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## Efficacy of extracorporeal shockwave therapy for knee osteoarthritis: a randomized controlled trial

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### ABSTRACT

**Background:** Extracorporeal shockwave therapy (ESWT) has been widely used for pain relief and treatment of musculoskeletal disorders. We aimed to assess ESWT for knee osteoarthritis (OA) over 12 wk by comparison with placebo treatment.

**Materials and methods:** We randomized 70 patients to receive placebo ( $n = 36$ ) or ESWT ( $n = 34$ ). For ESWT, patients received 4000 pulses of shockwave at  $0.25 \text{ mJ/mm}^2$  weekly for 4 wk. In the placebo group, patients received shockwave at  $0 \text{ mJ/mm}^2$  in the same area. The effect on OA was assessed by pain on a visual analog scale and disability on the Lequesne index, Western Ontario and McMaster University Osteoarthritis Index, and patient perception of the clinical severity of OA. Evaluation was performed at baseline and after 1, 4, and 12 wk.

**Results:** We found no adverse events during and after ESWT. ESWT was more effective than placebo in reducing pain on movement at each period ( $P < 0.01$ ). The mean visual analog scale score with ESWT was 3.83 at 12 wk versus 7.56 at baseline ( $P < 0.01$ ). The Lequesne index and the Western Ontario and McMaster University Osteoarthritis Index score were reduced with ESWT. Moreover, patient perception of clinical severity of OA was significantly greater with ESWT than that with placebo ( $P < 0.01$ ).

**Conclusions:** ESWT is effective in reducing pain and improving knee function, with better results than placebo during the 12-wk treatment. However, further pilot studies are needed to determine whether ESWT should be recommended at an early or later stage of OA or combined with conventional therapies.

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## 1. Introduction

Osteoarthritis (OA) is the most prevalent of the chronic rheumatic diseases and is a leading cause of pain and disability in most countries worldwide [1]. The prevalence of OA is strongly associated with aging and affects women more frequently than men. Furthermore, OA has been associated with heavy physical occupational activity. Most of the OA disability

burden is in the hips and knees [2]. Joint-replacement surgery is common and considered effective and cost-effective for end-stage knee or hip arthritis. The number of replacements has been increasing every year in most countries [3]. However, to ultimately reduce the demand for joint-replacement surgery, new strategies are needed to treat early-stage OA [4].

Pain is the main reason for OA patients to seek clinical services [5]. The management of early-stage OA is

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fundamental for effective symptom relief, management of functional limitations, and enhancing health-related quality of life. Both pharmacologic (i.e., paracetamol, nonsteroidal anti-inflammatory drugs, and topical agents) and non-pharmacologic (i.e., education, exercise, lifestyle changes, and physical therapy) treatments are recommended in the 2008 Osteoarthritis Research Society International guidelines [6]. Despite pharmacologic and nonpharmacologic treatment, most patients with OA continue to experience pain [5]. Therefore, we need new strategies to reduce pain and improve function.

Extracorporeal shockwave therapy (ESWT) was first used to break up kidney stones. Its use was proposed for musculoskeletal disorders by incidental observation of an osteoblastic response pattern during animal studies in the late 1980s [7]. ESWT has been widely used for pain relief and treatment of musculoskeletal disorders in recent years. It is noninvasive, has a low complication rate, does not require hospitalization, and has relatively low cost as compared with other conservative and surgical approaches. ESWT is effective in reducing pain, improving hip function, and preventing progression of avascular necrosis, which has been confirmed by several clinical studies [8,9]. Veterinarians first began to use ESWT to treat equine knee OA [10]. Several studies found that ESWT improved motor dysfunction and ameliorated pain in animals with OA [11–13]. However, few studies have investigated its use in human knee OA.

In this single-blind placebo-controlled randomized study, we evaluated the effectiveness of ESWT in reducing pain and improving knee function in knee OA of Kellgren and Lawrence stage II and III.

## 2. Materials and methods

We conducted a prospective, single-blinded, randomized placebo-controlled trial at the Department of Orthopaedic Surgery in The General Hospital of Chinese People's Army Police Force from July 2011 to February 2012. The study protocol was approved by our institutional research ethics board.

