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Efficacy and Safety of Extracorporeal Shockwave Therapy for Treatment of Knee Osteoarthritis: A Systematic Review and Meta-analysis

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Conflict of interest: There are no conflicts of interest to report.

Abstract

Objective. The objective of this study was to assess the efficacy and safety of extracorporeal shockwave therapy (ESWT) for treatment of knee osteoarthritis (OA) using a systemic review and meta-analysis. **Methods.** An extensive search of relevant articles from electronic databases Pubmed, Embase, and Cochrane Library from inception to March 2019 was conducted. The treatment outcomes (visual analog scale [VAS] and the Western Ontario and McMaster Universities Arthritis Index [WOMAC]) of the included articles were pooled to calculate effect sizes. The assessment of heterogeneity among articles was evaluated using I^2. Statistical analyses were conducted using RevMan software. **Results.** The results showed that the ESWT group had significant improvement in pain relief compared with the control group through 12 months based on WOMAC and VAS scores. Compared with the baseline level, the patients had significant improvement in pain relief at most follow-up points (one week to 12 months) based on WOMAC and VAS scores. The patients showed significant improvement in physical function at six- and 12-month follow-up when compared with the control group and for all follow-up (one to 12 months) when compared with the baseline level. Additionally, only minor complications were observed after ESWT treatment. **Conclusions.** The use of ESWT for treatment of knee OA had a beneficial effect on pain relief and physical function improvement for up to 12 months, and only minor complications occurred after ESWT treatment. However, there remains a lack of clarity regarding the frequency and dosage levels of ESWT required to achieve the maximum improvement.

Key Words: Knee Osteoarthritis; Shockwave; Meta-analysis

Introduction

Knee osteoarthritis (OA) is a prevalent degenerative disease and causes musculoskeletal disability. Pain, stiffness, and loss of physical function are the most common symptoms of knee OA [1]. The most vulnerable group is overweight females older than 50 years of age [2]. More than 10 million patients with knee OA have been reported in the United States [3], and treatment costs $42.3 million annually [4] .

Total knee arthroplasty is the finial therapy for knee OA. To prevent or delay knee replacement surgery, several treatments have been developed, such as nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular hyaluronic acid, physical therapy, exercise, and weight control [5–7]. The most relevant clinical guidelines provide recommendations for the management of knee OA via systematic literature reviews of evidence-based clinical practice and recommend strengthening and low-impact aerobic exercises, weight loss, NSAIDs, and opioids as strong recommendations [8–11]. Oral glucosamine and chondroitin are not recommended. Duloxetine and intra-articular corticosteroids have weak

recommendations for patients, and the efficacy of intra-articular hyaluronic acid is uncertain.

A shockwave is a steep rise in pressure amplitude, and it can propagate quickly via a medium. Shockwaves can be generated by three methods (electromagnetic, piezoelectric, or electrohydraulic) for producing shockwaves for focusing into a specific region of tissue [12] and have been reported since the early 1970s for medical purposes [13,14], proving to be effective for treating kidney, salivary, and urinary calculi [15]. More recently, shockwaves have been introduced for treatment of orthopedic pathologies such as bone non-unions, tendinopathies, and OA [15,16].

Although the precise biochemical mechanism of extracorporeal shockwave therapy (ESWT) for knee OA remains unclear, recent studies have shown the positive role of ESWT in treatment for knee OA [17–19]. Some studies have proven that ESWT may cause anti-inflammatory, angiogenic, anti-edema, and trophic effects in the repair of bone and cartilage [18,20–23]; however, there remains a conundrum regarding the efficacy and safety of ESWT in the treatment of knee OA. To achieve a maximum efficacy of ESWT, different dosage levels have been adopted to treat knee OA, and dose-related effects have been observed [24]. The objective of this study was to assess the evidence on ESWT for patients with knee OA via a systematic review and meta-analysis by comparing a placebo-controlled or control group before and after treatment. The efficacy and safety of this treatment were expected to be understood.

Methods

Literature Search

An extensive search of relevant articles from the electronic databases Pubmed, Embase, and Cochrane Library was carried out from inception to March 2019. The following search specifics were used across the databases: ("shockwave" OR "shock wave") AND "knee" AND ("osteoarthritis" OR "arthritis" OR "arthritic"). The identified articles were then screened individually for inclusion.

Study Selection

Articles in English that assessed outcome after ESWT for patients with knee OA were eligible. The inclusion criteria were as follows: 1) articles that were human studies, prospective studies, retrospective studies, and randomized controlled trials; and 2) data that contained at least one clinical measurement, including the visual analog scale (VAS) and the Western Ontario and McMaster Universities Arthritis Index (WOMAC). The exclusion criteria were as follows: 1) articles that were animal studies, in vitro studies, review studies, case reports, letters, and editorials; 2) data that had no VAS or WOMAC score. First, two authors (YCW and CLS) independently screened the title and abstract of each identified article; then, the remaining articles were screened through full-text review. Any disagreement about inclusion was discussed until a consensus was reached. The references of the included articles were also screened.

Data Extraction

Relevant data were extracted from the included articles, including the first author's family name, publication year, type of study design, intervention of each group, the mean age of patients, the percentage of males, body mass index, number of patients, disease severity, follow-up duration, details of treatment protocols and controls, dosage levels, WOMAC score, and VAS score. WOMAC was considered the primary outcome, and VAS score was the secondary outcome. If the articles did not provide detailed outcomes, we requested the data via e-mail.

Quality and Risk of Bias Assessment

The two authors independently assessed the quality of the included articles using the Cochrane Collaboration Tool for the risk of bias assessment. We followed the assessment method to conduct the risk of bias assessment as described in a previous study [25]. Any discrepancy between the authors was discussed until a consensus was reached.

Statistical Analysis

Statistical analyses were conducted using RevMan 5.3 software (The Cochrane Collaboration, Copenhagen, Denmark). For subgroup analysis, the need for at least two articles for the particular follow-up period and outcome to perform a meta-analysis was recommended by Cochrane. The number of patients, means, and standard deviations were pooled to calculated effect size, mean difference (MD), and 95% confidence interval (CI). The assessment of heterogeneity was evaluated using I^2. If $I^2 < 50\%$, a fixed-effect model was used; otherwise, a random-effect model was used. A P value <0.05 was considered significant.

Ethical Approval

Only published data from previous studies were adopted in the meta-analysis. This study did not require ethical approval.

