ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

Archives of Physical Medicine and Rehabilitation 2019;100:1695-702

ORIGINAL RESEARCH

A Randomized Controlled Trial on the Effects of Low-Dose Extracorporeal Shockwave Therapy in Patients With Knee Osteoarthritis

Zongye Zhong, MSc,[a] Bangzhong Liu, PhD,[a,b] Guanghua Liu, MSc,[a] Jun Chen, BS,[a] Yun Li, MSc,[a] Jianxin Chen, MSc,[a] Xinxin Liu, MSc,[a] Yiwen Hu, PhD[c]

From the [a]Department of Rehabilitation Medicine, Zhongshan Hospital, Fudan University, Shanghai; [b]Department of Rehabilitation Medicine, Zhujiajiao People's Hospital, Shanghai; and the [c]Deparment of Radiology, Huashan Hospital, Fudan University, Shanghai, China.

Abstract

Objective: To test the efficacy of low-dose extracorporeal shockwave therapy (ESWT) on osteoarthritis knee pain, lower limb function, and cartilage alteration for patients with knee osteoarthritis.

Design: Randomized controlled trial with placebo control.

Setting: Outpatient physical therapy clinics within a hospital network.

Participants: Eligible volunteers (N = 63) with knee osteoarthritis (Kellgren-Lawrence grade II or III) were randomly assigned to 2 groups.

Interventions: Patients in the experimental group received low-dose ESWT for 4 weeks while those in the placebo group got sham shockwave therapy. Both groups maintained a usual level of home exercise.

Main Outcome Measures: Knee pain and physical function were measured using a visual analog scale (VAS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the Lequesne index at baseline, 5 weeks, and 12 weeks. Cartilage alteration was measured analyzing the transverse relaxation time (T2) mapping.

Results: The VAS score, WOMAC, and Lequesne index of the ESWT group were significantly better than those of the placebo group at 5 and 12 weeks ($P<.05$). Both groups showed improvement in pain and disability scores over the 12-week follow-up period ($P<.05$). In terms of imaging results, there was no significant difference in T2 values between groups during the trial, although T2 values of the ESWT group at 12 weeks significantly increased compared to those at baseline ($P = .004$). The number and prevalence of adverse effects were similar between the 2 groups, and no serious side effects were found.

Conclusions: A 4-week treatment of low-dose ESWT was superior to placebo for pain easement and functional improvement in patients with mild to moderate knee osteoarthritis but had some negative effects on articular cartilage.

Archives of Physical Medicine and Rehabilitation 2019;100:1695-702

Osteoarthritis (OA) is a common orthopedic condition that affects about 14 million Americans.[1] It is estimated that by 2020, the prevalence of OA will double given increasing rates of obesity and an aging population.[2] Although OA may affect many joints, weight-bearing joints such as the knee joint are especially susceptible. There has been no cure for OA so far,[3] and therefore, the aim of treatment is to alleviate pain, reduce functional limitations, and improve quality of life while minimizing adverse reactions from therapeutic measures.[4]

Extracorporeal shockwave therapy (ESWT) is a noninvasive therapeutic modality whereby an appropriate generator conveys a sequence of single sonic pulses to specific target areas.[5] It has been widely used to treat various musculoskeletal disorders such as plantar fasciitis,[6] tennis elbow,[7] and nonunion or delayed fracture healing.[8] In recent years, researchers began to explore the

Supported by Shanghai Qingpu District Science and Technology Development Fund Project (grant no. 2016-03). The funding source had no involvement in the trial design, collection, analysis and interpretation of data, and in the decision to write and submit the paper for publication.

Clinical Trial Registration No.: ChiCTR-IOR-17012320.

Disclosures: none.

https://doi.org/10.1016/j.apmr.2019.04.020

effect of shockwave treatment for knee osteoarthritis. They found that ESWT reduced pain and improved disability in animal experiments.[9-11] However, effects of ESWT in managing knee osteoarthritis were still controversial in previous clinical trials.[12-14] Therefore, more evidence is required to appraise the efficacy and safety of ESWT on knee osteoarthritis.

Cartilage damage could lead to the development of degenerative joint diseases, such as osteoarthritis,[15] characterized by a progressive loss of articular cartilage, subchondral bone sclerosis, osteophyte formation, and narrowing of joint space. The management of articular cartilage defects is one of the most challenging clinical problems. ESWT appears to be able to influence the inflammatory processes and to promote bone repair processes as well as activate several cellular processes essential for neovascularization and tissue regeneration.[16] Whether ESWT is an intervention for cartilage healing must be seriously considered. Transverse relaxation time (T2) mapping can assess the water content and deterioration to the collagen network that precedes morphologic deterioration, namely, it is an efficient magnetic resonance quantitative technique to evaluate spontaneous cartilage repair.[17] To our knowledge, none of the previous studies performed biochemical magnetic resonance imaging (MRI) to display the effect of shockwaves on the knee cartilage.

Based on the reasons mentioned above, our hypothesis was that ESWT would improve symptoms of knee osteoarthritis and restore articular cartilage or inhibit cartilage degeneration.

