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Review

Extracorporeal shockwave therapy improves pain and function in subjects with knee osteoarthritis: A systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Objective: To examine the safety and effectiveness of extracorporeal shockwave therapy (ESWT) for reducing pain and improving functionality in people with knee osteoarthritis (KOA).

Methods: The Cochrane Library, PubMed, CINAHL, Physiotherapy Evidence Database (PEDro) and Google Scholar were systematically searched for randomized trials published up to September 30th of 2019. The main outcome measures to evaluate the treatment effect were pain, as reported on a visual analogue scale (VAS), and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Secondary outcome measures were the range of motion (ROM) and walking tests. A quantitative analysis was conducted using the inverse variance method and the random effects model.

Results: Fourteen studies were included (n = 782 participants and 877 knees). Moderate quality of evidence showed that ESWT causes a decrease on the pain VAS [mean difference (MD) = 1.7 cm; confidence interval (CI) 95%: 1.1–2.3] and WOMAC (MD = 13.9 points; CI 95%: 6.9–20.8). The effect of ESWT using medium energetic density was greater than with low or high density in the WOMAC ($Chi^2 = 9.8$, $p = 0.002$) and bordered statistical significance on the VAS ($Chi^2 = 3.8$, $p = 0.05$). Very low quality of evidence showed that ESWT causes moderate improvement in the knee ROM (MD = 17.5°; CI 95%: 9.4–25.5) and walking test [standardized mean difference (SMD) = 0.58; CI 95%: 0.35–0.81].

Conclusions: ESWT is an effective treatment for improving pain and functionality in patients with KOA in the short term with few minor side effects. Further clinical trials should include longer follow-up periods and be designed to lower the risk of bias.

1. Introduction

Knee and hip osteoarthritis were ranked as the 11th highest contributor to global disability when analyzing 291 pathological conditions worldwide. Knee osteoarthritis (KOA) can affect up to 3.8% of the population, with a higher prevalence in women [1], and a recent study in France with a five-year follow-up period estimated a yearly average cost of €2295 per patient. Drugs were the largest cost share followed by hospitalizations; hip and knee prosthetic surgery accounted for 27% of surgery hospitalization costs. On the contrary, physical therapy accounted only for 1–2% of direct costs [2].

The effectiveness of pharmacological treatment in the medium and long term is controversial, and adverse effects have been reported for both systemic and local applications. The effectiveness and safety of other conservative treatments, such as physical therapies, are not as well studied [3]. Interventions with physical therapies in the first stages of osteoarthritis could decrease the number of knee prosthetic surgeries, which has substantially increased in the last years [4]. Extracorporeal

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shockwave therapy (ESWT) is among the physical therapies used for treating osteoarthritis in the last years. Some pre-clinical studies have assessed the effect it has on the osteoarthritis progression, cartilage degradation, and even on the receding of the disease [5–8]. A qualitative review of available evidence concluded that ESWT can be effective for treating osteoarthritis [9]. Additionally, a recent meta-analysis including trials up to 2017 concluded that the effect of ESWT was superior to placebo and other physical therapies. However, this meta-analysis was based on quantitative analyses that included only seven studies [10]. In the two years prior to this meta-analysis, several clinical trials were conducted on ESWT for treating patients with KOA, which compared it with placebo or other conservative treatments. Hence, performing a systematic review and updated meta-analysis is justified.

The main objective of this systematic review and meta-analysis was to assess the safety and effectiveness of ESWT for reducing pain and improving functionality in people with knee osteoarthritis (KOA) compared to placebo and other conservative treatments.

2. Methods

This systematic review and meta-analysis followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement [11] and the recommendations by The Cochrane Collaboration [12]. Its protocol was registered in PROSPERO (reference number CRD42019126507).

2.1. Search strategy

Two independent researchers (JGM and NCS) searched bibliographic references on ESWT for treating KOA in the following databases: Google Scholar, The Cochrane Library, CINAHL, PubMed, and Physiotherapy Evidence Database (PEDro). The selection of articles was completed via an inverse manual search of the references cited in the articles found (Supplementary Appendix 1). The search included articles in English or Spanish, without restrictions regarding age and gender of participants, published since the initial dates of the relevant databases up to October 22nd of 2018. Once our report was finalized, a new search of articles published between that date and September 30th of 2019 was conducted to update the results.

2.2. Selection criteria

Randomized clinical trials (RCTs) assessing the effectiveness of focal and radial ESWT on KOA in humans were included. These studies compared the intervention with ESWT versus control groups that received no intervention, sham intervention, or other conservative treatments. The criteria for exclusion were: the availability of abstracts only or conference presentations; not reporting the dosage or application parameters of shockwave interventions; not reporting the location of application; lack of basal characteristics of the studied population; metabolic disorders or non-controlled radiculopathies. Two independent researchers (JGM and NCS) selected the articles based on the inclusion and exclusion criteria, and a third researcher (JAC) intervened to reach consensus in two cases of disagreement.

2.3. Data extraction

Two researchers (JAC and NCS) performed the data extraction by using a chart specifically designed for this purpose that they agreed upon. A third researcher (CAL) compared both charts and presented the final data collection.

The main outcome measures for the treatment effect were the subjective perception of pain as measured on a visual analogue scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The latter is a disease-specific self-administered questionnaire that has a multidimensional scale comprising 24 items grouped into three dimensions: pain (five items), stiffness (two items), and physical functioning (17 items). Its final score ranges from 0 to 100, where 0 represents the best and 100 the worst possible health status [13]. Additionally, adverse effects reported in the studies were recorded. Secondary variables were the range of motion (ROM) of the knee and functional tests, such as walking or climbing stairs. Authors of the selected studies were contacted to obtain or clarify missing or unclear data if needed. Data available only in graphs were extracted using Digitizelt software for graph digitalization (https://www.digitizeit.de/).

2.4. Assessment of risk of bias

Risk of bias was assessed based on recommendations by the Cochrane organization [12] using Review Manager (RevMan) (Computer program. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Two independent reviewers, a senior (JAC) and a junior (CAL) investigator, evaluated the risk of bias and a third senior investigator (JGS) resolved cases of disagreement between the former ones. Six items were addressed for evaluation and the relevant risk was expressed in three levels (unclear, low, and high). Previously, the researchers had agreed that: for the item “blinding of participants and personnel”, the risk would be qualified as unclear when either the participants or personnel were not blinded; and for the item “selective reporting”, studies without a registered protocol would be qualified as unclear or high risk depending on the final report. Additionally, funnel plots for the two main variables (pain VAS and WOMAC) were analyzed to evaluate publication bias.

2.5. Data synthesis and analysis

The inverse variance method and random effects model were used for the four assessed variables (pain VAS, WOMAC, ROM, and walking test). Statistical heterogeneity was evaluated using the chi-squared test (with statistical significance set at $p < 0.10$), and heterogeneity was measured calculating the I2, with 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively [14]. The mean difference (MD) was obtained for the pain VAS, WOMAC, and ROM variables, which were expressed in the same units, and confidence intervals were set at 95% (CI 95%). On the other hand, the standardized mean difference (SMD) was calculated for the walking test, since it is expressed in different scales and units, such as walked distance or time. For those studies that recorded the time for a walked distance in the walking test, a higher score implied higher disability, so this value was multiplied by −1 in order to align the effect direction. The analyzed results were those with the longest follow-up period for each of the included studies. When missing data were reported, the results of the intention-to-treat analysis were utilized rather than those of the per-protocol analysis. In studies including patients with bilateral KOA, the sample size was the number of knees. In the case of three-arm studies, splitting of the shared group was applied according to the Cochrane Group Guidelines [12] to avoid double recount. In addition to the global analysis, in the case of the pain VAS and WOMAC variables, an analysis was conducted by subgroups to account for the comparator (control or another intervention), follow-up period, type of shockwaves, and energetic density. The RevMan software was used for quantitative analysis. The quality of evidence was classified for each outcome as high, moderate, low, or very low following the Grades of Recommendation Assessment, Development and Evaluation (GRADE) method [15]. The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines.