Results

Search Results

The flow diagram of the article screening process is shown in Figure 1. After an initial literature search of three databases, a total of 145 articles were identified. Of these, 46 duplicates were excluded. The titles and abstracts of the remaining 86 articles were screened, and 69 articles were removed based on the inclusion/exclusion criteria. Ultimately, 17 articles were screened through full-text review, and nine articles met the inclusion criteria. One of the nine articles reported mean

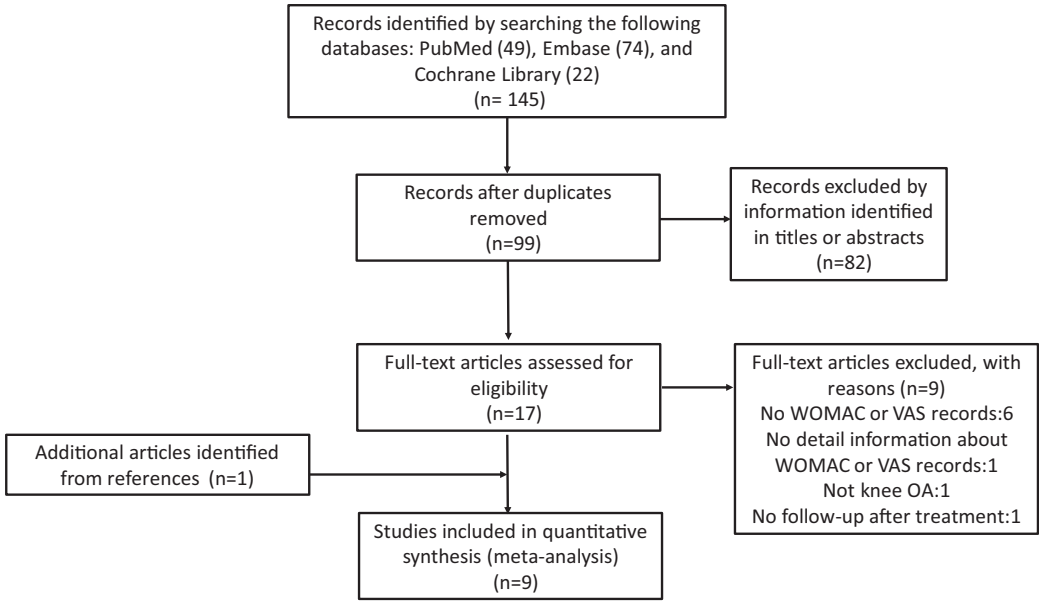

Figure 1. Flowchart of the study screening process.

WOMAC and VAS scores for their follow-up visits, but the corresponding standard deviation values were not reported [16]. We contacted the author of the article to request these data, but we did not receive a reply. Therefore, the article was excluded. An additional single article was screened from the references of the eight included articles; thus, a total of nine articles were included in the meta-analysis.

Study Characteristics

The characteristics of the included articles are shown in Table 1. Among the nine included articles, eight articles were randomized controlled trials [19,24,26–31], and one article was a retrospective study [18]. The sample sizes of each group ranged from nine to 82, with a total of 431 patients. One article had a total follow-up period of one week [29], one had one month [28], one had five weeks [19], two had three months [24,27], one had five months [30], one had eight months [31], and two had 12 months [18,26]. The mean age of patients ranged from 50.9 to 75.5 years. The percentage of males ranged from 35 to 90. All articles reported the severity of knee OA using the Kellgren and Lawrence grading scales except for two articles [19,30]. Most patients had a severity between class II and class III. The treatment protocol and the use of dosage levels of ESWT varied among these articles.

Risk of Bias

The risk of bias of the four RCTs that were placebo-controlled or controlled studies was assessed (Figure 2) [26,29–31]. Two RTCs mentioned the method used to generate random numbers [29,31]. Envelopes for allocation concealment were adopted by two RCTs [30,31]. Two RCTs reported that the study design included double-blinding trials [29,30]. The risk of incomplete outcome was low for the three RCTs [26,29,30]. The risk of selective outcome reporting was low for the four RCTs [26,29–31].

Outcomes of the Meta-analysis

WOMAC Total Score

WOMAC score was used to assess patients' functions. It contains three subscales measuring pain, stiffness, and physical function. Among the four RCTs that were placebo-controlled or controlled studies, only two reported WOMAC scores. The pooled analysis of the two RCTs showed that the patients in the ESWT group showed no greater improvement in WOMAC total score than those in the control group at five to six months of follow-up (MD = –12.02, 95% CI = –31.29 to 7.24, I^2 = 99%, $P = 0.22$); this became significant improvement at 12-month follow-up (MD = –2.29, 95% CI = –4.44 to –0.15, I^2 = 0%, $P = 0.04$) (Figure 3). In addition, the improvement in WOMAC score between the baseline level and follow-up was investigated. After ESWT treatment, the patients showed significant improvement in WOMAC total score from the one- to two-week follow-up to the three-month follow-up and reached the maximum improvement at three-months follow-up (Figure 4). The improvement showed an increased trend from the one- to two-week follow-up (MD = 19.45, 95% CI = 2.21 to 36.68, I^2 = 98%, $P = 0.03$) to the three-month follow-up (MD = 38.46, 95% CI = 17.27 to 59.66, I^2 = 99%, $P = 0.0004$) and then became nonsignificant from the five-month follow-up to the 12-month follow-up (MD = 22.95, 95% CI = –6.21 to 52.12, I^2 = 100%, $P = 0.12$, for five to six months; MD = 21.48, 95% CI = –18.12 to 61.08, I^2 = 100%, $P = 0.29$, for 12 months).

Table 1. Summary of main characteristics of the included articles

Obs	Study	Interventions	Additional Treatment	Study Design	With Bone Marrow Edema, %*	Sample Size	Age, Mean±SD, y	BMI, Mean±SD, kg/m^2	Male, %	Disease Severity (KL)	Shockwave		Extracted Outcome Type	Follow-up Time
											Treatment Process	Dose Level		
1	Kang et al. 2018 [18]	ESWT	Received intravenous alprostadil (10 μg, qd for 2 wk) after ESWT	RT	16.7	82	50.9±9.2	27.6±4.7	43	1∼3	A total of 2 sessions and the number of the frequency selected depends on the patient's condition	3,000–4,000 pulses of >0.44 mJ/mm^2 at a frequency of 2∼3 Hz	WOMAC and VAS	2 wk, 1 mo, 3 mo, 6 mo, and 12 mo
2	Ediz and Ozgokce 2018 [26]	Group 1: ESWT	No	RCT	7.5	37	69.74±3.91	27.12±5.09	35	2∼3	Two weekly sessions were performed for 5 wk	2,500 pulses at a pressure of 3 bar and a frequency of 12 Hz	WOMAC and VAS	6 and 12 mo
		Group 2: ESWT	No		0	38	70.48±4.18	26.91±4.67	53	2∼3	Two weekly sessions were performed for 5 wk	2,500 pulses at a pressure of 3 bar and a frequency of 12 Hz		
		Group 3: placebo	No		0	35	69.65±4.49	26.89±4.85	37	2∼3	Two weekly sessions were performed by sham ESWT for 5 wk	2,500 pulses at a pressure of 3 bar and a frequency of 12 Hz		
3	Lee et al. 2017a [27]	ESWT	No	RCT	0	31	67.7±5.5	24.9±3.9	81	2.3±0.5	A total of 3 sessions of shockwave were performed weekly for 12 wk	1,000 pulses of 0.05 mJ/mm^2	WOMAC and VAS	1 and 3 mo
4	Lee et al. 2017b [28]	ESWT	Received physical therapy consisting of heat pack (20 min), interference current therapy (15 min), and ultrasound (5 min) before ESWT	RCT	0	10	64.2±4.1	NA	NA	2	NA	1,000 pulses at a frequency of 4 Hz	VAS	1 mo
5	Lizis et al. 2017 [19]	ESWT	No	RCT	0	20	63.5 ± 8.0	24.92±1.91	35	NA	A total of 5 sessions of shockwave were performed weekly for 5 wk	8,000 pulses of 0.03∼0.4 mJ/mm^2 at a frequency of 8 Hz	WOMAC	5 wk