Methods

Trial design

This research was a randomized, placebo-controlled, parallel group trial during the period from September 2017 through February 2018. The study conformed to the principles of the Declaration of Helsinki. The trial was endorsed by the masked Hospital Ethics Committee. There was no commercial sponsorship of this study. The trial was conducted in outpatient physical therapy clinics within a hospital network. Our study was drawn up and reported in accordance with the Consolidated Standards of Reporting Trials recommendations and was registered.

Trial participants

The participants learned about research recruitment from outpatient rehabilitation physicians and recruitment posters. Eligible patients were men and women with a more than 6-month history of symptoms of knee osteoarthritis. Participants with clinical knee osteoarthritis were diagnosed by rehabilitation physicians in accordance to American College of Rheumatology criteria[18] and radiographic criteria (Kellgren-Lawrence grade).[19] In this research, we categorized mild to moderate knee osteoarthritis as radiographic alterations in tibiofemoral joint grades II or III based on the Kellgren-Lawrence scale. Patients had knee pain on most days of >4 cm on a 10-cm visual analog scale (VAS) on their worst knee over the past week.[20] The side with more severe symptoms was selected as the target knee in patients with bilateral knee osteoarthritis. When the symptoms of the 2 knees were similar, the right knee was selected as the target knee for evaluation.

Key exclusion criteria included previous joint replacement, a history of intra-articular injection, surgery, ESWT, the commencement of other medications within the past 6 months, loss of independent walking ability, or any major concomitant diseases that could interfere with participation in the trial. Participants with a history of diagnosis of significant neurologic or psychiatric impairments would be excluded in view of their difficulty in objectively answering the questionnaire. Prior to the start of the trial, all patients submitted written consent after being clearly advised about the trial.

List of abbreviations:

ESWT	**extracorporeal shockwave therapy**
MRI	**magnetic resonance imaging**
OA	**osteoarthritis**
ROI	**region of interest**
T2	**transverse relaxation time**
VAS	**visual analog scale**
WOMAC	**Western Ontario and McMaster Universities Osteoarthritis Index**

Randomization and blinding

An independent researcher not involved with the treatment or outcome measurement implemented randomization. Depending on a computer-generated random numbers list, eligible participants were randomly separated into one of the study groups: the ESWT group or the placebo group. Participants were kept blinded for the allocated treatment during the follow-up period. Outcome assessors were blind to group division and did not take part in implementing interventions. All physical therapists, radiologists, and statisticians were unaware of group assignment as well.

Interventions

Participants in the experimental group received ESWT. All ESWTs were given by a single, experienced physical therapist. ESWT was conducted using the Swiss DolorClast[a] instrument once a week for 4 consecutive weeks (4 sessions in total). Patients stayed supine with the target knee flexed at 90° in each session. The physical therapist determined the pain points of the target knee by palpation and marked the pain points and the patellofemoral and tibiofemoral borders. The shockwave probe (15mm) was attached to the marker while avoiding nerves or blood vessels. The skin contacted by the ESWT probe was coated with ultrasound gel. The parameters of therapy included a total of 2000 pulses of 8-Hz frequency at 2.5 bars of pneumatic pressure. The first 1000 pulses were evenly distributed to pain points (the maximum number of pain points is 4). The remaining pulses were slid back and forth on the patellofemoral and tibiofemoral borders. No local anesthesia or other injections was used. Participants assigned to the placebo group were managed by the same physical therapist with the same ESWT protocol, but the air pressure was set at 0.2 bar. The stress value was set by the researcher responsible for randomization. Patients and therapist could hear a sound similar to that of the regular ESWT, in order to enhance the sham design, but they were not able to see the dashboard.

As part of the treatment program, all participants, regardless of the group, were educated on a simple home exercise program for the first visit. The program was comprised of a single knee extensor muscle strengthening. The patient sat in a chair, straightened his/her knee as far as possible, kept it for 10 seconds, repeated 10 times, and did 3 groups per day. Therapist-applied

manual forces were not permitted in the exercise program. The home exercise was supervised by a physiotherapist once every 3 days over the phone.

Assessment

All patients were evaluated by an investigator who was blind to the group allocation and data acquisition at baseline, 5 weeks, and 12 weeks after intervention. Knee pain intensity was evaluated with a 10-cm VAS, with marking endpoints as "no pain at all" and "worst possible pain." The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Lequesne index assess symptoms of OA. The WOMAC contains 5 questions for severity of knee pain, 2 for stiffness, and 17 for limitations in physical function. The highest score is 96, which represents worse symptom severity.[21] The disease-specific Lequesne OA index consists of questions about knee discomfort, the endurance of ambulation, and difficulties in daily life.[22] The highest score of 24 points represents the most serious dysfunction.

The T2 mapping was a technique used to measure the biochemical cartilage characteristics of target knees. Images were taken using a 3T scanner, the Magnetom Verio,[b] with an 8-channel phased-array knee coil. Prior to MRI imaging, all patients were asked to restrain from any strenuous exercise for at least 1 hour to make sure that the cartilage condition was in a stable resting state.