3. Results

3.1. Selection of studies

Following removal of duplicates, 285 articles were identified as eligible, of which 238 were eliminated after reading of the title and abstract. Finally, after reading the full text, 14 RCTs were included [16–29] that complied with the inclusion criteria in this systematic review and meta-analysis (Fig. 1). Additional information was requested from the authors of five studies [20–22,27,28] regarding characteristics of the trial or outcome data, but no response was obtained from any author.

3.2. Qualitative summary of the included studies

Characteristics of the included studies are shown in Table 1. Of the 14 included studies, eight were controlled or sham-controlled [17–19,21,22,27–29], and six compared ESWT versus alternative treatment modalities [16,20,23–26]. The trials by Elerian et al. [19] and Shenouda [27] presented three arms where active ESWT and a control group were compared with intra-articular injection of corticosteroids and mobilization according to Mulligan's protocol [30], respectively. The treatment alternatives ESWT was compared with in the included RCTs were: interferential currents [16], intra-articular hyaluronic acid injection [23], therapeutic ultrasounds [20,24], and kinesiotherapy [25,26] (Table 1).

The sample size comprised a total of 782 participants, of which 501 (64%) were women; of note, two trials [22,27] did not report the gender of subjects. Average age ranged between 43 and 75 years and was ≥60 years in 10 of the 14 included trials. Five studies [16,18,21,28,29] reported losses to follow-up that totaled n = 41 (5.2%), with similar proportions in the ESWT group (n = 22) and in the non-ESWT group (n = 19). Missing data was accounted for in the intention-to-treat analysis in two studies [21,28], whereas a per-protocol analysis was performed in the other three studies [16,18,21]. The intervention in the KOA was applied both unilaterally and/or bilaterally in four trials [17,19,26,27], whereas the rest of studies applied it only unilaterally. Overall, 877 knees were analyzed, 410 in the ESWT group and 467 in the non-ESWT treatment group (Table 1).

Most studies employed clinical and/or radiological criteria for diagnosing the KOA: several used the clinical criteria by the American College of Rheumatology for KOA [31] and 11 trials were based on the radiological criteria of the Kellgren-Lawrence scale (K-L) [32]. The majority of studies included patients with K-L grade II or III [18–20,22,23,28,29]. Cho et al. [17] and Lizis et al. [24] included patients with grade ≥ I, Shenouda [27] with grades III and IV, and Imamura et al. [21] with grades II–IV. In terms of duration of pain of the KOA or related symptoms, patients had suffered them for >3 months in five studies [16,21,23,27,28], >6 months in two studies [18,29], and >1 year in one study [24]; the rest of studies did not provide these data (Table 1).

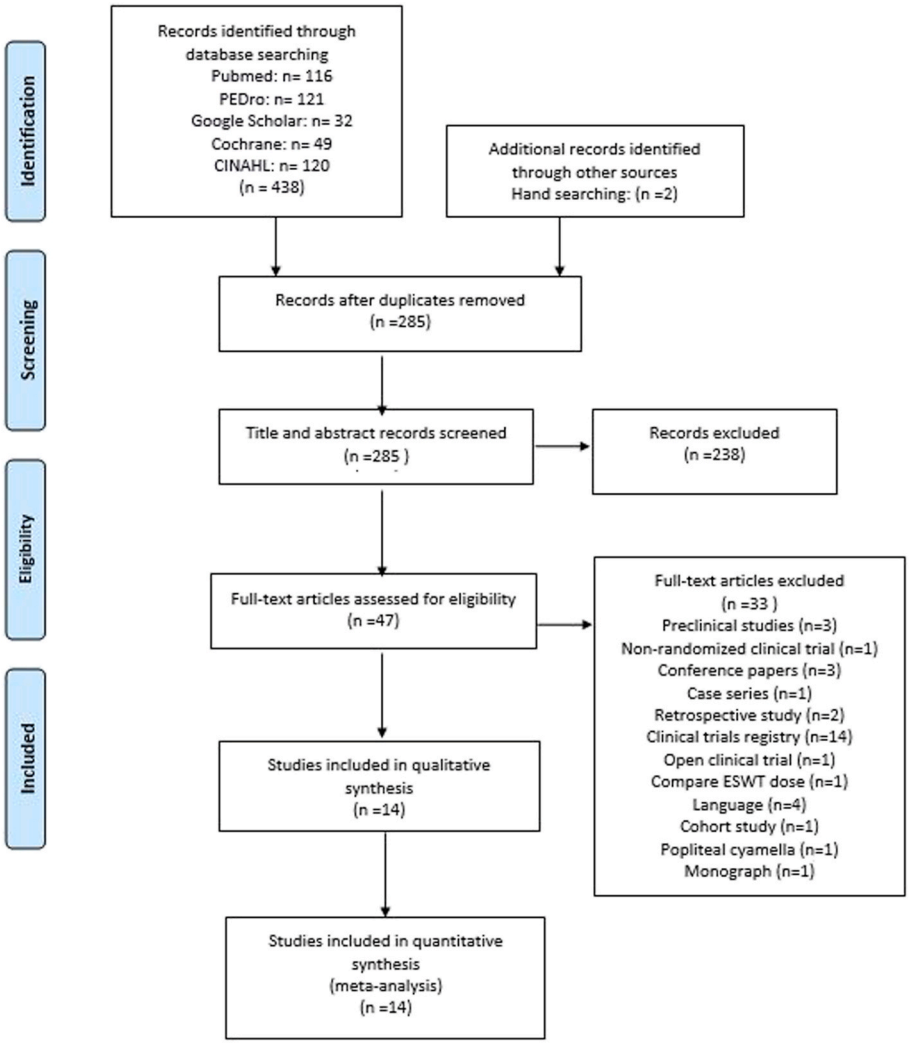

Fig. 1. Flowchart of the systematic review and meta-analysis.

Table 1
Summary of Randomized Clinical Trials (RCT) included in this review.