(continued)

Table 1. continued

Obs	Study	Interventions	Additional Treatment	Study Design	With Bone Marrow Edema, %*	Sample Size	Age, Mean±SD, y	BMI, Mean±SD, kg/m^2	Male, %	Disease Severity (KL)	Shockwave		Extracted Outcome Type	Follow-up Time
											Treatment Process	Dose Level		
6	Cho et al. 2016 [29]	ESWT	No	RCT	0	9	75.5±7.7	NA	89	2.0±1.1	Shockwaves were performed weekly for 3 wk	1,000 pulses of 0.05 mJ/mm^2	VAS	1 wk
		Placebo	No		0	9	72.7±5.9	NA	78	1.8±1.1	Shockwaves were performed weekly for 3 wk	1,000 pulses of 0 mJ/mm^2		
7	Elerian et al. 2016 [30]	ESWT	No	RCT	0	20	NA	NA	NA	NA	A total of 3 sessions of shockwave were performed weekly for 3 wk	2,000 pulses at a frequency of 5 Hz	WOMAC and VAS	1, 5, and 21 wk
		Placebo	No		0	20	NA	NA	NA	NA	A total of 3 sessions of shockwave were performed weekly for 3 wk	2,000 pulses of 0 mJ/mm^2		
8	Kim et al. 2015 [24]	ESWT: low-energy	No	RCT	0	30	65.1±6.3	23.8±1.7	87	2∼3	A total of 3 sessions of shockwave were performed weekly for 12 wk	1,000 pulses of 0.04 mJ/mm^2	WOMAC and VAS	1 wk, 1 mo, and 3 mo
		ESWT: high-energy	No		0	30	63.5±5.4	24.2±2.1	90	2∼3	A total of 3 sessions of shockwave were performed weekly for 12 wk	1,000 pulses of 0.093 mJ/mm^2		
9	Chen et al. 2014 [31]	ESWT	Received isokinetic muscular strengthening exercises 3 times weekly for 8 wk	RCT	0	30	NA	NA	NA	NA	Shockwaves were performed weekly for 6 wk	2,000 pulses of 0.03∼0.4 mJ/mm^2 at a frequency of 1∼4 Hz	VAS	2 and 8 mo
		Control	No		0	30	NA	NA	NA	NA	NA	NA		

BMI = body mass index; ESWT = extracorporeal shockwave therapy; KL = Kellgren-Lawreance classification; RCT = randomized controlled trial; RT = retrospective trial; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; VAS = visual analog scale.

*The percentage of pain related to diagnosis among the total number of patients.

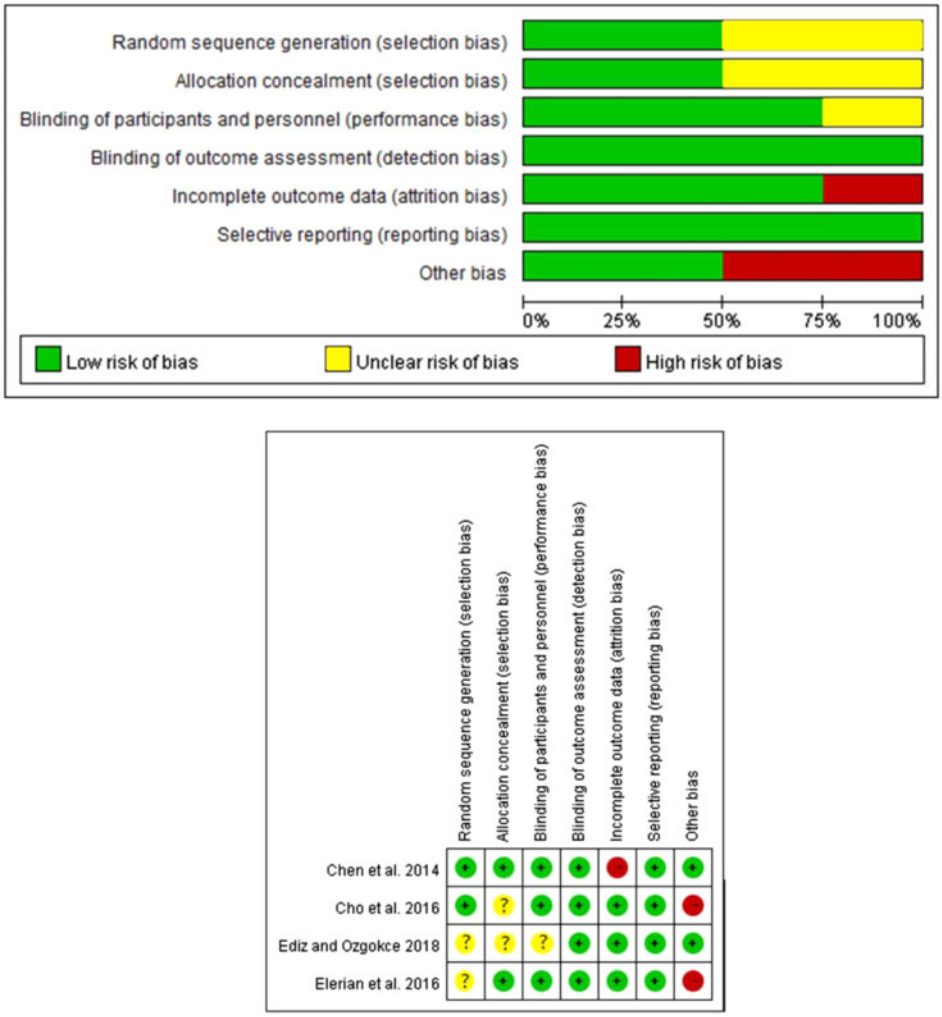

Figure 2. Risk of bias for the included four randomized controlled trials that were placebo-controlled or controlled studies.

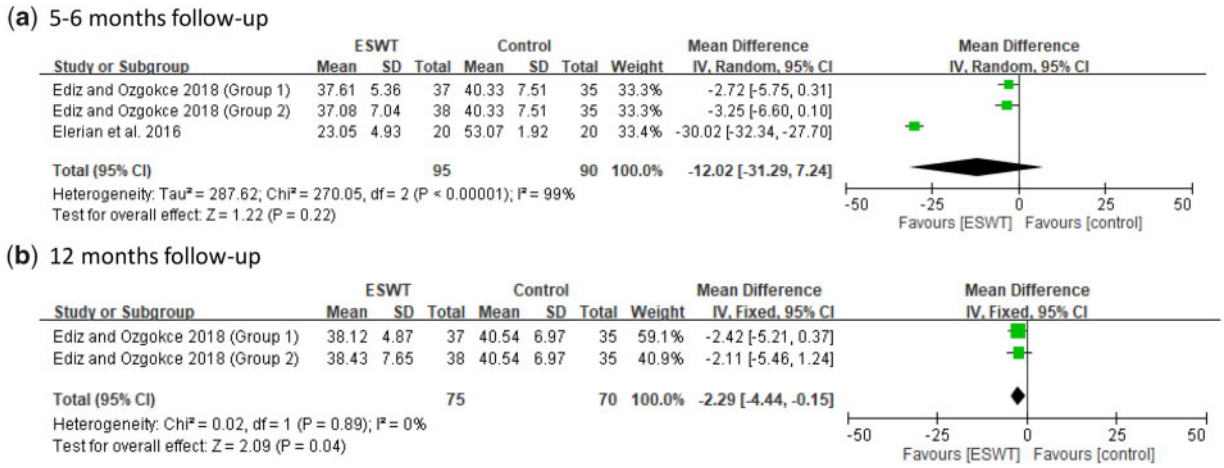

Figure 3. Forest plots of meta-analysis in comparison of Western Ontario and McMaster Universities Osteoarthritis Index total score improvement between the extracorporeal shockwave therapy and control groups at five- to six-month (A) and 12-month (B) follow-up. BMI = body mass index; KL = Kellgren-Lawreance classification; RCT = randomized controlled trial; RT = retrospective trial; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; VAS = visual analog scale.