### 2.1. Participants

Patients recruited from two rheumatology clinics had a diagnosis of primary symptomatic knee OA according to the criteria of the American College of Rheumatology [14]. Patients included were aged  $\geq 45$  y and had knee pain for the previous 3 mo. They had Kellgren and Lawrence grade II or III OA [15]. For patients with both knees symptomatic, the more painful knee or, when symptoms were similar bilaterally, the right knee was chosen as the target knee. We excluded patients with a history of spinal stenosis, evidence of neurologic disease by history or physical examination, or secondary causes of arthritis (inflammatory or metabolic); those who had a surgical intervention or intra-articular injection in the affected knee in the previous 6 mo or any contraindication to magnetic-resonance imaging or radiography. All patients gave their written informed consent to participate in the study.

### 2.2. Randomization to groups

We used a block randomization list generated by a simple computerized random-number generator. After baseline assessment, an independent researcher assigned patients to ESWT or placebo according to the randomization of odd and even numbers but was not involved in the intervention or data assessment.

### 2.3. Shockwave intervention

Shockwave treatment involved the use of an **Electro Medical Systems (EMS) instrument (Swiss DolorClast; Nyon, Switzerland)**. ESWT and placebo interventions were administered by a technologist. In the ESWT group, patients underwent four treatments at weekly intervals. At each treatment session, patients were positioned in a supine position with the affected knee unbent or flexed at 90°. The shockwave probe was held stationary on a trigger point around the knee or at the patellofemoral and tibiofemoral borders of the target knee, avoiding direct placement on the peroneal nerve or vessel. To reduce loss of shockwave energy at the interface, an aqueous gel was used as a coupling medium between the probe of the device and the skin and applied in circular motions. Shockwaves of 4000 pulses in total were applied at 0.25 mJ/mm<sup>2</sup> and a frequency of 6 Hz/s. The placebo group received shockwave at 0 mJ/mm<sup>2</sup> to the same area in the same manner. Patients were not able to see the device parameters in each group. No bed rest was required after treatment, but a low level of physical activity was recommended for 48 h. To avoid the immediate effects of shockwave application, clinical evaluation was performed 1 d after treatment.

### 2.4. Outcome measures

Clinical assessments included assessment of pain on movement, physical function, and patient global assessment. The primary outcome measure was pain on movement measured by a 10-cm visual analog scale (VAS) [16], with 0 indicating no pain and 10 for maximal pain. The secondary outcome was disability on the Lequesne index, the Western Ontario and McMaster University Osteoarthritis Index (WOMAC), and patient perception of the clinical severity of their OA. Evaluation was performed at baseline and after 1, 4, and 12 wk by the physician, who was not involved in the selection and treatment of patients.

The disease-specific, aggregated multidimensional Lequesne index includes questions about knee discomfort, endurance of ambulation, and difficulties in daily life [17]. A maximum score of 24 indicates the greatest degree of dysfunction, and a score of  $>13$  indicates extremely severe disease.

The WOMAC assesses symptoms of OA and is a validated disease-specific self-reporting questionnaire referring to the 48 h before assessment [18]. The index consists of five questions for severity of knee pain, two for stiffness, and 17 for limitations in physical function. The WOMAC score ranges from 0 (best) to 96 (worst), with high score representing worse symptom severity.

**Table 1 – Demographic and baseline clinical characteristics of patients in the intent-to-treat population.**

Characteristics	Placebo (n = 36)	ESWT (n = 34)
Age (y)	61.8 ± 9.8	59.9 ± 11.3
Women, n (%)	25 (69)	20 (59)
Weight (kg)	67.3 ± 9.1	69.9 ± 10.6
Height (cm)	162.0 ± 7.5	163.4 ± 8.3
BMI (kg/m <sup>2</sup> )	25.6 ± 2.5	26.1 ± 2.6
Kellgren and Lawrence grade II and III, n (%)	26 (72)/10 (28)	26 (76)/8 (24)
Pain on walking (10-cm VAS)	7.6 ± 1.1	7.6 ± 1.3
Lequesne index	10.1 ± 2.4	10.2 ± 2.3
WOMAC score		
Pain	8.0 ± 2.4	8.1 ± 2.4
Stiffness	2.5 ± 1.5	2.5 ± 1.6
Function	22.3 ± 9.4	25.7 ± 8.9
Total	32.8 ± 10.9	36.4 ± 10.3
Patient perception of disease severity (poor/fair/good), n (%)	6 (17)/20 (55)/10 (28)	6 (18)/19 (56)/9 (26)

BMI = body mass index.  
Data are expressed as mean ± standard deviation unless otherwise indicated.