First author, year. Country.	Method	Participants number, gender, age, inclusion criteria (current disease severity and duration, mean ± SD years)	Interventions	Time points and Outcome measurements	Losses to follow-up and adverse effects
Ammar, 2018 [16]. Egypt.	Randomized, non-controlled, clinical trial.	30 patients. 16 women & 13 men. 1) fESWT group: 45.7 ± 5.5 years. 2) IFC group: 43.1 ± 6.1 years. Unilateral KOA. Clinical criteria (ACR). Pain duration >3 months. Tenderness in the medial tibial plateau.	2 groups without demographic and baseline clinical differences. fESWT + CPT (n = 15). IFC + CPT (n = 15). Parameters: 0.05 mJ/mm^2, 1000 pulses, 4 sessions (1 per week).	Baseline, 4 weeks. Pain (VAS), physical function, and disability (WOMAC and 6MDW).	Three patients from the ESWT group (n = 12/15) and 2 patients from the IFC group (n = 13/15) withdrew. The reported adverse events were joint effusion.
Cho, 2016 [17]. South Korea.	Prospective, double blind, randomized controlled pilot trial.	18 patients. 3 women & 15 men. 1) ESWT group: 75.5 ± 7.7 years. 2) Sham group: 72.7 ± 5.9 years. Bilateral or unilateral KOA. Radiographic criteria (K-L grade ≥ I).	2 groups without demographic and baseline clinical differences. fESWT (n = 9, 16 knees) Sham fESWT (n = 9, 17 knees). Parameters: 0.05 mJ/mm^2, 1000 pulses, 3 sessions (1 per week).	Baseline and 1 week after the final treatment session. Pain (VAS and PPOA), functional state (K-MBI and FIM), and ultrasonographic (articular cartilage thickness, joint effusion height, Doppler activity).	There were not losses to follow-up or adverse events related to the intervention.
Ediz, 2018 [18]. Turkey.	Prospective, randomized, controlled, clinical trial.	120 patients. 70 women & 40 men. Group 1: 69.74 ± 3.91 years. Group 2:70.48 ± 4.18 years. Group 3: 69.65 ± 4.49 years. Unilateral KOA. Clinical (ACR) and radiographic criteria (K-L grade II or III). Pain duration >6 months.	3 groups without demographic and baseline clinical differences. 1) rESWT with BME + TENS (n = 40). 2) rESWT without BME + TENS (n = 40). 3) Sham without BME + TENS (n = 40). Parameters: 2500 pulses, 3 bar, 12 Hz, 10 sessions (2 per week).	Baseline, 6, and 12 months. Pain (VAS), physical functional state (WOMAC and Lequesne index), and joint space narrowing (radiography).	Three patients from group 1, two from group 2, and five from group 3 were lost to follow-up. The adverse events were minor bruising or soft tissue swelling.
Elerian, 2016 [19]. Egypt.	Randomized, placebo-controlled, double-blind clinical trial.	60 patients. 50 women & 10 men. 51 ± 3.5 years. Bilateral KOA. Clinical criteria (ACR) and radiographic criteria (K-L grade II or III).	3 groups without demographic and baseline clinical differences. rESWT (n = 20, 40 knees). Intra-articular corticosteroid injections (n = 20, 40 knees). Sham rESWT (n = 20, 40 knees) Parameters: 2000 pulses, 5 Hz, 20 bar, 3 sessions (1 per week).	Baseline, 4, 8, 24 weeks. Pain at rest and in activity (VAS), functional state (WOMAC), and ROM (electro goniometer).	The trial did not report on losses to follow-up and adverse effects.
El-Sakka, 2019 [20]. Egypt.	Randomized uncontrolled, clinical trial	30 patients. 21 women & 9 men. 1) ESWT group: 53.47 ± 7.76 years. 2) US group: 51.53 ± 5.74 years. Unilateral KOA. Clinical (ACR) and radiographic criteria (K-L grade II-III). Primary KOA.	2 groups without demographic and baseline clinical differences. rESWT/fESWT (n = 15). US (n = 15). Parameters rESWT: 1000 pulses, 8 Hz, 2.5–4 bars. Parameters fESWT: 0.15 mJ/mm^2, 1000 pulses, 6 Hz. Total sessions: 3 sessions (1 per week).	Baseline, 1 week, and 1 month of follow-up. Pain (VAS), physical performance (CST, SCT, 6-MWT), and functional state (WOMAC), radiological assessment (K-L) and active ROM.	There was not any mention about the number of dropped outs and neither adverse effects.
Imamura, 2017 [21]. Brazil.	Randomized, placebo-controlled, double blind, clinical trial.	105 patients (females). 1) rESWT group: 70.0 ± 6.5 years. 2) Sham group: 72.4 ± 6.5 years. Unilateral KOA. Clinical and radiographic diagnosis of primary KOA (K-L grade II-IV). VAS ≥5. Failure of 2 or more conservative treatments. Pain duration between 3 months and 480 months.	2 groups without demographic and baseline clinical differences. rESWT (n = 52). SHAM (n = 53). Parameters: 2000 pulses, 2.5–4.0 bar, 8 Hz, 3 sessions (1 per week).	Baseline, 1 week and 3 months after the final treatment. Pain on movement (VAS), functional state (WOMAC) and pain to pressure (Fischer algometer).	There were 6 dropouts in the rESWT group (46/52) and 6 in the sham group (47/53). No complications were observed. The trial did not report on adverse effects.
Lee JH, 2017 [22].		20 patients. Women & men (NA).	2 groups without demographic and baseline clinical		

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Table 1 (*continued*)

First author, year. Country.	Method	Participants number, gender, age, inclusion criteria (current disease severity and duration, mean ± SD years)	Interventions	Time points and Outcome measurements	Losses to follow-up and adverse effects
South Korea.	Randomized, controlled, clinical trial.	1) fESWT group: 64.2 ± 4.1 years. 2) CPT group: 67.2 ± 5.9 years. Unilateral KOA. Clinical and radiographic criteria (K-L grade II).	differences. fESWT + CPT (n = 10). CPT (n = 10). Parameters: energy intensity according to the level of pain, 1000 pulses, 4 Hz, 12 sessions (3 per week).	Baseline, 4 weeks. Pain (VAS) and functional state (K-WOMAC).	The trial did not report on patient's withdrawals or adverse effects.
Lee JK, 2017 [23]. South Korea.	Randomized, non-controlled, clinical trial.	61 patients. 51 women & 10 men. 1) fESWT group: 67.7 ± 5.5 years. 2) HA group: 69.1 ± 6.2 years. Unilateral KOA. Clinical (ACR) and radiographic criteria (K-L grade II or III). Pain duration >3 months. Tenderness in the medial tibial plateau.	2 groups without demographic and baseline clinical differences. fESWT (n = 31). HA injection (n = 30). Parameters: 0.05 mJ/mm^2, 1000 pulses, 3 sessions (1 per week).	Baseline, 1 and 3 months after the last treatment session. Pain (VAS), functional state (WOMAC, Lequesne index, 40-m fast-paced walk, SCT).	The trial did not report on patient's withdrawals. Some patients complained of light side effects in the area of treatment, which were not specified.
Lizis, 2017 [24]. Poland.(a)	Randomized, non-controlled, single-blind, pilot trial.	60 patients. 18 women & 42 men. 1) rESWT group: 59.8 ± 3.9 years. 2) US group: 60.7 ± 4.8 years. Unilateral KOA. Clinical (ACR) and radiographic criteria (K-L grade I). Duration of complaints ≥1 year.	2 groups without demographic and baseline clinical differences. rESWT (n = 30) US (n = 30) Parameters: 1st session 1000 pulses, 2nd and 3rd sessions 1500 pulses, 4th and 5th sessions 2000 pulses. 8 Hz, 2.5 bar, 5 sessions (1 per week).	Baseline, 5 weeks. Pain (VAS and PPT), physical function (KOOS), mobility (walking 15 m, get up and go, walk upstairs and downstairs).	The trial did not report on the number of dropouts. Minor pain during the intervention. No other adverse effects were reported.
Lizis, 2017 [25]. Poland.(b)	Randomized, non-controlled, single-blind, pilot trial.	40 patients. 22 women & 18 men. 1) rESWT group: 63.5 ± 8.0 years. 2) KIN group: 65.0 ± 8.4 years. Unilateral KOA. Clinical criteria (ACR).	2 groups without demographic and baseline clinical differences. rESWT (n = 20) KIN (n = 20) Parameters: 1st session 1000 pulses, 2nd and 3rd sessions 1500 pulses, 4th and 5th sessions 2000 pulses. 8 Hz, 2.5 bar, 5 sessions (1 per week).	Baseline, 5 weeks. Physical function (WOMAC) and ROM.	There was not any mention about the number of dropouts. No adverse events were observed during the treatment.
Lizis, 2017 [26]. Poland.(c)	Randomized, non-controlled, single-blind, clinical trial.	60 patients (all women). 1) rESWT group: 61.0 ± 9.0 years. 2) KIN group: 59.0 ± 9.0 years. Bilateral KOA. Clinical criteria (ACR) and radiographic criteria (evidence of osteophytes).	2 groups without demographic and baseline clinical differences. rESWT (n = 30, 60 knees) KIN (n = 30, 60 knees) Parameters: 1st session 1000 pulses, 2nd and 3rd sessions 1500, 4th and 5th sessions 2000 pulses. 2.5 bar, 5 Hz, 5 sessions (1 per week).	Baseline, 5 weeks. Pain (VAS), physical function (WOMAC), ROM, and functional capacity (6-MWT).	There was not any mention about the number of dropouts. No adverse events were observed during the treatment.
Shenouda, 2013 [27]. Egypt.	Randomized, controlled, single-blind clinical trial.	45 patients. Females & males (NA). A) rESWT group: 52.20 ± 5.44 years. B) MWM group: 51.93 ± 6.51 years. C) Control group: 50.07 ± 5.73 years. Bilateral or unilateral KOA. Clinical and radiographic criteria (K-L grade III and IV). Pain duration >3 months.	3 groups without demographic and baseline clinical differences. A) fESWT + exercise (n = 15). B) MWM + exercise (n = 15). C) Exercise (n = 15). Parameters: 0.18 mJ/mm^2, 2000 pulses, 6 Hz, 5 sessions (1 per week).	Baseline, 5 weeks. Pain (VAS), functional disability (WOMAC), and ROM.	The trial did not report on losses to follow-up or adverse effects.
Zhao, 2013 [28]. China.	Randomized, controlled, single-blind clinical trial.	70 patients. 45 females & 25 males. 1) rESWT group: 59.9 ± 11.3 years. 2) Sham group: 61.8 ± 9.8 years.	2 groups without demographic and baseline clinical differences. rESWT (n = 34) Sham rESWT (n = 36) Parameters: 0.25 mJ/mm^2, 4000 pulses, 6 Hz, 4 sessions (1 per week).	Baseline, 1, 4, and 12 weeks. Pain on movement (VAS) and functional disability (WOMAC, Lequesne index, and PPOA).	5 patients from the rESWT and 4 from the sham groups dropped out. No adverse effects were found, except for skin reddening and swelling after treatment.