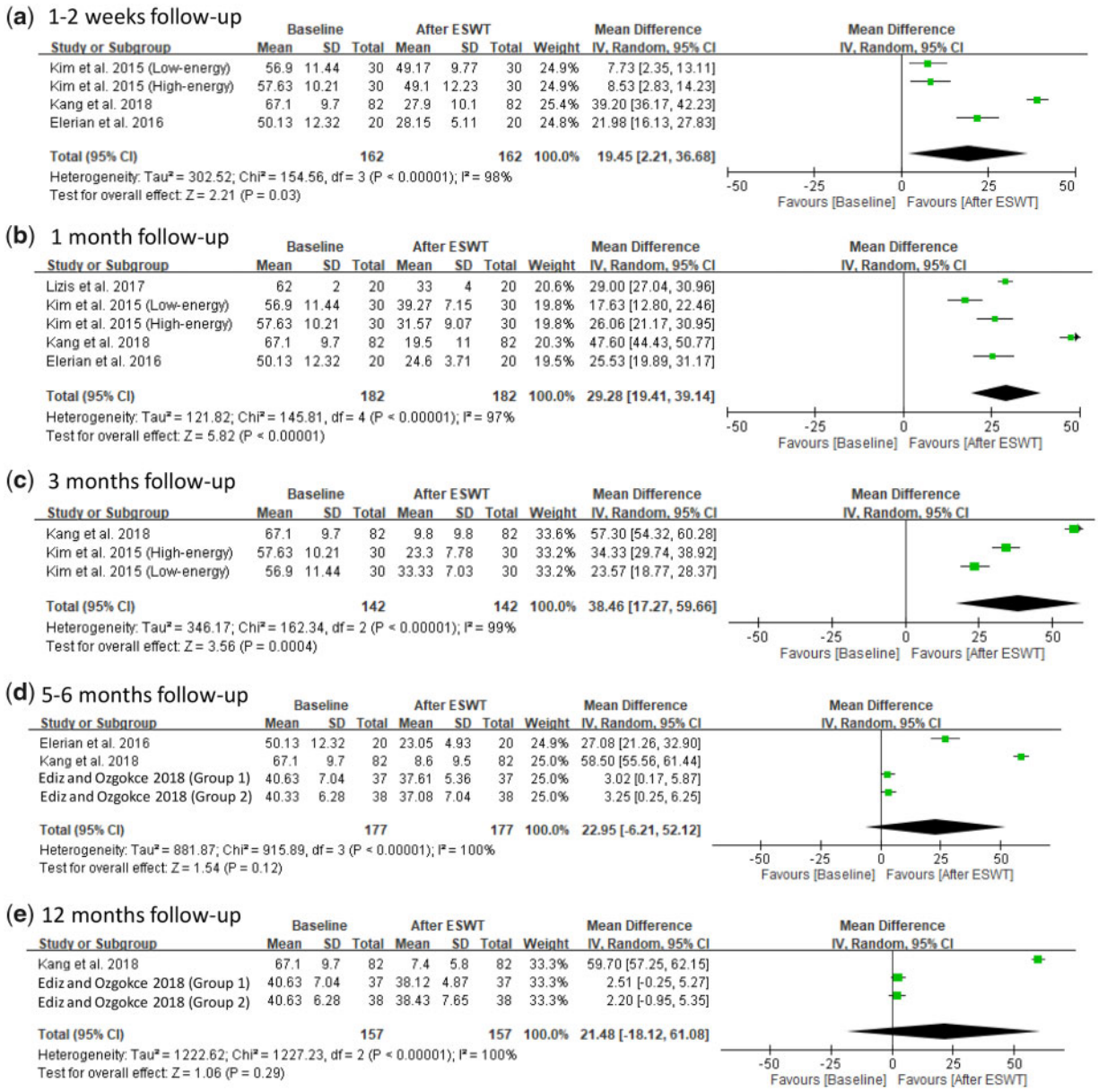

Figure 4. Forest plots of meta-analysis in comparison of Western Ontario and McMaster Universities Osteoarthritis Index total score improvement after extracorporeal shockwave therapy treatment at one- to two-week (A), one-month (B), three-month (C), five- to six-month (D), and 12-month (E) follow-up.

WOMAC Pain Score

The patients in the ESWT group showed greater improvement in pain score than those in the control group at six-month and 12-month follow-up (MD = –2.48, 95% CI = –3.71 to –1.25, $I^2 = 0\%$, $P < 0.0001$, for six-month; MD = –1.81, 95% CI = –3.28 to –0.33, $I^2 = 0\%$, $P = 0.02$, for 12-month) (Figure 5A). After ESWT treatment, the patients had significant improvement in pain relief for all follow-up time points (MD = 2.78, 95% CI = 1.64 to 3.93, $I^2 = 0\%$, $P < 0.00001$, for six months; MD = 2.46, 95% CI = 1.34 to 3.58, $I^2 = 0\%$, $P < 0.0001$, for 12 months) (Figure 6).

WOMAC Stiffness Score

The ESWT group showed greater improvement in stiffness score than the control group at six-month follow-up (MD = –0.47, 95% CI = –0.86 to –0.07, $I^2 = 0\%$, $P = 0.02$), but the score was not significant at 12-month follow-up (MD = –0.28, 95% CI = –0.66 to 0.11, $I^2 = 0\%$, $P = 0.16$) (Figure 5B). After treatment, the patients had significant improvement in stiffness at six-month follow-up (MD = 0.50, 95% CI = 0.14 to 0.86, $I^2 = 0\%$, $P = 0.006$) (Figure 7). However, the improvement become nonsignificant at 12-month follow-up (MD = 0.33, 95% CI = –0.07 to 0.72, $I^2 = 0\%$, $P = 0.11$).