Participants lay supine in the magnet bore with target knee in slight flexion, stabilizing in an MRI-compatible device. T2 mapping was derived with use of a sagittal, multislice, multi-echo-spin-echo sequence (field of view, 160mm; acquisition matrix, 384×384; repetition time [ms], 1680; echo times [ms], 13.8, 27.6, 41.4, 55.2, 69.0; flip angle, 180°; slice thickness, 3.0mm; pixel size, 0.4×0.4×3.0; bandwidth, 228 Hz/pixel; acquisition time, 5:48 min). The region of interest (ROI) was drawn manually by a skilled musculoskeletal radiologist with considerable care to avoid accidental interference of subchondral bone. The ROIs were located involving the medial femoral condyle cartilage. T2 was obtained from T2-mapping images by using a pixel-wise, mono-exponential, nonnegative least square fit analysis. T2 maps were fused with T2-weighted images using an MRWP workstation.[b]

Side effects

Adverse reactions defined as any unexpected events that occurred during the trial were noted and recorded. Serious adverse events were defined as events that were life threatening or resulted in death, hospitalization, or significant disability.[23]

Statistical analysis

All statistical analysis was conducted using the SPSS[c] version 19.0 and P values of $<.05$ were considered to be statistically significant. Baseline characteristics between groups were compared using independent t tests or Mann-Whitney U tests for continuous variables (depending on normality) and chi-square tests for categorical variables. The outcome measures were submitted to a 2×3 repeated measures analysis of variance with time (baseline, week 5, and week 12) as the within-subject factor and group (ESWT or placebo) as the between-subject factor. The Greenhouse-Geisser correction was used when the sphericity assumption was violated. Bonferroni correction was applied to adjust significance levels. Unless otherwise stated, all values were reported as mean ± SD.

The VAS score was chosen as the primary outcome measure. The study was powered to detect 2-cm differences in a 10-cm VAS between the ESWT and placebo groups with an SD of 2 cm which is adjusted based on the results of one previous publication.[12] In consideration of a type I error rate of 5%, a power of 80%, and at least 10% losses to follow-up, 18 patients were required per group at baseline. To improve the reliability of our study, we increased the sample size to 30 patients per group.

Results

Characteristics of the patients

A total of 89 patients (all Mongolians) were screened for the trial, of whom 63 were eligible. Of these patients, 32 were assigned to undergo ESWT; 31 were assigned to receive placebo. Three and 2 patients in the experimental group and control group, respectively, dropped out during follow-up period. Figure 1 shows the flow of participants' enrollment in the study. The general characteristics of the patients in each group are displayed in table 1. The mean duration of knee pain was 34.4 weeks. There are no statistical differences concerning age, sex, weight, height, body mass index, Kellgren-Lawrence grade, VAS, WOMAC score, Lequesne index, and T2 values between the 2 groups.

Outcomes

At 5 and 12 weeks, there was a significant difference in VAS scores between the 2 groups ($P<.001$) (table 2). VAS scores of the patients in both groups were found to improve significantly in both later visits ($P<.001$) (table 3). A significant group by time interaction was evident between ESWT and placebo groups ($P<.001$).

There was a statistically significant difference between groups in WOMAC pain scores at 5 and 12 weeks ($P<.001$) (see table 2), which was consistent with VAS results. Both groups showed significantly improved in WOMAC pain scores during the follow-up period ($P<.001$) (see table 3). A significant group by time interaction was evident between ESWT and placebo groups ($P<.001$).

WOMAC stiffness scores and WOMAC function scores of 2 groups were both significantly different at 5 and 12 weeks ($P<.001$) (see table 2). Significant improvements in WOMAC stiffness scores and WOMAC function scores were seen in 2 groups in both follow-up periods ($P<.05$) (see table 3). There was a statistically significant group by time interaction at WOMAC stiffness scores and WOMAC function scores ($P<.001$).

In both subsequent visits, the ESWT group had a statistical difference compared to the placebo group for the Lequesne index ($P<.001$) (see table 2). Table 3 demonstrated that ESWT group had statistical amelioration on the Lequesne index at 5 weeks. However, there was no statistically significant difference ($P=.062$) on the Lequesne index at 5 weeks in the placebo group. There was a statistically significant group by time interaction at Lequesne index ($P<.001$).

There was no statistically significant difference between the ESWT group and placebo group at 5 and 12 weeks ($P=.973$, $P=.796$, respectively) (see table 2). T2 values of the ESWT group

