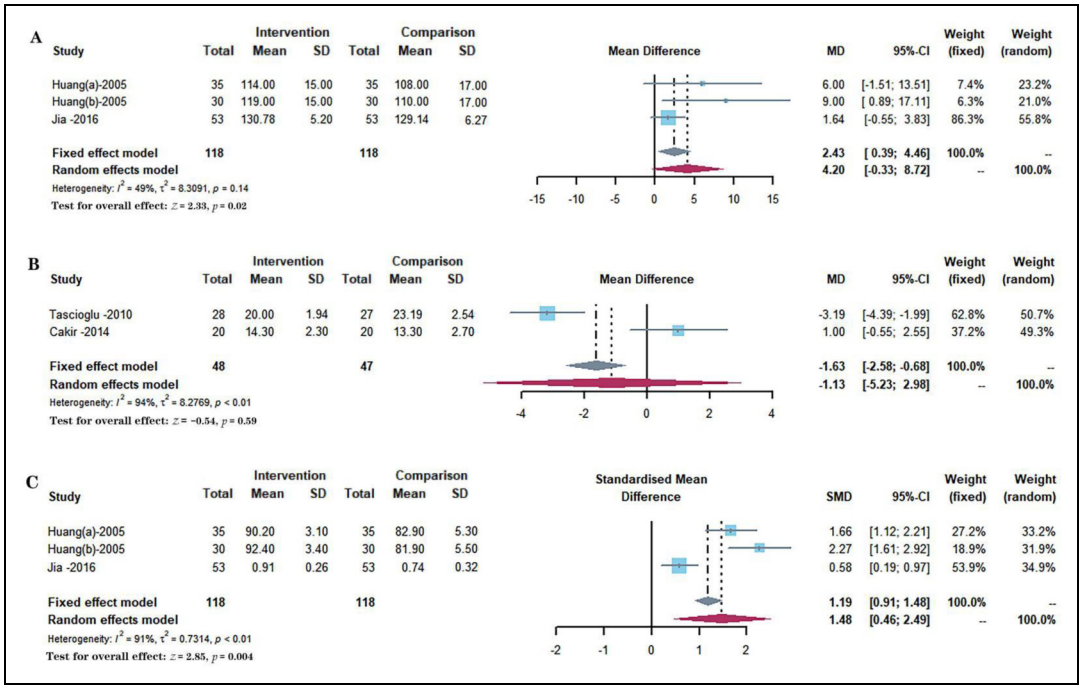

Figure 5. Forest plots demonstrated the effect of low-intensity pulsed ultrasound on joint mobility and walking ability by range of motion and walking tests. A.Range of motion, B. 20 meters walking time, C. 50 meters walking time.

Index score (MD = −5.76, 95% CI: −9.12 to −2.40, $I^2 = 39.8\%$).[40] The sensitivity analysis table is available in Appendix 2.

Discussion

This meta-analysis included 13 studies involving 807 patients to explore the efficacy of LIPUS for the treatment of KOA. In this study, the data suggested that LIPUS could significantly ameliorate pain and promote functional recovery in KOA individuals. LIPUS may be available as an alternative non-pharmacological therapy in the rehabilitation program of KOA.

KOA is characteristic of knee cartilage damage. Degeneration and inflammation can lead to knee pain and dysfunction. Currently, the primary goals in KOA management are to relieve arthritic symptoms, including pain and stiffness, to avoid disability.[38] Our findings showed significant improvements in pain and physical function with the LIPUS, consistent with the results of the two similar previous studies in 2018 and 2019.[14, 15] However, the meta-analysis in 2018 only included five studies, with high heterogeneity existed and without subgroup analysis due to the limited number of studies.[14] Another meta-analysis in 2019 only assessed the effect of LIPUS therapeutic ultrasound on the pain in patients with KOA.[15] On the contrary, our meta-analysis included more studies and participants and performed more subgroup analyses.