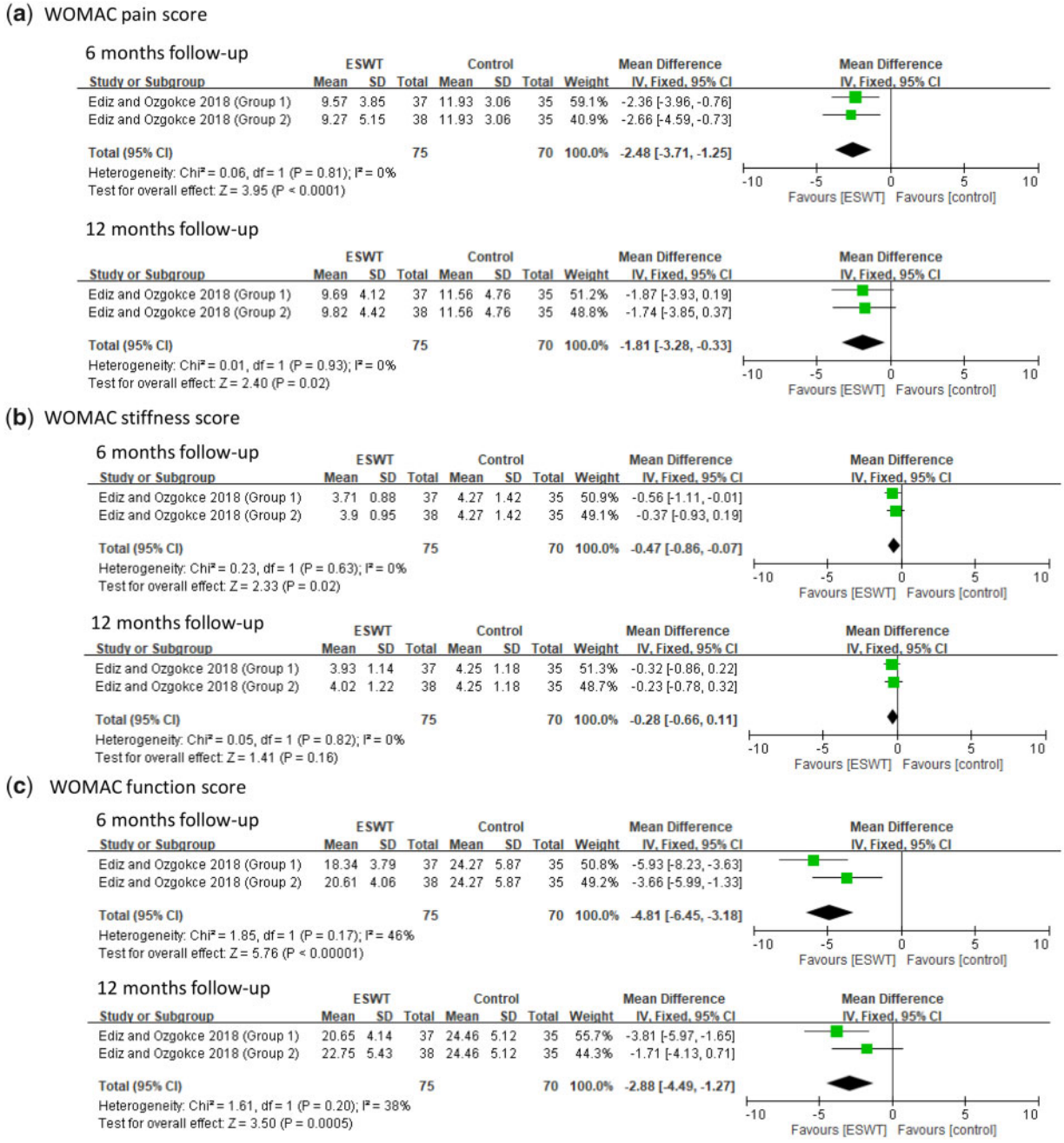

Figure 5. Forest plots of meta-analysis in comparison of Western Ontario and McMaster Universities Osteoarthritis Index pain (A), stiffness (B), and function (C) scores between the ESWT and control groups at six-month and 12-month follow-up.

WOMAC Function Score

The patients in the ESWT group showed greater improvement in physical function than those in the control group at six- and 12-month follow-up (MD = –4.81, 95% CI = –6.45 to –3.18, I^2 = 46%, $P < 0.00001$, for six-month; MD = –2.88, 95% CI = –4.49 to –1.27, I^2 = 38%, $P = 0.0005$, for 12-month) (Figure 5C). After treatment, significant improvement in physical function started at the one-month follow-up and was maintained up to the 12-month follow-up. The improvement reached the maximum improvement at one-month follow-up (MD = 12.88, 95% CI = 2.25 to 23.50, I^2 = 92%, $P = 0.02$) (Figure 8). The improvement showed a decreased trend between six-month and 12-month follow-up (MD = 5.38, 95% CI = 3.45 to 7.32, I^2 = 59%, $P < 0.00001$, for six months; MD = 3.31, 95% CI = 1.94 to 4.67, I^2 = 38%, $P < 0.00001$, for 12 months).

VAS Score

VAS score was used to measure pain severity. Among the included articles, four RCTs [26,29–31] were placebo-controlled or controlled studies and reported VAS scores. The pooled analysis of the four RCTs showed that the

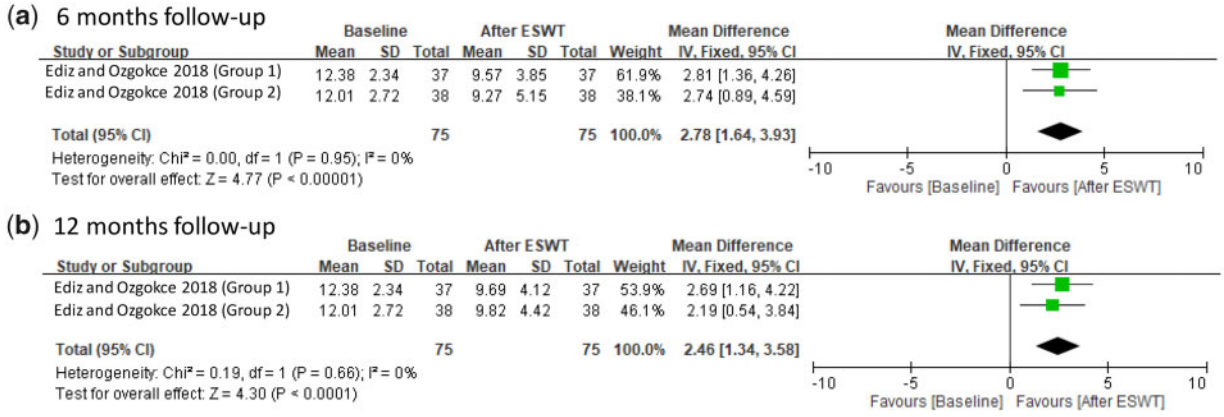

Figure 6. Forest plots of meta-analysis in comparison of Western Ontario and McMaster Universities Osteoarthritis Index pain score improvement after extracorporeal shockwave therapy treatment at six-month (A) and 12-month (B) follow-up.