Patient perception of clinical severity was measured by a direct question [19]: Considering all the ways knee OA affects you, how would you rate your condition today? It was rated on a 5-point Likert scale, from 1, very poor; 2, poor; 3, fair; 4, good; to 5, very good.

### 2.5. Statistical analysis

The primary comparison was between ESWT and placebo over 12 wk. A sample size of 30 per group was required for a statistical significance of  $\alpha = 0.05$ , effect size of  $>0.7$ , and power of 80%. Taking into account an expected dropout rate of 10%, we needed to enroll 34 patients per group [20].

Data are reported as mean ± standard deviation. The t test or chi-square test was used to demonstrate the homogeneity of the baseline variables between the two treatment groups. The one-way analysis of variance was used for comparing mean change in VAS score for pain, Lequesne index, and WOMAC score between the pretreatment and follow-up times within each group. The independent samples t test or Mann–Whitney test was used for comparing mean change from baseline between the groups, and 95% confidence intervals were calculated. A P value of  $<0.05$  was considered statistically significant. SPSS 13.0 for Windows (SPSS Inc, Chicago, IL) was used for statistical analysis.

## 3. Results

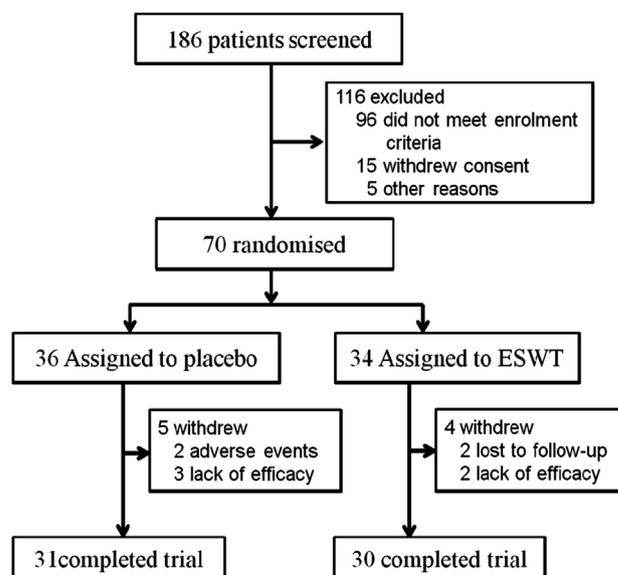
### 3.1. Clinical characteristics of patients

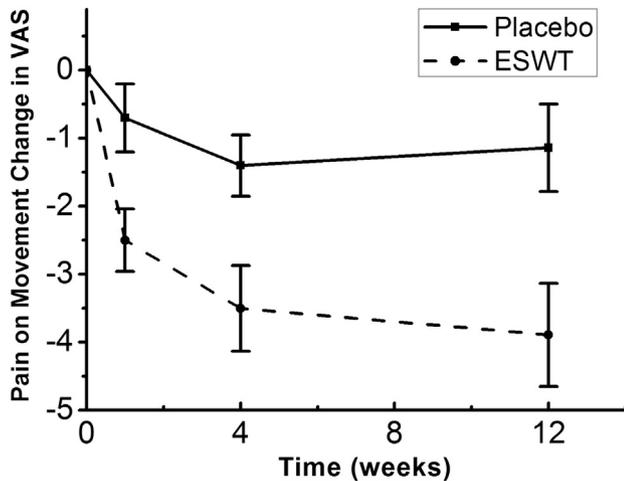
We included 70 patients (25 male): 36 in the placebo and 34 in the ESWT groups. The patient groups did not differ in characteristics or outcome measures at baseline (Table 1). The mean age of patients was  $61.8 \pm 9.8$  and  $59.9 \pm 11.3$  y in the placebo and ESWT groups, respectively. Most patients in both groups were female (69% in the placebo and 59% in the ESWT groups). Patients in general were overweight (with an average body mass index of  $>25$  kg/m<sup>2</sup>). For about three-quarters of the patients, the Kellgren and Lawrence grade was II. In this