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Table 1 (*continued*)

First author, year. Country.	Method	Participants number, gender, age, inclusion criteria (current disease severity and duration, mean ± SD years)	Interventions	Time points and Outcome measurements	Losses to follow-up and adverse effects
Zhong, 2019 [29]. China.	Randomized placebo-control double blind, clinical trial.	Unilateral KOA. Clinical (ACR) and radiographic criteria (K-L grade II or III). Pain duration ≥3 months. 63 patients. 40 females & 23 males. 62.8 ± 7.9 years. Unilateral KOA. Clinical criteria (ACR) and radiographic criteria (K-L grades II or III). Symptoms duration >6 months.	2 groups without demographic and baseline clinical differences. rESWT (n = 32) Sham rESWT (n = 31) Parameters: 2000 pulses, 8 Hz, 2.5 bar, 4 sessions (1 per week).	Baseline, 5, 12 weeks. Pain (VAS), physical function (WOMAC and Lequesne index), and cartilage alteration (T2 mapping).	3 patients in the ESWT and 2 in the placebo groups dropped out during the follow-up. Adverse effects were noted and recorded, such as pain, reddening of skin, and burning sensation.

Note. SD (Standard deviation), fESWT (focal extracorporeal shockwave therapy), IFC (Interferential current), KOA (Knee osteoarthritis), ACR (American College of Rheumatology), mJ (millijoule), Hz (Hertz) CPT (conservative physical therapy), VAS (Visual Analogue Scale), WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index), 6MDW (6-min distance walk test), ESWT (extracorporeal shockwave therapy), K-L (Kellgren-Lawrence grade), PPOA (patient perception of the clinical severity of osteoarthritis), K-MBI (Korean version of the Modified Barthel Index), FIM (Functional Independence Measure Scale), K-WOMAC (Korean Western Ontario and McMaster Universities Osteoarthritis Index), rESWT (radial extracorporeal shockwave therapy), BME (bone marrow edema), TENS (transcutaneous electrical nerve stimulation), ROM (range of motion), HA (hyaluronic acid), SCT (Stair Climb Test), US (ultrasound), KOOS (Knee injury and Osteoarthritis Outcome Score), PPT (pressure pain threshold), KIN (kinesiotherapy), 6-MWT (Six-minute walk test), NA (not available), MWM (mobilization with movement), CST (Chair Stand Test).

Regarding the type of shockwaves and parameters for applying ESWT, protocols were heterogeneous. Five studies used focal ESWT [16,17,22,23,27], eight used radial ESWT [18,19,21,24–26,28,29], and another trial applied a combination of both [20]. Trials applied three to five sessions of ESWT (one session per week), with the exception of Ediz et al. [18] and Lee et al. [22] that applied 10 (two per week) and 12 (three per week) sessions, respectively. The number of pulses per session ranged between 1000 and 2500 except for Zhao et al. [28] that applied 4000 pulses/session. The frequency of pulses ranged between 4 Hz and 12 Hz. Energetic density was medium (0.08–0.25 mJ/mm2 or 1.5–2.5 bar) in eight studies [19,22,24–29], low (0.05 mJ/mm2 or <1.5 bar) in three trials [16,17,23], and high (>0.25 mJ/mm2 or >2.5 bar) in other three trials [18,20,21] (Table 1).