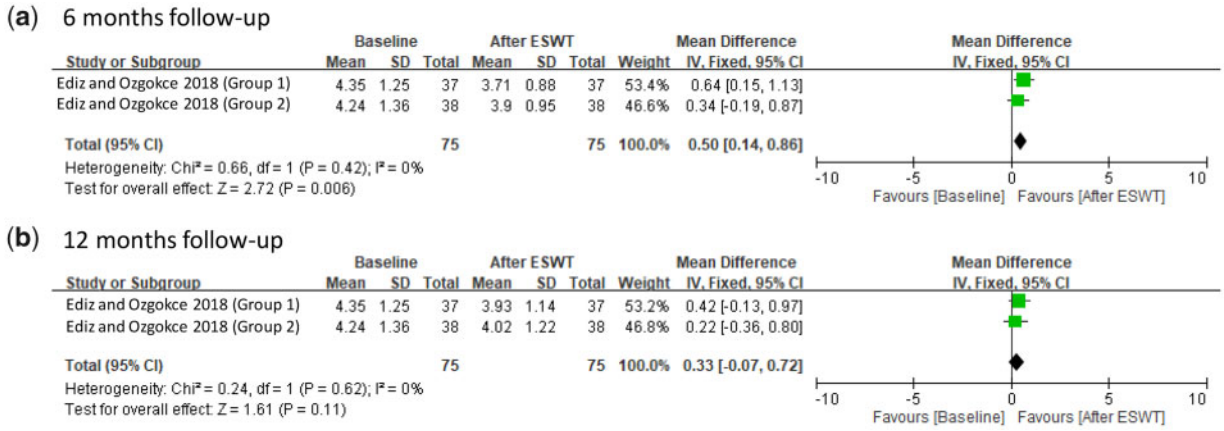

Figure 7. Forest plots of meta-analysis in comparison of Western Ontario and McMaster Universities Osteoarthritis Index stiffness score improvement before and after extracorporeal shockwave therapy treatment at six-month (A) and 12-month (B) follow-up.

patients in the ESWT group experienced significantly more pain relief than those in the control group at short-term follow-up (MD = –2.01, 95% CI = –2.86 to –1.16, $I^2 = 6\%$, $P < 0.00001$, for one week; MD = –2.67, 95% CI = –3.09 to –2.24, $I^2 = 0\%$, $P < 0.00001$, for one to two months) (Figure 9); their pain relief became non-significant at long-term follow-up (MD = –1.60, 95% CI = –3.33 to 0.14, $I^2 = 94\%$, $P = 0.07$, for five to six months; MD = –2.06, 95% CI = –4.56 to 0.45, $I^2 = 97\%$, $P = 0.11$, for eight to 12 months) (Figure 3). Eight articles reported VAS scores, and the improvement in pain relief compared with the baseline level was analyzed. The patients experienced significant pain relief at all follow-up time points and reached the maximum improvement at two to three months of follow-up (Figure 10). The improvement showed an increased trend from one- to two-week follow-up (MD = 2.38, 95% CI = 0.70 to 4.07, $I^2 = 97\%$, $P = 0.006$) to two- to three-month follow-up (MD = 4.16, 95% CI = 2.51 to 5.82, $I^2 = 98\%$, $P < 0.00001$) and then decreased from the five-month to 12-month follow-up (MD = 3.82, 95% CI = 0.29 to 7.34, $I^2 = 99\%$, $P = 0.03$, for five to six months; MD = 3.65, 95% CI = 0.18 to 7.11, $I^2 = 99\%$, $P = 0.04$, for eight to 12 months).

Adverse Effects

Four articles reported minor complications after ESWT treatment [18,19,26,27], such as minor bruising, transient soft tissue swelling, or transient skin reddening. No clinically detectable neuromuscular, device-related, or systemic adverse effects after ESWT treatment were reported by five articles [7,19,26–28].

Discussion

ESWT has been applied to treat knee OA, but its efficacy and safety have not been well investigated. In this study, we used a systematic review and meta-analysis to assess the efficacy and safety of ESWT for knee OA. We adopted WOMAC and VAS scores to assess efficacy, and the two measurements have been proven to be reliable and valid [32,33]. Thus, the results of our meta-analysis should be reliable. The meta-analysis showed that the patients receiving ESWT had significant improvement in

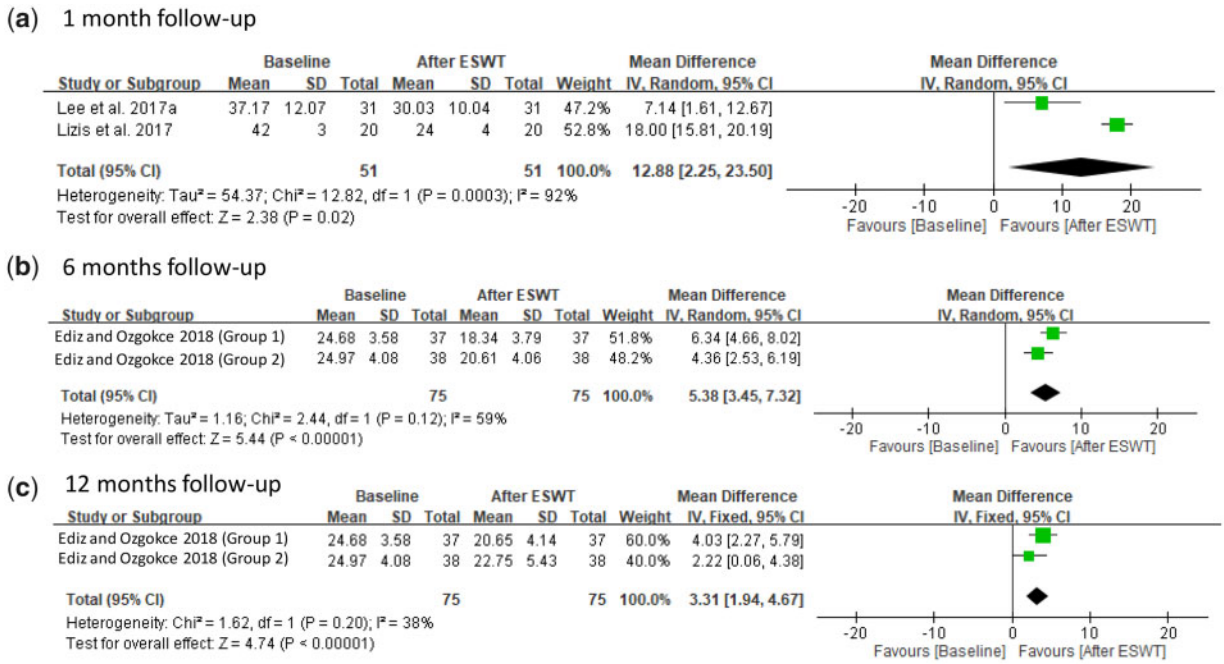

Figure 8. Comparison of Western Ontario and McMaster Universities Osteoarthritis Index function score improvement after extracorporeal shockwave therapy treatment at one-month (A), six-month (B), and 12-month (C) follow-up.