Our meta-analysis demonstrated that LIPUS therapeutic ultrasound significantly alleviated pain (Visual analog scale score) and improved physical function (Western Ontario and McMaster Universities Osteoarthritis Index score, Lequesne index, and Lysholm score). The benefits of these treatments were the same as those of the included randomized controlled trials. In addition, several randomized controlled trials have evaluated the effectiveness of LIPUS to other outcomes (Range of motion and Walking tests) for patients with KOA. So, we pooled randomized controlled trials' data to analyze the effectiveness of LIPUS

Table 2. Subgroup analysis of visual analog scale, Western Ontario and McMaster Universities Osteoarthritis Index score, and Lequesne index in the intervention and comparison groups.

Outcome	Subgroup	Article numbers	participants	MD (95% CI)	Heterogeneity I^2% (*P* value)	Subgroup difference Q (*P* value)
VAS	Therapeutic periods					
	≤4 weeks	4	261	−0.79 [−1.57 to 0.00]	65.0% (*P* = 0.04)	0.21 (*P* = 0.6443)
	> 4 weeks	8	522	−1.02 [−1.63 to −0.41]	89.0% (*P* < 0.01)	
	Therapeutic schedule					
	LIPUS monotherapy	3	219	−1.96 [−2.79 to −1.14]	63.7% (*P* = 0.06)	7.70 (*P* = 0.0213)
	LIPUS + pharmacotherapy	4	281	−0.87 [−1.53 to −0.21]	89.7% (*P* < 0.01)	
	LIPUS + non-pharmacological treatment	5	283	−0.51 [−1.14 to 0.13]	61.4% (*P* = 0.03)	
	Time per treatment					
	< 20 min	6	360	−0.89 [−1.43 to −0.35]	49.8% (*P* = 0.08)	0.09 (*P* = 0.7619)
	≥20 min	6	423	−1.03 [−1.74 to −0.32]	92.9% (*P* < 0.01)	
WOMAC	Therapeutic periods					
	≤4 weeks	3	201	−6.92 [−10.10 to −3.74]	34.2% (*P* = 0.22)	6.96 (*P* = 0.0083)
	> 4 weeks	3	140	1.68 [−3.86 to 7.22]	0.0% (*P* = 0.44)	
	Therapeutic schedule					
	LIPUS monotherapy	2	82	−3.26 [−16.27 to 9.76]	71.2% (*P* = 0.06)	3.27 (*P* = 0.1948)
	LIPUS + pharmacotherapy	2	146	−6.69 [−11.24 to −2.14]	55.3% (*P* = 0.13)	
	LIPUS + non-pharmacological treatment	2	113	1.20 [−6.09 to 8.50]	28.1% (*P* = 0.24)	
	Time per treatment					
	< 20 min	2	130	−5.91 [−12.41 to 0.59]	44.8% (*P* = 0.18)	0.12 (*P* = 0.7266)
	≥20 min	3	184	−4.32 [−10.45 to 1.81]	72.1% (*P* = 0.03)	
Lequesne	Therapeutic periods					
	≤4 weeks	2	166	−1.60 [−3.35 to 0.15]	79.7% (*P* = 0.03)	0.06 (*P* = 0.8055)
	> 4 weeks	3	205	−1.37 [−1.70 to −1.04]	46.6% (*P* = 0.15)	
	Therapeutic schedule					
	LIPUS monotherapy	1	60	−2.65 [−4.17 to −1.13]	—	3.47 (*P* = 0.1766)
	LIPUS + pharmacotherapy	2	181	−1.13 [−1.66 to −0.60]	64.8% (*P* = 0.09)	
	LIPUS + non-pharmacological treatment	2	130	−1.38 [−1.97 to −0.80]	73.1% (*P* = 0.05)	
	Time per treatment					
	< 20 min	3	190	−1.55 [−2.19 to −0.92]	69.0% (*P* = 0.04)	1.01 (*P* = 0.3147)
	≥20 min	2	181	−1.13 [−1.66 to −0.60]	64.8% (*P* = 0.09)	

MD: random effects mean difference, 95% CI: 95% confidence interval, LIPUS: low-intensity pulsed ultrasound, VAS: Visual analog scale score, Lequesne: Lequesne index, WOMAC: Western Ontario and McMaster Universities Osteoarthritis index score, —: None.

on Range of motion and walked ability. Fortunately, our meta-analysis demonstrated that LIPUS improved the Range of motion and walking ability.