The assessed main outcome variables were: pain measured on a VAS

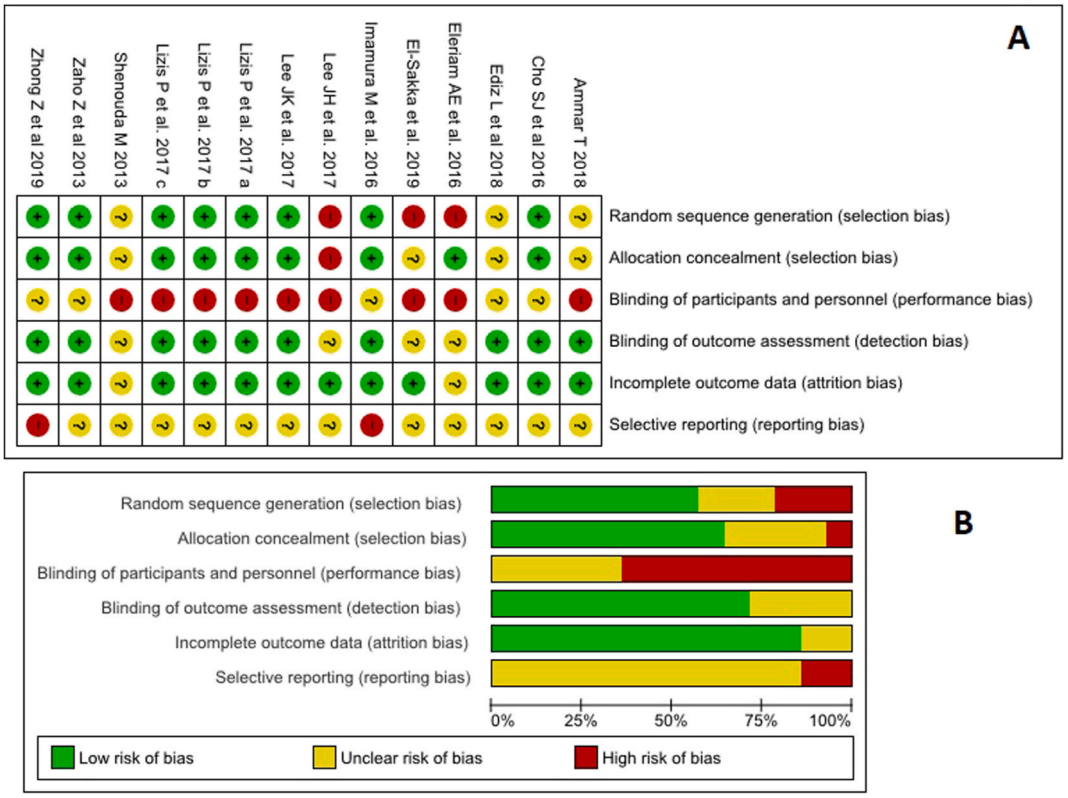

Fig. 2. A: Risk of bias summary: review authors' judgements about each risk of bias item for each included study. B: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

in 13 of the 14 included studies [16–24,26–29] and functionality as measured via the WOMAC total score in 11 trials [16,18–20,22,23,25–29]. Additionally, five studies [19,20,25–27] measured the ROM and five [16,20,23,24,26] performed different walking functionality tests. The follow-up period was ~1 month (1–5 weeks) in most cases [16,17,20,24–27], 12 weeks (3 months) in four studies [21,23,28,29], 24 weeks (6 months) in one study [19], and 12 months in another study [18] (Table 1).

Adverse effects and/or complications were specifically stated in 10 of the 14 included studies. Of them, four trials did not report any related to ESWT [17,21,25,26] and the other six reported mild adverse effects or complications, such as pain in the area of application during the intervention [24,29], minor bruising [18], soft tissue swelling [18,28], redness [28,29], burning sensation [29], effusion [16], or minor non-specified side effects in the treatment area [23] (Table 1).

3.3. Risk of bias in the included studies

Fig. 2 shows the risk of bias for the 14 included studies. Three trials presented a high selection bias: Elerian et al. [19] randomized the active and sham ESWT groups, but not the group receiving corticosteroids; and El-Sakka et al. [20] and Lee et al. [22] did not specify the manner in which participants were allocated in groups. In terms of performance bias, all of the included studies were categorized as unclear or high risk, since blinding of the therapist that applied the ESWT was not possible. Twelve of the 14 assessed trials were tagged with unclear risk of reporting bias, since the protocol had not been previously registered. Imamura et al. [21] was evaluated as high risk since the WOMAC total score was established as a variable in the previously registered protocol but the results were presented on the WOMAC sub-scales. Similarly, the study by Zhong et al. [29] established the ROM as a variable in its former registration but the final report did not include outcomes for it (Fig. 2). The risk of publication bias was considered low, since the distribution of the two main variables (pain VAS and WOMAC) in funnel plots did not show asymmetries (Fig. 3).

3.4. Quantitative summary: effects of extracorporeal shockwave therapy (ESWT)

3.4.1. Effect on pain

Fig. 4 summarizes trials that assessed the effect of the interventions on pain as measured on a VAS. ESWT was more effective compared with control groups or other interventions (MD = 1.7 cm; CI95%: 1.1–2.3) and showed a high level of heterogeneity (I2 = 86%, p < 0.001). In six [17,19,22,27–29] of the eight controlled trials that evaluated the effect on pain, the outcome using ESWT was superior compared to the control or sham groups (Fig. 4). In the trial by Ediz et al. [18], the effect was at the limit of statistical significance when comparing ESWT with the control group in patients without bone marrow edema after a 12-month follow-up period (Fig. 4). However, the effect on pain in patients with bone marrow edema was superior for the ESWT group; this arm was not included in the quantitative analysis since the clinical characteristics of participants in the experimental and control groups were different. The effect of ESWT on the pain VAS was superior than that of other conservative treatments, such as interferential currents [16], ultrasounds [20], mobilization according to Mulligan's protocol [27], and kinesiotherapy [25] (Fig. 4). Lizis et al. (a) [24] also compared ESWT with ultrasounds and observed that the effect on pain was at the limit of statistical significance; however, no differences were found when ESWT was contrasted against intra-articular injections of hyaluronic acid [23] or corticosteroids [19] (Fig. 4). As previously mentioned, this trial presented a high selection bias, since participants in the corticosteroids group were not randomly allocated [19].

In the subgroup analysis for the pain VAS, no significant differences were found between the effect of ESWT when compared with a control group or with other treatments (Chi2 = 2.1, p = 0.15) (Fig. 4). For the subgroups of trials with follow-up periods of ≤5 weeks, 12 weeks, and 24–52 weeks, no differences were found when comparing the effect between them (Table 2 and Supplementary Appendix 2). In addition, no differences were observed in terms of type of ESWT when comparing the effect of radial versus focal applications. A trial [20] that employed both types of ESWT was excluded from this analysis (Table 2 and Supplementary Appendix 2). However, the comparison between subgroups in terms of dosage showed that medium energetic density doses (0.08–0.25 mJ/mm2 or 1.5–2.5 bar) produced a greater effect on pain than using low or high ones (<0.08 and >0.25 mJ/mm2 or <1.5 and >2.5 bar), which was at the limit of clinical significance (Chi2 = 3.8, p = 0.05) (Table 2 and Supplementary Appendix 2). The quality of evidence according to GRADE was moderate in terms of factors to rating down (very serious risk of bias and serious inconsistency or heterogeneity of results) and factors to rating up (dose response and magnitude of effect).

3.4.2. Effect on the multidimensional WOMAC score

Fig. 5 summarizes trials that assessed the effect of the intervention on the WOMAC. The overall effect of ESWT on the WOMAC score was greater than that observed in control or other interventions groups (MD = 13.9 points; CI95%: 6.9–20.8), showing high heterogeneity. The effect of ESWT on the WOMAC score was superior to that of a control or sham group in five [19,22,27–29] of the six controlled trials that assessed this outcome. Only the study by Ediz et al. [18] did not observe differences in the long term (12-month follow-up) (Fig. 5). The effect of ESWT on the WOMAC was superior compared to some conservative treatments, such