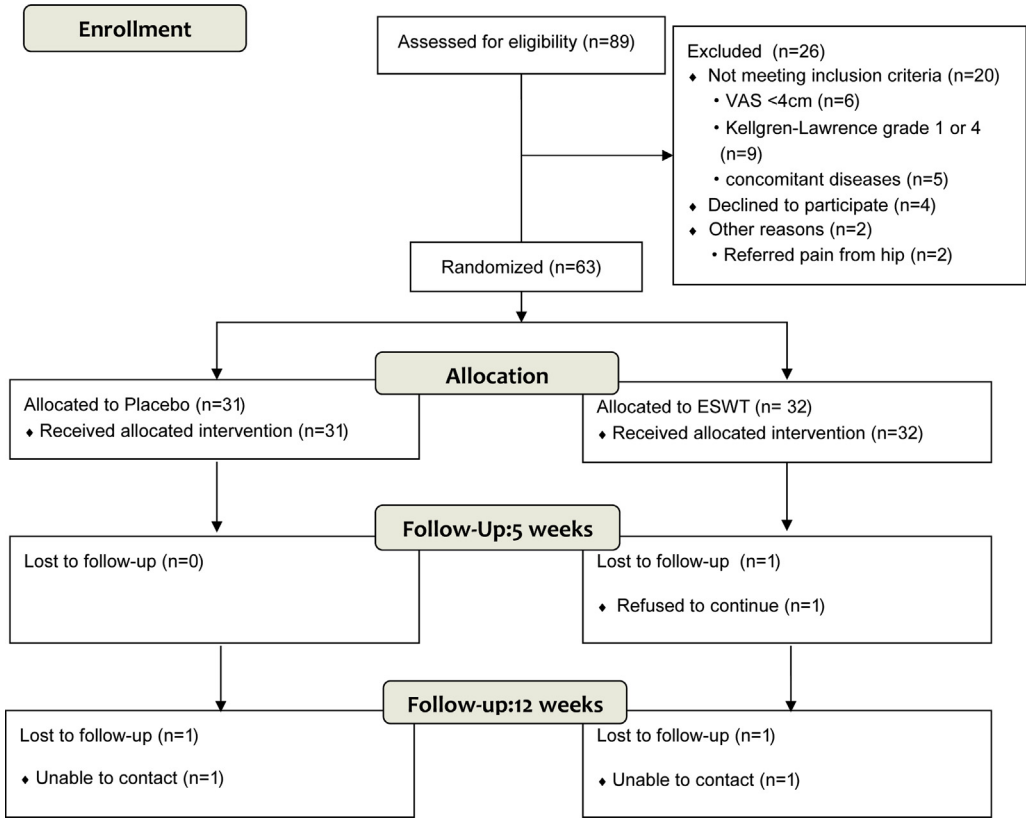

Fig 1 Consolidated Standards of Reporting Trials flow chart.

at 5 weeks, as well as 12 weeks, were higher than that of the ESWT group at baseline ($P=.034$, $P=.004$, respectively) (see table 3). However, the T2 values of the placebo group showed no significant variation between baseline and 5 weeks ($P=.077$) as well as baseline and 12 weeks ($P=.539$) (fig 2). There was no statistically significant group by time interaction at T2 values ($P=.214$).

Table 1 Baseline characteristics of the patients

Characteristic	Placebo (n=31)	ESWT (n=32)	Total Group (n=63)
Age (y)	63.2±7.7	62.5±8.2	62.8±7.9
Male sex, n (%)	12 (38.7)	11 (34.4)	23 (36.5)
Weight (kg)	67.5±9.2	67.2±8.0	67.4±8.5
Height (cm)	163.1±7.8	162.8±8.1	163.0±7.9
BMI (kg/m^2)	25.4±2.9	25.3±2.3	25.4±2.6
Duration of knee pain (mo)	34.1±14.2	34.7±15.4	34.4±14.7
Kellgren-Lawrence grade, n (%)			
II	24 (77.4)	23 (71.9)	47 (74.6)
III	7 (22.6)	9 (28.1)	16 (25.4)
VAS (cm)	5.5±1.1	5.3±0.8	5.4±1.0
WOMAC pain	7.0±1.9	6.6±1.5	6.8±1.7
WOMAC stiffness	2.9±0.9	2.6±0.8	2.8±0.8
WOMAC function	23.7±6.4	22.3±5.1	23.0±5.7
Lequesne index	11.3±2.8	10.6±2.4	10.9±2.6
T2 (ms)	49.2±5.8	49.1±5.5	49.2±5.6

NOTE. Data are given as mean ± SD unless otherwise indicated.
Abbreviations: BMI, body mass index.

Adverse events

There were a few adverse events, but no serious adverse events were identified (table 4). Pain, reddening of skin, and burning sensation, etc were reported in a few patients, probably related to the stress response, but did not lead to dropping out of patients. There was not any statistical between-group difference in the frequency of untoward reactions. No persistent adverse effects were found, and all of these effects were resolved before the end of the assessment.

Discussion

In this randomized controlled trial, ESWT is found to be an effective and safe modality for controlling pain and decreasing disability in patients diagnosed with moderate knee OA. Moreover, to our knowledge, this research first demonstrated the response of ESWT on the biochemical components of femoral cartilage.