Our present study included substantial heterogeneity. To investigate the source of the heterogeneity, we next carried out the subgroup analysis. Subgroup analyses indicated no statistically significant difference among single LIPUS, LIPUS combined drug therapy, LIPUS combined non-drug therapy in Western Ontario and McMaster Universities Osteoarthritis Index score, and Lequesne index for different treatment protocols. Compared with a control group, the longer duration time of every therapy (≥20 min) showed a significant improvement in the Visual analog scale score and Western Ontario and McMaster Universities Osteoarthritis Index scores. In comparison, the shorter duration time of every therapy (< 20 min) showed no significant difference. In addition, for different therapeutic periods, subgroup analyses indicated the shorter therapeutic periods (≤4 weeks) produced a more significant effect on reducing the Lequesne index. In contrast, more extended therapeutic periods (> 4 weeks) showed no significant difference, which could explain the source of the heterogeneity. Therefore, it is necessary to increase the number of randomized controlled trials to investigate the treatment period of LIPUS and the effectiveness of treating KOA symptoms.

Researchers have carried out studies on the potential mechanisms of LIPUS on KOA. For one thing, LIPUS can induce extracellular matrix synthesis, and the migration and proliferation of chondrocytes can also be increased.[42, 43] For another thing, the synthesis of type II collagen in articular cartilage can be increased by LIPUS and shows the ability to slow down cartilage degeneration.[44, 45] These data supported that LIPUS could improve KOA by inducing extracellular matrix synthesis and chondrocyte proliferation.

The present study has several limitations. (1) Only studies published in English and Chinese were considered in the present study, and consequently, we were unable to analyze further. (2) KOA is common in older women and is more common with advancing age.[46] Due to the differences in the effects of pain treatment and functional recovery among patients of different gender and age, more high-quality studies need to be carried out on more men or patients of different age groups.[47, 48] (3) The severity of KOA was not consistent in the included population, so the effect of LIPUS treatment on pain relief and functional recovery may have been overestimated. (4) The parameters of the LIPUS device and intervention protocols differed in the included studies, contributing to heterogeneity. (5) The long-term efficacy of LIPUS treatment cannot be determined as there are only two weeks to 1 year of follow-up. Moreover, due to the lack of follow-up studies, it is unclear how long the therapeutic effect of LIPUS on KOA will last. (6) There may be publication bias in the included trials, as positive trials are more likely to be published than negative results. Furthermore, this study focuses only on pain relief and functional recovery in patients and needs further investigation for other metrics, such as changes in radiological parameters. (7) There is still a lack of data on the adverse effects of LIPUS on patients with KOA. (8) Only studies from countries and regions in Asia were included in our meta-analysis. However, different national customs and even religious practices can also affect the extent of the disease and the outcome of the patient's recovery.[49, 50]

In conclusion, current evidence suggests that LIPUS guides the short-term clinical use of KOA patients. However, In the future, new and high-quality randomized controlled trials should be conducted to determine the cost and safety of LIPUS for KOA, as well as the possible long-term side effects. When interpreting the results, evidence of lower or moderate improvement in outcomes should be considered, and sufficiently broad sample sizes and inadequate follow-up should be taken into account. At the same time, the study should have the selection criteria of LIPUS in favor of the type, intensity, frequency, and duration of KOA patients so that clinicians and patients can effectively implement these findings in the real world.

Clinical messages

- Low-intensity pulsed ultrasound could significantly ameliorate pain and promote functional recovery for patients with KOA.Monotherapy of LIPUS produced a better effect on ameliorating pain, and the shorter therapeutic period (≤4 weeks) produced a more significant effect on promoting functional recovery for patients with KOA.