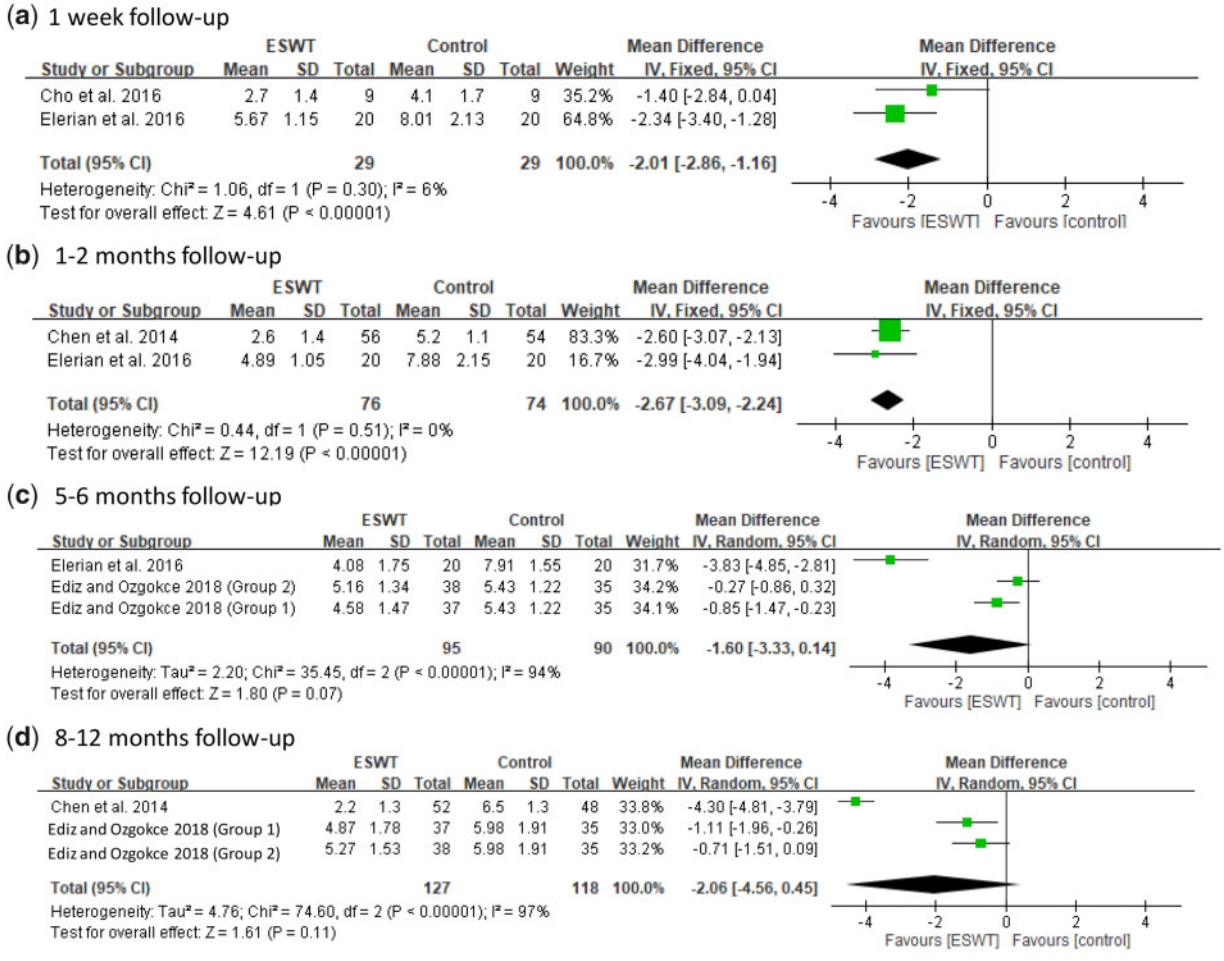

Figure 9. Forest plots of meta-analysis in comparison of visual analog scale score improvement between the extracorporeal shockwave therapy and control groups at one-week (A), one- to two-month (B), five- to six-month (C), and eight- to 12-month (D) follow-up.

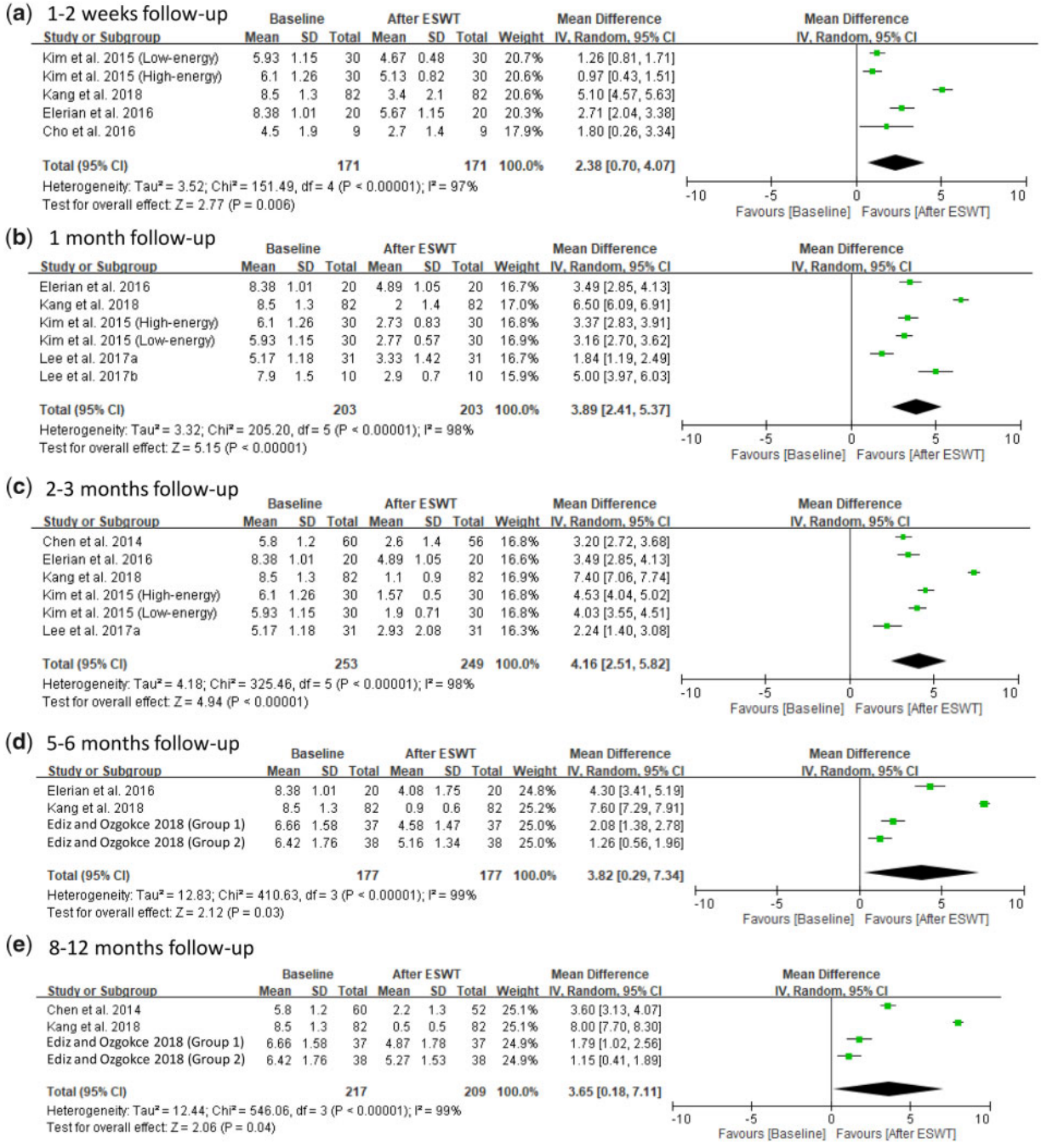

Figure 10. Forest plots of meta-analysis in comparison of improvements in visual analog scale score after extracorporeal shock-wave therapy treatment at one- to two-week (A), one-month (B), two- to three-month (C), five- to six-month (D), and eight- to 12-month (E) follow-up.