Currently, there is no consensus view on the impact of ESWT on knee OA. In our research, we attempted to primarily determine the efficacy of low-dose ESWT to reduce pain and to enhance function and mobility in knee OA patients (Kellgren-Lawrence grade II or III). We have demonstrated that a 4-week course of low-dose ESWT was superior to placebo in easing pain and maintained a 12-week benefit trend in most patients. There were no patients who declined due to treatment. For VAS scores, we

Table 2 Outcome measures at baseline, week 5, and week 12 (post hoc analysis)

	Placebo		ESWT		Placebo vs ESWT		
Parameter (time)	Mean ± SD	95% CI	Mean ± SD	95% CI	Difference of Mean	*P*	95% CI
VAS, baseline	5.5±1.1	5.1-5.9	5.3±0.8	5.0-5.6	0.155	.453	-0.261 to 0.571
VAS, wk 5	4.8±1.1	4.4-5.2	3.1±1.0	2.8-3.5	1.684	<.001	1.128-2.239
VAS, wk 12	4.3±1.1	3.9-4.7	2.3±1.2	1.9-2.7	1.803	<.001	1.146-2.461
WOMAC pain, baseline	7.0±1.9	6.3-7.8	6.6±1.5	6.2-7.2	0.323	.410	-0.466 to 1.111
WOMAC pain, wk 5	6.1±2.0	5.3-6.9	3.0±1.4	2.5-3.6	3.065	<.001	2.156-3.973
WOMAC pain, wk 12	5.1±2.2	4.3-5.9	2.4±1.4	1.8-2.9	2.600	<.001	1.559-3.661
WOMAC stiffness, baseline	2.9±0.9	2.6-3.2	2.6±0.8	2.3-2.9	0.258	.161	-0.108 to 0.624
WOMAC stiffness, wk 5	2.5±0.9	2.2-2.8	1.2±0.6	1.0-1.5	1.290	<.001	0.946-1.634
WOMAC stiffness, wk 12	2.1±0.8	1.8-2.4	1.0±0.6	0.8-1.2	1.033	<.001	0.647-1.419
WOMAC function, baseline	23.7±6.4	21.3-26.2	22.3±5.1	20.6-24.5	1.226	.359	-1.462 to 3.914
WOMAC function, wk 5	20.5±6.7	17.9-23.1	10.3±4.9	8.6-12.2	10.258	<.001	7.176-13.340
WOMAC function, wk 12	17.3±7.2	14.6-19.9	7.9±4.9	6.1-9.8	8.833	<.001	5.400-12.267
Lequesne index, baseline	11.3±2.8	10.3-12.4	10.6±2.4	9.9-11.6	0.613	.274	-0.510 to 1.736
Lequesne index, wk 5	10.5±3.3	9.3-11.8	5.0±2.1	4.2-5.8	5.516	<.001	4.025-7.007
Lequesne index, wk 12	8.7±3.5	7.4-10.0	3.9±2.7	2.9-4.9	4.467	<.001	2.865-6.068
T2, baseline	49.2±5.8	47.0-51.4	49.1±5.5	46.7-50.8	0.248	.872	-2.876 to 3.372
T2, wk 5	49.2±5.7	47.0-51.3	49.2±5.6	47.0-51.2	-0.052	.973	-3.177 to 3.074
T2, wk 12	49.1±5.8	47.0-51.3	49.2±5.6	47.1-51.2	-0.407	.796	-3.599 to 2.786

Abbreviation: CI, confidence interval.

divided the degree of change into 4 levels: deterioration (<0), improved by a little (0-1), moderate improvement (1-2), and improved by a lot (>2). We found that 78.1% of patients improved a lot, 12.5% of patients had moderate improvement, and 9.4% of patients improved a little; none got worse in the ESWT group.

Several studies[12,14] described positive effects of ESWT in knee OA. Zhao et al[12] reported that the mean WOMAC function score after 12 weeks was -13.9 for the ESWT group, similar to the results of our study. Kim et al[14] found ESWT was successful in easing the pain for knee OA patients as well. Nevertheless, in one prior clinical trial, ESWT was not efficient for managing patients with disabling pain as a result of primary knee OA.[13] In the view of Imamura et al,[13] the reasons for the negative outcome of their study were that the average duration of pretreatment pain was longer and the total energy flux densities were lower than in the study by Zhao et al.[12] In addition, there also was a difference in treatment position between the 2 studies.[12,13] The effects of ESWT in knee OA seems to be site-specific.[24] Therefore, this difference in treatment position may account for the different results. In our trial, we not only held shockwave probe on painful areas according to palpation (as did Imamura et al) but also on the patellofemoral and tibiofemoral edges of knees in our trial (as did Zhao et al).

We chose air pressure of 2.5 bars and 2000 impulses per session according to our past clinical practice. Our results indicate that fewer impulses can alleviate pain in participants with knee OA compared with trial by Zhao et al[12] although the longer duration of symptoms of patients before treatment in our study (>6mo in our study; >3mo in the study of Zhao et al). Physiotherapists may consider using ESWT when patients failed other conservative therapies. Our protocol may contribute to guiding informed decision-making regarding parameters of ESWT on knee OA.