Author contributions

MLS, XAZ contributed to the study concept and design. HQC, ZW, and MLS conducted the literature review and statistical analysis. All authors contributed to the interpretation of data. HQC and MLS contributed to drafting the paper. All authors revised the text for intellectual content and have read and approved the final version of the manuscript.

Declaration of Conflicting Interests

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ORCID iD

Mingli Sun https://orcid.org/0000-0001-5007-4241

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Appendix

Appendix 1

Search Strategies for Pubmed, Cochrane Library, Physiotherapy Evidence Database (PEDro), Web of Science, and China National Knowledge Infrastructure (CNKI)

We included papers published from their inception to 11 February 2022 in English and Chinese.

PubMed

1."Osteoarthritis, Knee"[Mesh]

2.((((Knee Osteoarthritis[Title/Abstract]) OR (Knee Osteoarthritides[Title/Abstract])) OR (Osteoarthritis of Knee[Title/Abstract])) OR (Osteoarthritis of the Knee[Title/Abstract])) OR (Osteoarthritis, Knee[Title/Abstract])

3.1 OR 2

4.(((((((LIPUS[Title/Abstract]) OR (Low-Intensity Pulsed Ultrasound[Title/Abstract])) OR (Low Intensity Pulsed Ultrasound[Title/Abstract])) OR (Low-Intensity Pulsed Ultrasounds[Title/Abstract])) OR (Pulsed Ultrasound, Low-Intensity[Title/Abstract])) OR (Pulsed Ultrasounds, Low-Intensity[Title/Abstract])) OR (Ultrasound, Low-Intensity Pulsed[Title/Abstract])) OR (Ultrasounds, Low-Intensity Pulsed[Title/Abstract])) OR (Low Intensity Pulsed Ultrasound Radiation[Title/Abstract])

5.3 AND 4

the Cochrane Library

#1 MeSH descriptor: [Osteoarthritis, Knee] explode all trees

#2 (Osteoarthritis, Knee):ti,ab,kw OR (Knee Osteoarthritis):ti,ab,kw OR (Knee Osteoarthritides):ti,ab,kw OR (Osteoarthritis of Knee):ti,ab,kw OR (Osteoarthritis of the Knee):ti,ab,kw

#3 #1 OR #2

#4 (LIPUS):ti,ab,kw OR (Low-Intensity Pulsed Ultrasound):ti,ab,kw OR (Low Intensity Pulsed Ultrasound):ti,ab,kw OR (Low-Intensity Pulsed Ultrasounds):ti,ab,kw OR (Pulsed Ultrasound, Low-Intensity):ti,ab,kw OR (Pulsed Ultrasounds, Low-Intensity):ti,ab,kw OR (Ultrasound, Low-Intensity Pulsed):ti,ab,kw OR (Ultrasounds, Low-Intensity Pulsed):ti,ab,kw OR (Low Intensity Pulsed Ultrasound Radiation):ti,ab,kw

#5 #3 AND #4

Physiotherapy Evidence Database (PEDro)

Abstract & Title: Knee Osteoarthritides Title Only: " Low-Intensity Pulsed Ultrasound *" Match any search term (OR)

Web of Science

1 ((((TS = (Osteoarthritis, Knee)) OR TS = (Knee Osteoarthritis)) OR TS = (Knee Osteoarthritides)) OR TS = (Osteoarthritis of Knee)) OR TS = (Osteoarthritis of the Knee)

2 (((((((TS = (LIPUS)) OR TS = (Low-Intensity Pulsed Ultrasound)) OR TS = (Low Intensity Pulsed Ultrasound)) OR TS = (Low-Intensity Pulsed Ultrasounds)) OR TS = (Pulsed Ultrasound, Low-Intensity)) OR TS = (Pulsed Ultrasounds, Low-Intensity)) OR TS = (Ultrasound, Low-Intensity Pulsed)) OR TS = (Ultrasounds, Low-Intensity Pulsed)) OR TS = (Low Intensity Pulsed Ultrasound Radiation)