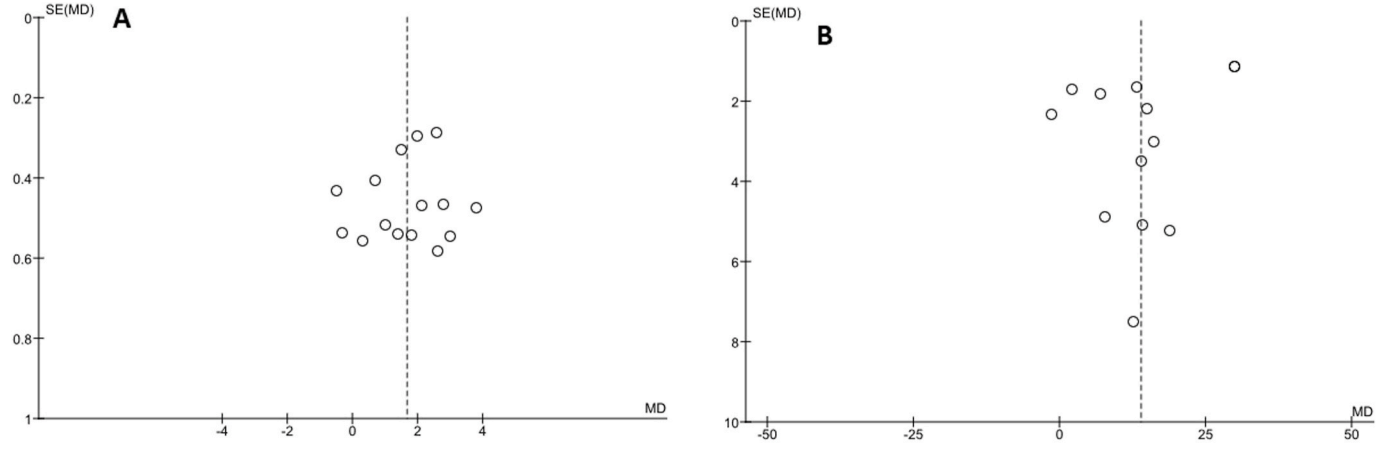

Fig. 3. Funnel plot for the comparison of extracorporeal shockwave therapy vs. control/another intervention. A) Left figure: pain outcome as measured on a VAS. B) Right figure: WOMAC outcome.

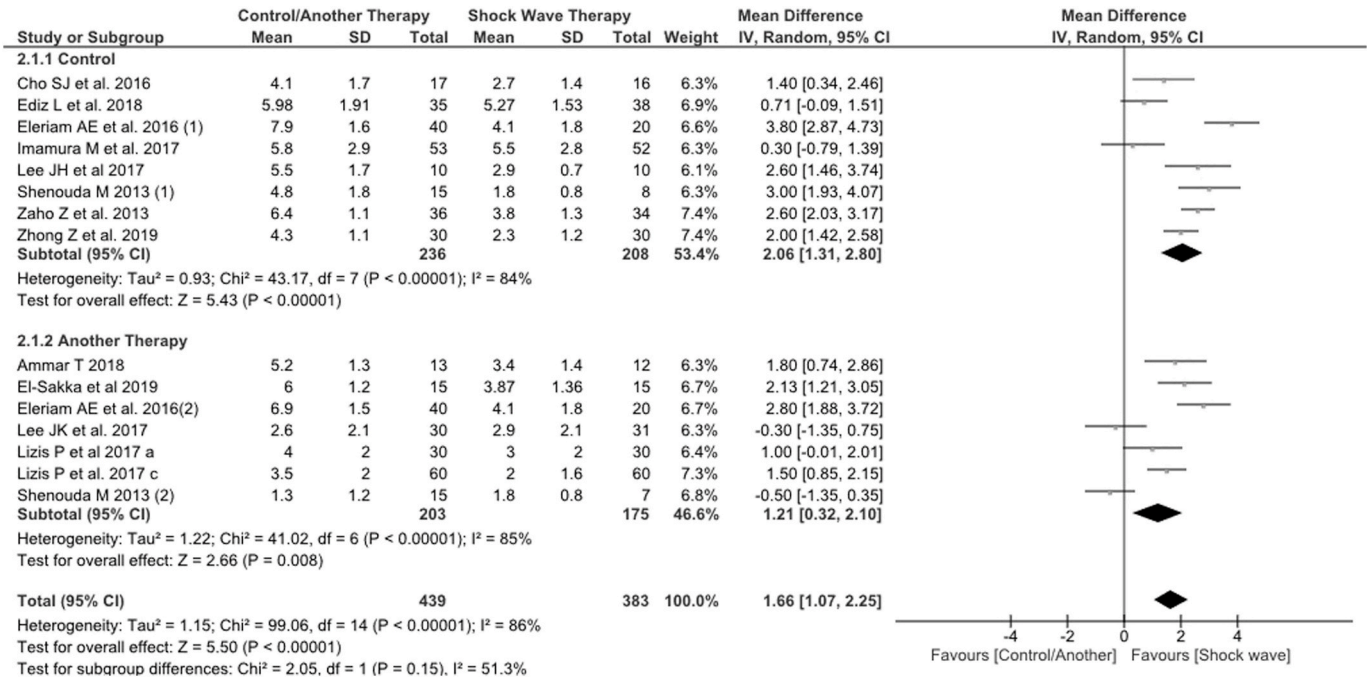

Fig. 4. Forest plot for the overall effect on the pain VAS comparing ESWT vs. control/another intervention and subgroup analysis depending on the comparator (ESWT vs. control/ESWT vs. another therapy). For studies with three arms (1), Comparator: control or sham control (2). Comparator: another therapy.

Table 2
Subgroups analysis in VAS pain and WOMAC score of Extracorporeal Shock-Wave Therapy versus control or other intervention for knee osteoarthritis.

Outcome	Subgroup	Studies or arms, n	Knees n	Heterogeneity I^2% (p value)	Random effects Mean difference (95% CI)	Subgroups difference Chi^2 (p value)
VAS	Follow-up period					
	≤5 weeks	8	333	80% (p < 0.001)	1.6 (0.8–2.3)	1.1 (p = 0.57)
	12 weeks	4	296	90% (p < 0.001)	1.2 (0.01–2.4)	
	24–52 weeks	3	194	92% (p < 0.001)	2,4 (0.6–4.3)	
	Dosage [1]					
	Medium	9	495	88% (p < 0.001)	2.1 (1.3–2.8)	3.83 (p = 0.05)
	Low or High	6	327	70% (p < 0.001)	1.0 (0.3–1.8)	
	Type					
	Radial	8	608	85% (p < 0.001)	1.9 (1.2–2.6)	0.58 (p = 0.45)
	Focused	6	184	88% (p < 0.001)	1.3 (0.1–2.5)	
WOMAC	Follow-up period					
	≤5 weeks	7	280	0% (p = 0.81)	14.6 (11.9–17.3)	4.5 (p = 0.10)
	12 weeks	3	191	92% (p < 0.001)	6.4 (−1.4 to 14.3)	
	24–52 weeks	3	193	99% (p < 0.001)	20.8 (5.5–36.0)	
	Dosage [a]					
	Medium	9	475	96% (p < 0.001)	17.7 (10.9–24.5)	9.81 (p = 0.002)
	Low or High	4	189	67% (p = 0.03)	4.0 (−1.2 to 9.2)	
	Type					
	Radial	7	483	98% (p < 0.001)	16.0 (6.9–25.0)	0.67 (p = 0.41)
	Focused	6	181	83% (p < 0.001)	10.9 (2.9–18.9)	

Bold text indicates statistically significant for subgroup differences (p-value < 0.05) and no statistically significant for heterogeneity (p-value >0.05).
[a] Medium dosage: (0.08–0.25 mJ/mm^2 or 1.5–2.5 bar). Low or High dosage: (<0.08 and >0.25 mJ/mm^2 or <1.5 and >2.5 bar).

as interferential currents [16], intra-articular injections with corticosteroids [19], and kinesiotherapy [25,26], but not when compared to ultrasounds [20], intra-articular injections with hyaluronic acid [23], or mobilization according to Mulligan's protocol [27] (Fig. 5).