Table 3 Within-subjects analysis of outcome measures (post hoc analysis)

Parameter	Group	Difference of Mean Baseline vs Wk 5, Mean ± SD	*P*	95% CI	Difference of Mean Baseline vs Wk 12, Mean ± SD	*P*	95% CI
VAS	Placebo	0.658±0.159	<.001	0.334-0.982	1.335±0.215	<.001	0.896-1.775
	ESWT	2.187±0.185	<.001	1.810-2.564	2.973±0.239	<.001	2.485-3.461
WOMAC pain	Placebo	0.903±0.224	<.001	0.446-1.361	2.065±0.282	<.001	1.489-2.640
	ESWT	3.645±0.326	<.001	2.979-4.312	4.333±0.319	<.001	3.680-4.986
WOMAC stiffness	Placebo	0.387±0.120	.003	0.142-0.632	0.871±0.137	<.001	0.591-1.151
	ESWT	1.419±0.145	<.001	1.123-1.715	1.633±0.155	<.001	1.316-1.951
WOMAC function	Placebo	3.194±0.679	<.001	1.807-4.580	7.000±0.931	<.001	5.099-8.901
	ESWT	12.226±1.098	<.001	9.983-14.468	14.600±1.140	<.001	12.268-16.932
Lequesne index	Placebo	0.806±0.416	.062	-0.043 to 1.656	2.903±0.469	<.001	1.945-3.861
	ESWT	5.710±0.500	<.001	4.689-6.731	6.833±0.512	<.001	5.786-7.881
T2	Placebo	0.055±0.030	.077	-0.006 to 0.116	0.139±0.223	.539	-0.317 to 0.594
	ESWT	-0.245±0.110	.034	-0.471 to -0.020	-0.373±0.118	.004	-0.614 to -0.133

Abbreviation: CI, confidence interval.

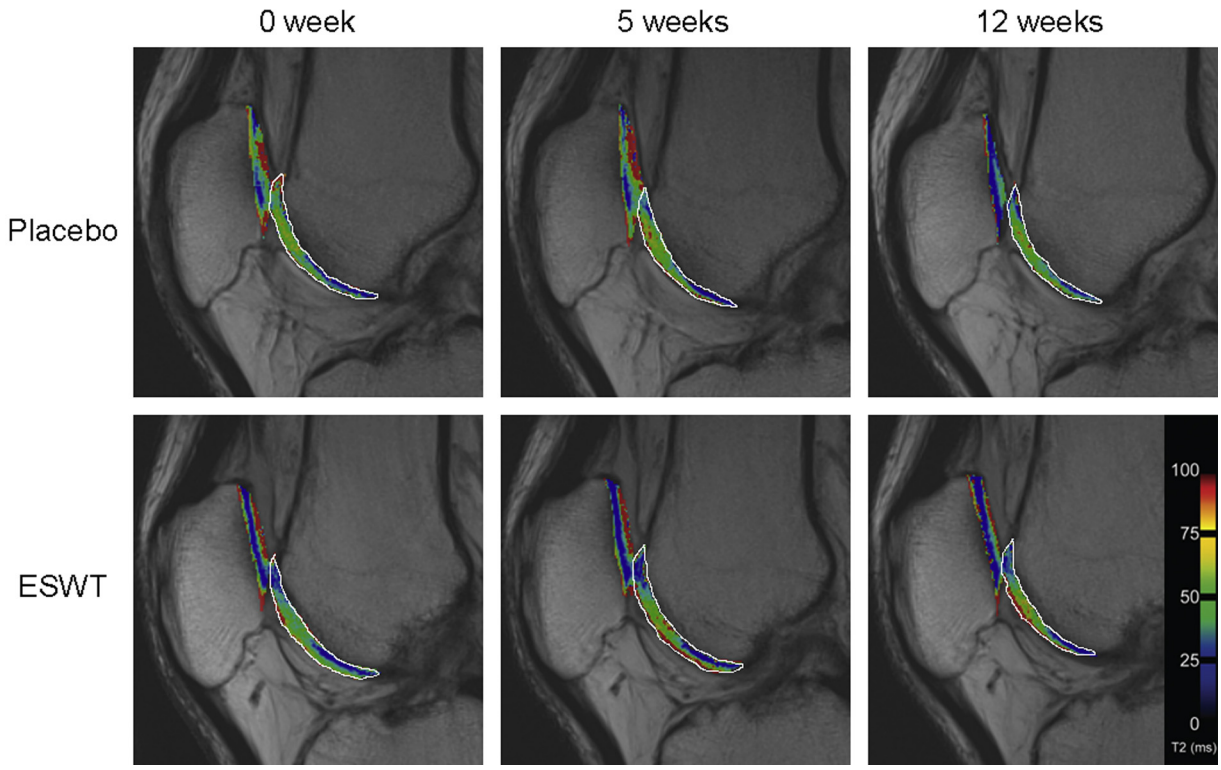

Fig 2 Sagittal spin-echo T2 maps show images of 1 subject per ESWT group and placebo group at baseline and follow-up period. Note. ROIs were outlined by white lines.