clinical trial, patients were not offered other therapies, except for nine patients who dropped out of the study because of increased pain, lack of efficacy, and use of analgesics. After 12-wk follow-up, five and four patients in the placebo and ESWT groups, respectively, dropped out. The dropout rate did not differ between the two groups ( $P > 0.05$ ). In the placebo group, two patients dropped out because of increased pain and use of analgesics and three because of lack of efficacy. In the ESWT group, two patients dropped out because of work-related commitments and two because of lack of efficacy (Fig. 1).

### 3.2. Measurement of pain severity (VAS score)

In the intent-to-treat population, both groups showed reduced pain on movement, as measured on a VAS, after the intervention (Fig. 2), with greater decrease in pain with ESWT than that with placebo in each period ( $P < 0.01$ ). At 12 wk, the mean VAS score had decreased 3.73 points in the ESWT group (7.56

**Fig. 1 – Flow of patients in the study.**



**Fig. 2 – Pain on movement change in VAS score after 1, 4, and 12 wk of treatment, in the intent-to-treat population ( $n = 36$  in the placebo group and  $n = 34$  in the ESWT group).**

at pretreatment to 3.83 at 12 wk;  $P < 0.01$ ). At 12 wk, the mean VAS score had decreased 1.14 points in the placebo group (7.55 at pretreatment to 6.41 at 12 wk;  $P < 0.01$ ). Patients were able to resume most of their daily or working activities.

### 3.3. Disability by the Lequesne index and WOMAC

From Table 2, symptoms were ameliorated with ESWT compared with those with placebo as measured by the Lequesne index and WOMAC, with greater improvement in per-protocol completers than that in the intent-to-treat population (Fig. 3). In the placebo and ESWT groups, the baseline Lequesne index was  $10.1 \pm 2.4$  and  $10.2 \pm 2.3$ , respectively, and the baseline WOMAC score was  $32.8 \pm 10.9$  and  $36.4 \pm 10.3$ , respectively. For the Lequesne index, at 12 wk, the decrease in disability was almost  $-2.0$  for the placebo group but  $-4.1$  for the ESWT group ( $P < 0.01$ ). Similarly, the mean change in WOMAC score after 12 wk was  $-8.5$  for the placebo group and  $-19.1$  for the ESWT group ( $P < 0.01$ ). Despite overall improvement in WOMAC scores, WOMAC stiffness scores did not differ between the placebo and ESWT groups ( $P > 0.05$ ).

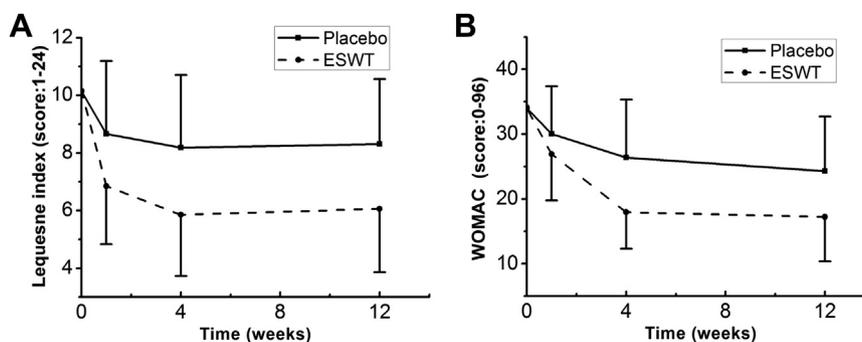
### 3.4. Disability by patient perception of clinical severity

The baseline patient perception of clinical severity was  $3.11 \pm 0.67$  and  $3.09 \pm 0.67$  in the placebo and ESWT groups, respectively. After 12 wk, the patient perception was  $3.42 \pm 0.81$  and  $3.94 \pm 0.92$ , respectively. The mean change in patient perception at 12 wk was  $-0.3$  and  $-0.9$ , respectively ( $P < 0.01$ ; Table 2). Patient perception of clinical severity was better for the ESWT group than that for the placebo group ( $P < 0.01$ ).