VAS scores compared with the control group at short-term (one week to two months) follow-up and had significant improvement in WOMAC pain score at long-term follow-up (six and 12 months). In general, after ESWT treatment patients had significant improvement in pain relief (WOMAC or VAS pain score) for all follow-up time points (one week to one year) compared with the baseline level. Patients had significant improvement in stiffness at six-month follow-up, but their stiffness scores became nonsignificant at 12-month follow-up compared with the baseline level, and similar results (significant at six months and nonsignificant at 12 months) were obtained when the ESWT group was compared with the control group. The patients had significant improvement in physical function from one- to 12-month follow-up compared with the baseline level, and similar results at six- and 12-month follow-up were obtained when the ESWT group was compared with the control group. Otherwise, only minor complications were observed after ESWT treatment. A systematic review also reported that

ESWT was safe for the treatment of orthopedic conditions [34].

In comparing efficacy between the ESWT and control groups, four articles reported VAS scores, and their controls were placebo [26,29,30] or nontreatment [31]. The meta-analysis revealed that the ESWT group had significant improvement in VAS scores only at short-term follow-up (one week to two months) compared with the control group. The outcome in group 2 of Ediz and Ozgokce [26] included the major data that resulted in no significant differences between ESWT and control groups at long-term follow-up (five to 12 months). However, the ESWT group showed significant improvement compared with the control group at long-term follow-up (six and 12 months) in a previous study [26]. They used individual changes from baseline to follow-up to compare the difference between the ESWT and control groups, and this method indicated true improvement after treatment. However, VAS values at follow-up were adopted to compare the difference in the meta-analysis, and this method may have produced bias. This could explain why the data of group 2 from Ediz and Ozgokce [26] included in the meta-analysis resulted in no significant improvement in pain relief between ESWT and control groups at long-term follow-up. In addition, the ESWT group showed significant improvement in WOMAC pain scores at long-term follow-up (six and 12 months) compared with the control group. This result could support that the ESWT group had both short-term and long-term effects.

However, we found that the efficacy of the ESWT decreased with time compared with the baseline level based on WOMAC and VAS scores. Some clinical reasons may have caused this decrease in efficacy, such as the effect wearing off, increased activity secondary to less pain, which then results in more pain and the effect wearing off, and change in other treatments. This decrease in efficacy could be prevented by repeating ESWT at every time interval (such as two months) or maintaining the same activity despite pain.

In comparison with the baseline level, knee OA patients showed significant improvement in pain at most follow-up time points, and the results of improvement in pain were similar between WOMAC and VAS pain scores. A systematic review that included various orthopedic conditions, such as calcifying tendonitis of the shoulder, plantar fasciopathy, achilles tendinopathy, proximal hamstring tendinopathy, subacromial pain, and knee osteoarthritis, investigated the efficacy of ESWT for the tendon and other pathologies of the musculoskeletal system [34]. They reported that the ESWT group was better than the placebo and control groups, and no serious adverse events were observed in the included studies. These results are similar to our conclusions. Based on these results, we could conclude that ESWT seems to be an effective treament for pain relief in knee OA.

The mechanism of ESWT in the treatment of knee OA has been investigated. The expression of some growth factors and cytokines can be induced through mechanical stimulation of ESWT, such as insulin-like growth factor 1 and transforming growth factor β1 [35]. Several studies have reported that collagen synthesis and cell growth can be promoted by ESWT via releasing other active substances and growth factors [36–38]. The improvement in pain relief may be through matrix formation and cartilage cell growth stimulation after ESWT treatment [39]. These results could explain the possible mechanism of ESWT for pain relief improvement in knee OA patients.

In this study, the improvement in stiffness compared with the baseline level showed significance after ESWT treatment at six-month follow-up but become nonsignificant at 12-month follow-up. Similar results (significant at six months and nonsignificant at 12 months) were obtained when compared with the control group. Although the included articles provided WOMAC scores, few articles provided the WOMAC stiffness score, thereby possibly causing uncertainty in our meta-analysis. Although the efficacy of ESWT for stiffness was unclear, pain relief and physical function improvement are the main concerns in knee OA.

Dose-related effects of ESWT for treatment of knee OA have been observed, and the high-energy group (0.093 mJ/mm^2) showed greater improvement in pain relief and functional outcomes compared with the low-energy group (0.040 mJ/mm^2) [24]. In our included articles, two articles [18,24] used high-energy (≥0.093 mJ/mm^2) ESWT and two articles [24,27] used low-energy (0.04–0.05 mJ/mm^2) ESWT (Table 1). We also found that patients treated with high-energy ESWT [18,24] had greater improvement in VAS scores at two to three months of follow-up than those treated with low-energy ESWT (Figure 4C) [18,27]. These results indicate that high-energy ESWT seems to have better improvement in pain relief than low-energy ESWT.

There are some possible limitations that may have affected the results of this study. The limits of language (only English-language studies were included in our meta-analysis) could be a limitation of this study. High heterogeneity among the studies was detected in some of the outcomes. In addition, women are at greater risk for developing knee OA compared with their male counterparts [40]. This makes it very difficult to generalize the results. The number of treatment sessions, the energy levels, and the number of impulses of ESWT in treatment of knee OA were varied among the included articles. Among all articles, ESWT was performed weekly, but the time courses of ESWT varied from three to 12 weeks. In addition, the number of impulses ranged from 1,000 to 8,000, and the energy flux density ranged from 0.03 to 0.4 mJ/mm^2. Dose-related effects of ESWT have been observed in knee OA patients [24], and time-course effects of EWST in knee OA patients have also been observed [41]. The variation in ESWT treatment protocol adopted among these articles might produce potential bias in our

meta-analysis. In three of the nine included articles, patients received other treatments at the same time as ESWT or after ESWT, including intravenous alprostadil [18], physical therapy [28], and isokinetic muscular strengthening exercises [31]. These additional treatments may have affected the efficacy of ESWT and could be a significant confounder to our meta-analysis. In addition, only a limited number of clinical studies have investigated the efficacy of ESWT in the treatment of knee OA. The available data for meta-analysis were rare, especially for long-term follow-up, and the current evidence from our meta-analysis might be weak. In general, ESWT was effective for knee OA, but the optimal treatment protocol related to the efficacy of ESWT should be further investigated.

Conclusions

This was the first time that the efficacy and safety of ESWT for the treatment of knee OA were assessed using a systematic review and meta-analysis. This study provides results that suggest that using ESWT for treatment of knee OA has a beneficial effect on pain relief and physical function for up to 12 months, and only minor complications occurred after ESWT treatment. However, there remains a lack of clarity regarding the frequency and dosage levels of ESWT required to achieve maximal improvement.

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