In patients with OA, it is recognized that cartilage degeneration is often present and correlates with osteoarthritis severity. The gradual abrasion of hyaline cartilage is one of the hallmarks of osteoarthritis damage. Impairment of cartilage function and joint mobility may be due to injury to cartilage integrity, which can also lead to affecting the state and metabolic activities of neighboring cells and tissues, such as the synovium.[25] The degeneration of articular cartilage results from a decrease of proteoglycan and a gain in water content, followed by a reduction of type II collagen and changes in collagen fiber orientation.[26] There is growing concern about defining the role ESWT plays in the cartilage of OA patients. A prior animal trial demonstrated that it is hard to quantify the severity of osteoarthritis changes with radiographs of the knee.[24] The T2 is susceptible to the water content, concentration, and anisotropic structure of type II collagen in cartilage.[27] The elevated T2 value is closely linked to the loss or destruction of the collagen fiber network and the increase in water content, indicating that the cartilage is degraded.[28] Therefore, we observed T2 mapping to quantitatively measure the cartilage changes of knees after shockwave treatment. According to what we have learned, this is the first time that changes in T2 mapping were indicated in a shockwave intervention experiment. We found that the results of T2 values in the ESWT group significantly increased after the intervention. Our results suggest that ESWT may produce an increase in hydration of articular cartilage and damage of integrity and orientation of the collagen fibers, which are characteristics of OA progression. There is a decline of T2 values in the placebo group, which is similar to a study reported by Munukka and Waller[29] who demonstrated a considerable decrease in T2 values occurred after 4 months of resistance training. However, no difference in T2 values was found between the ESWT group and the placebo group at the time of each observation. This finding was unexpected and suggested that the changes of cartilage caused by the shockwave are within the normal range.

Table 4 Number and prevalence of adverse events

Adverse Event	Placebo (n=31)	ESWT (n=32)	*P**
Pain, n (%)	6 (19.4)	11 (34.3)	.179
Reddening of skin, n (%)	3 (9.7)	10 (31.3)	.071
Burning sensation, n (%)	2 (6.5)	5 (15.6)	.449
Swelling, n (%)	1 (3.2)	3 (9.3)	.628
Tremor, n (%)	1 (3.2)	2 (6.3)	1.000
Hypesthesia, n (%)	0	2 (6.3)	.492
Petechiae, n (%)	0	1 (3.1)	1.000

* *P* values from Fisher exact test, comparing number and prevalence of adverse events in the ESWT group to that in the placebo group.

The exact mechanisms triggered by ESWT are not fully understood but have been explained by various views. Previous studies demonstrated that ESWT promotes neovascularization and upregulates angiogenic and osteogenic growth factors including endothelial nitric oxide synthase, vascular endothelial growth factor, proliferating cell nuclear antigen, and human bone morphogenetic protein 2.[30,31] Besides, one study reported that ESWT inhibits the production of nitric oxide in knee synovia and decreases chondrocyte apoptosis.[32] Moreover, ESWT may reduce the expression of calcitonin gene-related peptide in dorsal root ganglia, which may assist in the relief of clinical pain.[33] Some scholars believe that the shockwave can produce different stress on soft tissues and skeletal muscles, promote microcirculation, and thus, relieve the pain.[34]

Overall, we found no serious side effect in our trial, consistent with previous studies. Although more side effects were reported in the ESWT group than in the placebo groups, there was no statistical difference between the 2 groups. Most consisted of transitory pain and reddening of the skin or a burning sensation during the use of the shockwaves. The adverse events caused by shockwaves never forced the treatment to be discontinued or the dose to be reduced during the study. Although shockwaves have negative effects on cartilage, our radiologist found no patients whose cartilage was damaged during the follow-up period. Therefore, they were deemed to be of minimal risk. Given the efficacy of ESWT for patients with knee OA mentioned above, we believed that ESWT, a noninvasive conservative therapy, has greater benefits than risks.

Study limitations

There are several limitations to this study. Patients had similar degrees of knee pain and radiographic knee OA before treatment (Kellgren-Lawrence score of II or III). It is ambiguous whether patients with higher level of pain and more severe knee OA would benefit from ESWT. The optimal treatment protocol has not been established and the parameter settings of ESWT applied in this trial were chosen on the basis of our prior clinical practice. In addition, high expectations and large placebo responses may influence the assessment of effect. Moreover, because we examined only 63 patients, our results may have been due to chance. Our data covered only 3 months, and the sustained effects for longer duration remain unknown. Future studies should recruit more samples to observe the long-term effects of ESWT on knee OA and cartilage.

Conclusions

As indicated by our results, ESWT is an effective, safe, and promising option to reduce pain and improve disability status of patients with symptoms of mild to moderate knee OA, although it has an adverse effect on cartilage within the limits of security. Further studies are needed to confirm these findings in a larger cohort of patients, and determine the effect of ESWT on knee OA and cartilage.

Suppliers

a. Swiss DolorClast; EMS Electro Medical Systems SA.
b. Siemens Healthcare.
c. SPSS version 19; IBM Corp.

Keywords

Cartilage; Extracorporeal shockwave therapy; Osteoarthritis, knee; Randomized controlled trial; Rehabilitation

Corresponding author

Bangzhong Liu, PhD, Department of Rehabilitation Medicine, Zhongshan Hospital Fudan University, 180 Fenglin Road, Xuhui District, Shanghai, China. *E-mail address:* liu.bangzhong@zs-hospital.sh.cn.