3 1 AND 2

China National Knowledge Infrastructure (CNKI)

1 SU % = 'Osteoarthritis, Knee' OR TKA = 'Knee Osteoarthritis' OR TKA = 'Knee Osteoarthritides' OR TKA = 'Osteoarthritis of Knee' OR TKA = 'Osteoarthritis of the Knee'

2 TKA = 'LIPUS' OR TKA = 'Low-Intensity Pulsed Ultrasound' OR TKA = 'Low Intensity Pulsed Ultrasound' OR TKA = 'Low-Intensity Pulsed Ultrasounds' OR TKA = 'Pulsed Ultrasound, Low-Intensity' OR TKA = 'Pulsed Ultrasounds, Low-Intensity' OR TKA = 'Ultrasound, Low-Intensity Pulsed' OR TKA = 'Ultrasounds, Low-Intensity Pulsed' OR TKA = 'Low Intensity Pulsed Ultrasound Radiation'

3 1 AND 2

Appendix 2

Sensitivity analysis table for Visual analog scale score

Omitting	mean difference (MD)	95% confidence interval (CI)	*P* value	Heterogeneity I^2
Huang(a)-2005	-0.9342	-1.4574; -0.4110	0.0005	87.8%
Huang(b)-2005	-0.9348	-1.4561; -0.4136	0.0004	87.8%
Tascioglu -2010	-0.9141	-1.4220; -0.4061	0.0004	87.8%
Li -2013	-1.0109	-1.5101; -0.5117	< 0.0001	87.2%
Cakir -2014	-1.0657	-1.5400; -0.5914	< 0.0001	86.4%
Yildiz -2015	-0.9127	-1.4138; -0.4116	0.0004	87.8%
Gao -2016	-0.9979	-1.5104; -0.4854	0.0001	85.9%
Jia -2016	-0.9693	-1.5066; -0.4319	0.0004	86.4%
Cheng -2019	-0.8076	-1.2153; -0.3999	0.0001	77.3%
Kim -2019	-1.0337	-1.5253; -0.5420	< 0.0001	86.7%
Luo -2019	-0.8627	-1.3909; -0.3345	0.0014	85.2%
Karakas -2020	-1.0013	-1.4990; -0.5036	<0.0001	87.4%
Pooled estimate	-0.9547	-1.4339; -0.4755	<0.0001	86.6%

Sensitivity analysis table for Western Ontario and McMaster Universities Osteoarthritis Index scores

Omitting	mean difference (MD)	95% confidence interval (CI)	*P* value	Heterogeneity I^2
Tascioglu −2010	−3.1271	−7.8250; 1.5707	0.1920	59.3%
Loyola −2012	−5.1209	−9.0205; −1.2214	0.0101	56.5%
Gao −2016	−3.0351	−7.4206; 1.3504	0.1750	53.4%
Jia −2016	−3.4329	−9.3539; 2.4881	0.2558	65.1%
Kim −2019	−5.7568	−9.1161; −2.3974	0.0008	39.8%
Karakas −2020	−4.5866	−9.1615; −0.0117	0.0494	63.1%
Pooled estimate	−4.3474	−8.2954; −0.3993	0.0309	56.5%

Appendix 3

Methodological quality assessment for studies by Jadad score

First author	Randomization	Double blinding	Withdrawals and dropouts	Score
Li.	2	1	1	4
Luo	2	1	1	4
Chen	2	1	1	4
Gao	2	1	1	4
Karakas.	2	2	0	4
Jia	2	2	1	5
Kim	2	1	1	4
Loyoia	2	2	1	5
Yildiz	2	2	1	5
Tascioglu.	2	2	1	5
Cakir.	2	2	0	4
Huang (a)	2	2	1	5
Huang (b)()	2	2	1	5