When analyzing the WOMAC score by subgroups, no significant differences were found between the effect of ESWT compared with a control group and the effect of ESWT compared with other treatments (Chi2 = 0.02, p = 0.88) (Fig. 5). In addition, no differences were found when comparing follow-up periods of ≤5 weeks, 12 weeks, and 24–52 weeks; however, the group with a shorter follow-up period did not show heterogeneity (Table 2 and Supplementary Appendix 2). Similarly, no differences were found when comparing the effect of radial ESWT versus the effect of focal ESWT (Table 2 and Supplementary Appendix 2). In terms of dosage, a greater effect was observed (Chi2 = 9.8, p = 0.002) when using medium intensity doses (0.08–0.25 mJ/mm2 or 1.5–2.5 bar) compared to low or high ones (<0.08 and >0.25 mJ/mm2 or <1.5 and >2.5 bar) (Table 2 and Supplementary Appendix 2). The quality of evidence according to GRADE was moderate in terms of factors to rating down (very serious risk of bias and serious inconsistency or heterogeneity of results) and factors to rating up (dose response and magnitude of effect).

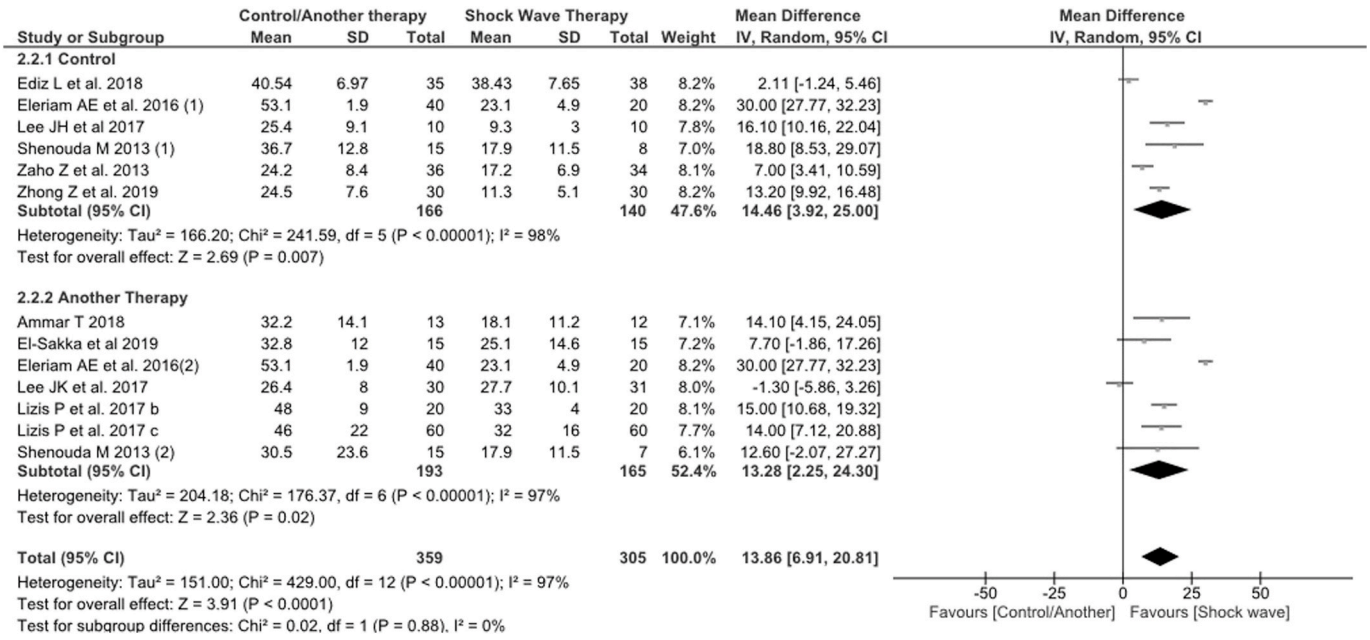

Fig. 5. Forest plot for the overall effect on the WOMAC comparing ESWT vs. control/another intervention and subgroup analysis depending on the comparator (ESWT vs. control/ESWT vs. another therapy). For studies with three arms (1), Comparator: control or sham control (2). Comparator: another therapy.

3.4.3. Effect on the range of motion (ROM) and walking tests

All clinical trials that assessed the effect of ESWT on the ROM observed a significant increase in this variable compared to control or other interventions. Specifically, the average increase in the ROM was 17.5° greater (CI95%: 9.4–25.5) using ESWT compared to other treatments (Fig. 6). The quality of evidence according to GRADE was very low in terms of factors to rating down (very serious risk of bias and serious inconsistency or heterogeneity of results). The overall effect on walking tests was also superior using ESWT (SMD = 0.58; CI95%: 0.35–0.81). No differences were found for this variable between ESWT and ultrasounds [20,24] or intra-articular hyaluronic acid injection [23] (Fig. 6). The quality of evidence according to GRADE was very low in terms of factors to rating down (very serious risk of bias and serious inconsistency or heterogeneity of results).

4. Discussion

This systematic review examined the effectiveness of ESWT on pain and functionality versus that of control or conservative treatments in patients suffering from KOA. The outcome of this meta-analysis showed a clinically significant reduction of pain on a VAS (1.7 cm; CI95%: 1.1–2.3) using ESWT compared to that experienced by the control or other conservative treatments groups, with a "moderate" recommendation level according to GRADE. Some trials have determined that a change of 1.4–2.0 cm in muscle-skeletal pain can be considered clinically significant [33,34]. Patients treated with ESWT also obtained a clinically significant reduction (13.9 points; CI95%: 6.9–20.8) in the WOMAC compared to that experienced by the control or other conservative treatments groups, with a "moderate" recommendation level

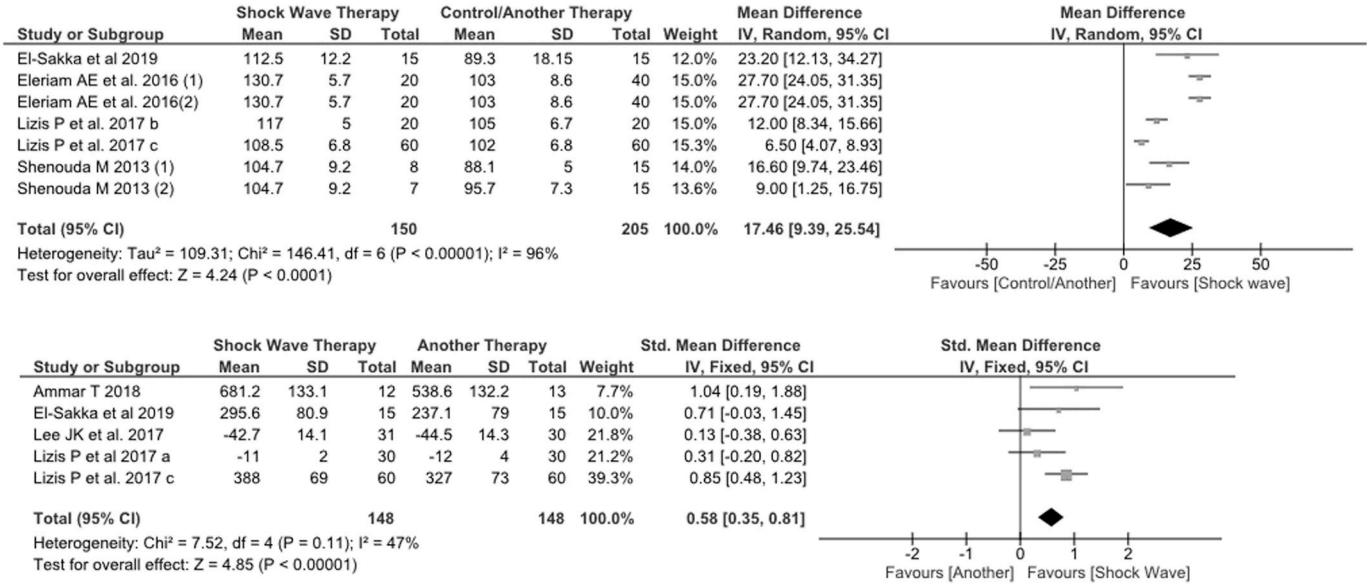

Fig. 6. Top figure: forest plot for the overall effect on ROM comparing ESWT vs. control/another intervention. Bottom figure: forest plot for the overall effect on the walking test comparing ESWT vs. another intervention. For studies with three arms (1), Comparator: control or sham control (2). Comparator: another therapy.

according to GRADE. Angst et al. determined that the minimal clinically important rehabilitation effect in patients with KOA ranged between 8 and 10 points in the WOMAC score [35]. In addition, ESWT could be considered a safe therapy, since only few, mild adverse effects were observed in the included studies. However, it was not possible to perform a quantitative analysis of them because the included studies did not report quantitative data on adverse effects.