**Table 2 – Mean change from baseline to 12 wk for patients treated with placebo or ESWT in terms of disability by the Lequesne index, WOMAC, and patient perception of disease severity for the intent-to-treat population and per-protocol completers.**

Outcome	Intent-to-treat population		Per-protocol completers	
	Placebo ( $n = 36$ )	ESWT ( $n = 34$ )	Placebo ( $n = 31$ )	ESWT ( $n = 30$ )
Lequesne index				
Change	$-2.0$ ( $-2.9$ to $-1.0$ )	$-4.1$ ( $-4.9$ to $-3.3$ )	$-2.3$ ( $-3.4$ to $-1.2$ )	$-4.6$ ( $-5.4$ to $-3.9$ )
Difference versus placebo	—	$-2.1$ ( $-3.4$ to $-0.9$ )	—	$-2.3$ ( $-3.6$ to $-1.1$ )
P		$<0.01$		$<0.01$
WOMAC				
Total				
Change	$-8.5$ ( $-12.4$ to $-4.6$ )	$-19.1$ ( $-22.7$ to $-15.6$ )	$-10.3$ ( $-14.3$ to $-5.8$ )	$-21.5$ ( $-24.4$ to $-18.5$ )
Difference versus placebo	—	$-10.6$ ( $-15.8$ to $-5.4$ )	—	$-11.4$ ( $-16.6$ to $-6.3$ )
P		$<0.01$		$<0.01$
Pain				
Change	$-2.2$ ( $-3.2$ to $-1.2$ )	$-4.5$ ( $-5.4$ to $-3.6$ )	$-2.5$ ( $-3.6$ to $-1.3$ )	$-4.4$ ( $-5.4$ to $-3.5$ )
Difference versus placebo	—	$-2.3$ ( $-3.6$ to $-1.0$ )	—	$-2.0$ ( $-3.4$ to $-0.5$ )
P		$<0.01$		$<0.01$
Function				
Change	$-6.0$ ( $-9.2$ to $-2.8$ )	$-13.9$ ( $-17.2$ to $-10.6$ )	$-7.2$ ( $-10.7$ to $-3.7$ )	$-16.3$ ( $-18.9$ to $-13.6$ )
Difference versus placebo	—	$-7.9$ ( $-12.5$ to $-3.4$ )	—	$-9.0$ ( $-13.3$ to $-4.8$ )
P		$<0.01$		$<0.01$
Stiffness				
Change	$-0.3$ ( $-0.8$ to $0.2$ )	$-0.7$ ( $-1.0$ to $-0.4$ )	$-0.4$ ( $-1.0$ to $0.2$ )	$-0.8$ ( $-1.1$ to $-0.5$ )
Difference versus placebo	—	$-0.4$ ( $-1.0$ to $0.2$ )	—	$-0.4$ ( $-1.1$ to $0.3$ )
P		$>0.05$		$>0.05$
Patient perception of disease severity				
Change	$-0.3$ ( $-0.5$ to $-0.1$ )	$-0.9$ ( $-1.1$ to $-0.6$ )	$-0.3$ ( $-0.6$ to $-0.8$ )	$-0.8$ ( $-1.1$ to $-0.6$ )
Difference versus placebo	—	$-0.6$ ( $-0.9$ to $-0.2$ )	—	$-0.5$ ( $-0.9$ to $-0.2$ )
P		$<0.01$		$<0.01$

Data are expressed as mean (95% confidence intervals).



**Fig. 3 – Values of (A) the Lequesne index and (B) WOMAC in the intent-to-treat population. Data are expressed as mean  $\pm$  standard deviation.**

#### 4. Discussion

We aimed to assess ESWT compared with placebo over 12 wk in patients with knee OA. ESWT was effective in reducing pain and improving the knee function of patients with OA, with better results than placebo over 12 wk.