In the analysis by subgroups of the main variables (pain VAS and WOMAC), dosage was the principal factor likely to affect the treatment effectiveness on pain and functionality. Medium energy flux densities of ESWT (0.08–0.25 mJ/mm2 or 1.5–2.5 bar) showed a superior effect to applying low or high densities (<0.08 and >0.25 mJ/mm2 or <1.5 and >2.5 bar). Additionally, applying ESWT at low or high doses did not show a superior effect on the WOMAC score compared to the control or other interventions. Similarly, a comparative study that was not included in this meta-analysis observed that medium energy densities of ESWT (0.093 mJ/mm2) exerted a greater effect on pain and functionality of the knee in patients with KOA than low densities (0.04 mJ/mm2) [36]. On the other hand, some pre-clinical studies have reported that doses >0.25 mJ/mm2 could have a negative effect on the cellular death of human chondrocytes in vitro [37] and could reduce the positive effects of ESWT on proliferation, apoptosis, and cellular migration of human bone marrow stromal cells [38]. In addition, a previous study of a model of KOA in rats showed that energetic densities of 0.5 mJ/mm2 caused degradation of cartilage [39].

In terms of secondary variables, the ROM also experienced a greater improvement in patients treated with ESWT compared to those in control or other interventions arms in the seven clinical trials included. The improvement in the ROM could positively correlate with achievement of expectations, increased satisfaction, perception of a “normal” knee, and functional improvement, as has been observed in patients with KOA after total knee arthroplasty [40,41]. Additionally, a low ROM is a predictive factor for limitations in functional activities in patients with KOA [42]. The observed improvement in walking tests in patients treated with ESWT compared to other interventions can be considered as “moderate” (SMD >0.4 and < 0.7) according to the Cochrane Group Guidelines [12]. However, combining ESWT with exercising and functional training might improve the effect on walking speed. The recommendation level according to GRADE was very low for the ROM and walking tests for two reasons: the magnitude of the effect was moderate, and determining its relationship with dosage was not possible given the scarce number of trials analyzing these variables in the subgroup analysis.

In view of the individual outcomes of the included studies that compared the effect of ESWT with that of other conservative treatments, this review observed that ESWT was superior in at least one of the four assessed outcome variables, with the exception of hyaluronic acid injection, where no differences were found [23]. However, intra-articular hyaluronic acid injection is an invasive technique that could cause more complications or adverse effects [43] than ESWT, which has shown to produce few, minor side effects. On the other hand, almost all studies included in this review are from developing countries, suggesting that ESWT is more widely used for the treatment of KOA in these countries. This may potentially be related to a lower access of the population to knee replacement surgery. The average yearly rate of knee arthroplasties per 100,000 citizens was 126 in The Organization for Economic Co-operation and Development (OECD) countries, but the included studies reported lower rates of 40, 67, or 121 in countries like Poland, Turkey, or South Korea [44], respectively, which were considerably lower in Brazil [45] with 4 or Egypt [46] with 15.

Although there are three meta-analysis previously published, this study includes a higher number of RCTs (n = 14) involving 782 patients and 877 knees. The meta-analysis published by Li et al. [10] included seven RCTs involving 366 patients, Ma et al. [47] included three RCTs and four cohorts studies involving 589 patients, and Wang et al. [48] included nine studies (eight RCTs and one retrospective study) of which only four (involving 318 subjects) were finally included in the quantitative analysis to verify the main hypothesis. Furthermore, the three above-mentioned meta-analyses included one RCT [49] was that was excluded from this study since its objective was studying the effect of ESWT on pain and functional disabilities produced by popliteal sesamoid cyamella in patients with KOA [49]. The study by Li et al. [10] observed an improvement similar to ours (~2 points on the VAS when comparing ESWT to sham stimulation, slightly less than 15 points on the WOMAC and ~17° on the knee ROM). However, Ma et al. [47] detected a substantially lower improvement than ours, with a change on the VAS of 0.4 to 0.2 points and 2.3 to 3.6 points in the WOMAC. Similarly to our study, Wang et al. [48] observed an improvement of 2 points on the VAS for a follow-up period of <2 months compared to sham stimulation, but not with longer follow-up periods. The three previously mentioned meta-analyses [10,47,48] did not analyze the effect on walking nor performed specific analyses by subgroups to account for follow-up periods or the comparator. Furthermore, the differences this study observed in the subgroup analysis by dosage provides relevant information for the clinical application of ESWT and the design of future studies.

An important limitation of this review is the large heterogeneity in the results of the assessed variables. The only factor that decreased such heterogeneity for the WOMAC variable was a short follow-up period (≤5 weeks). Although it was not possible to determine factors accounting for this high heterogeneity or inconsistency of the results, it could stem from the large variability in demographic and clinical characteristics of the samples. The average age range was very broad (43–75 years) and the duration of symptoms for the included patients ranged between three months to over one year. Both age and symptoms duration are predictive factors for functional limitations as measured via the WOMAC or walking tests [42]. Included patients also showed high heterogeneity in terms of severity of KOA according to radiological criteria, with levels ranging from K-L I to K-L IV. Additionally, protocols for applying ESWT were also heterogeneous. Other considerable limitations of this meta-analysis were the high risk of bias and short follow-up periods (≤12 weeks) of the included trials, with only two studies having a follow-up period of >12 weeks [18,19].

In conclusion, the current review supports ESWT as being effective for improving pain and functionality in patients with mild and moderate KOA in the short term (≤12 weeks) and with few, minor side effects. However, the certainty of this evidence was graded “moderate”. Energy flux density for applying ESWT can be a key factor for treatment effectiveness, yet further investigation is required to determine the optimal dosage and parameters for its application. This work found a superior effect of ESWT compared to other conservative treatments, so this therapy should be considered as first line treatment prior to using them or others of an invasive or surgical nature. Future clinical research and reviews should be designed with longer follow-up periods and lower risk of bias in order to improve the certainty of this evidence.

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Ethical approval

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Author contribution

Juan Avendaño Coy: conceptualization, methodology, software, formal analysis, writing-review, project administration.

Natalia Comino Suárez: conceptualization, methodology, data collections, visualization, resources.

Jesús Grande Muñoz: conceptualization, methodology, data collections.

Carlos Avendaño López: data analysis and investigation.

Julio Gómez Soriano: data analysis, investigation, editing and review.

Trial registry number

1. Name of the registry: PROSPERO.
2. Unique Identifying number or registration ID: CRD42019126507.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=12 6507.

Guarantor

Natalia Comino Suárez and **Juan Avendaño Coy** are responsible of the integrity of this work as a whole from inception to finished article.

Declaration of competing interest

Nothing to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2020.07.055.

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