Nonpharmacologic management of knee OA is fundamental for effective symptom relief and management of functional limitations [21]. In the 2008 Osteoarthritis Research Society International guidelines for management of hip and knee OA, nonpharmacologic therapies include physical therapy, education and self-management, weight loss, thermal modalities, transcutaneous electrical nerve stimulation, and acupuncture. In recent years, ESWT has been the leading therapeutic choice in orthopedic diseases such as chronic tendinopathies, nonunion of long bone fracture, and early stage of avascular necrosis of the femoral head [7]. More recently, the use of ESWT had expanded to the treatment of OA in animals, improved motor dysfunction, and ameliorated pain [11–13]. ESWT improved the walking ability of rats on a treadmill [12]. The degree of lameness in horses receiving ESWT improved significantly compared with horses treated with placebo or polysulfated glycosaminoglycan [11].

Our results in humans confirmed these findings. The baseline values for pain were better with ESWT than those with placebo. Symptoms were ameliorated with ESWT compared with those with placebo as measured using the Lequesne index and WOMAC, with greater improvement in per-protocol completers than that in the intent-to-treat population. Improvements noted in the placebo group could reflect spontaneous remission or the natural history of OA. Intent-to-treat analysis confirmed the beneficial effect of ESWT on joint symptoms.

Basic science studies have shown that ESWT application for OA is safe with proper dosing [22]. Shockwaves applied at  $>0.50$  mJ/mm<sup>2</sup> caused degenerative changes in hyaline cartilage in OA of rats [23]. We selected an energy flux density of 0.25 mJ/mm<sup>2</sup> and found no adverse damage to knees of patients; only the skin of the knee showed transient reddening after treatment and swelling for several days.

To our knowledge, no clinical trials have tested the effect of ESWT on human knee OA. ESWT could have a beneficial effect

for pain and physical function in patients with knee OA. However, the exact mechanism of action of ESWT has not been fully elucidated. The mechanisms of action of ESWT on OA are likely complex and may include inhibiting afferent pain-receptor function and be influenced by cartilage and noncartilaginous structures in the joint. ESWT leads to selective dysfunction of sensory unmyelinated nerve fibers without affecting the larger myelinated nerve fibers [24]. The level of neuropeptide calcitonin gene-related peptide was decreased in the dorsal root ganglion in a rat OA knee model after ESWT treatment; the peptide is expressed by nociceptors and is thought to play a role in the sensation of joint pain [12].

Because of ongoing joint destruction in OA, ESWT could reduce the progression of OA [13,25,26]. Application of shockwaves for damaged anterior cruciate ligament in rats improved subchondral bone remodeling and decreased cartilage degradation [25]. Moreover, our previous study demonstrated that ESWT reduced the progression of OA in rabbits, which may be related to decreased level of NO and is likely mediated by reduced chondrocyte apoptosis [13]. Indeed, the mechanisms of action of ESWT for treatment of OA are multifactorial.

Our study contains some limitations. We did not address factors such as dose, intensity, or frequency that may influence the effect of ESWT on OA. Optimal treatment needs to be studied by comparing dosing intervals and energy flux densities. We used the treatment parameters of ESWT according to our experience in previous research and clinical application. In addition, the efficacy of ESWT was evident at 12-wk follow-up and possibly beyond. Future study of long-term effects is needed to confirm this finding. However, we cannot exclude the effect of no placebo on the results. In future study, we will add another group that will receive no ESWT and placebo treatment on the target area.

#### 5. Conclusions

We confirmed that ESWT can be effective in the management of OA at Kellgren and Lawrence stages II and III. Compared with most other options, ESWT is noninvasive and seems to be beneficial in some instances. ESWT is safe with proper

dosing, has a low complication rate, does not require hospitalization, and has relatively low cost compared with other conservative and surgical approaches. However, the role of ESWT in treating OA remains unclear. Further pilot studies are needed to determine whether ESWT should be recommended at early or late stages of OA and whether it can be combined with conventional therapies.

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Conflict of interest: the authors declare no conflict of interest.

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