References

1. Deshpande BR, Katz JN, Solomon DH, et al. Number of persons with symptomatic knee osteoarthritis in the US: impact of race and ethnicity, age, sex, and obesity. Arthritis Care Res (Hoboken) 2016;68:1743-50.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58:26-35.
3. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum 2012;64:1697-707.
4. Lluch GE, Nijs J, Torres-Cueco R, Lopez CC. Pain treatment for patients with osteoarthritis and central sensitization. Phys Ther 2013;93:842-51.
5. Guo P, Gao F, Zhao T, Sun W, Wang B, Li Z. Positive effects of extracorporeal shock wave therapy on spasticity in poststroke patients: a meta-analysis. J Stroke Cerebrovasc Dis 2017;26:2470-6.
6. Gerdesmeyer L, Frey C, Vester J, et al. Radial extracorporeal shock wave therapy is safe and effective in the treatment of chronic recalcitrant plantar fasciitis: results of a confirmatory randomized placebo-controlled multicenter study. Am J Sports Med 2008;36:2100-9.
7. Rompe JD, Decking J, Schoellner C, Theis C. Repetitive low-energy shock wave treatment for chronic lateral epicondylitis in tennis players. Am J Sports Med 2004;32:734-43.
8. Alvarez RG, Cincere B, Channappa C, et al. Extracorporeal shock wave treatment of non- or delayed union of proximal metatarsal fractures. Foot Ankle Int 2011;32:746-54.
9. Ochiai N, Ohtori S, Sasho T, et al. Extracorporeal shock wave therapy improves motor dysfunction and pain originating from knee osteoarthritis in rats. Osteoarthritis Cartilage 2007;15:1093-6.
10. Frisbie DD, Kawcak CE, McIlwraith CW. Evaluation of the effect of extracorporeal shock wave treatment on experimentally induced osteoarthritis in middle carpal joints of horses. Am J Vet Res 2009;70:449-54.
11. Wang CJ, Sun YC, Wong T, Hsu SL, Chou WY, Chang HW. Extracorporeal shockwave therapy shows time-dependent chondroprotective effects in osteoarthritis of the knee in rats. J Surg Res 2012;178:196-205.
12. Zhao Z, Jing R, Shi Z, Zhao B, Ai Q, Xing G. Efficacy of extracorporeal shockwave therapy for knee osteoarthritis: a randomized controlled trial. J Surg Res 2013;185:661-6.
13. Imamura M, Alamino S, Hsing W, Alfieri F, Schmitz C, Battistella L. Radial extracorporeal shock wave therapy for disabling pain due to severe primary knee osteoarthritis. J Rehabil Med 2017;49:54-62.
14. Kim JH, Kim JY, Choi CM, et al. The dose-related effects of extracorporeal shock wave therapy for knee osteoarthritis. Ann Rehabil Med 2015;39:616-23.
15. Jiang Y, Tuan RS. Origin and function of cartilage stem/progenitor cells in osteoarthritis. Nat Rev Rheumatol 2015;11:206-12.
16. Yu L, Liu S, Zhao Z, et al. Extracorporeal shock wave rebuilt subchondral bone in vivo and activated Wnt5a/Ca2+ signaling in vitro. Biomed Res Int 2017;2017:1-10.
17. Watrin-Pinzano A, Ruaud JP, Cheli Y, et al. T2 mapping: an efficient MR quantitative technique to evaluate spontaneous cartilage repair in rat patella. Osteoarthritis Cartilage 2004;12:191-200.
18. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039-49.
19. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494-502.
20. Atamaz FC, Durmaz B, Baydar M, et al. Comparison of the efficacy of transcutaneous electrical nerve stimulation, interferential currents, and shortwave diathermy in knee osteoarthritis: a double-blind, randomized, controlled, multicenter study. Arch Phys Med Rehabil 2012;93:748-56.

21. Bellamy N, Campbell J, Stevens J, Pilch L, Stewart C, Mahmood Z. Validation study of a computerized version of the Western Ontario and McMaster Universities VA3.0 Osteoarthritis Index. J Rheumatol 1997; 24:2413-5.
22. Lequesne MG, Mery C, Samson M, Gerard P. Indexes of severity for osteoarthritis of the hip and knee. Validation–value in comparison with other assessment tests. Scand J Rheumatol Suppl 1987;65:85-9.
23. Tonstad S, Davies S, Flammer M, Russ C, Hughes J. Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: a pooled analysis. Drug Saf 2010;33:289-301.
24. Wang CJ, Sun YC, Siu KK, Wu CT. Extracorporeal shockwave therapy shows site-specific effects in osteoarthritis of the knee in rats. J Surg Res 2013;183:612-9.
25. Pap T, Korb-Pap A. Cartilage damage in osteoarthritis and rheumatoid arthritis–two unequal siblings. Nat Rev Rheumatol 2015;11:606-15.
26. Hada S, Kaneko H, Sadatsuki R, et al. The degeneration and destruction of femoral articular cartilage shows a greater degree of deterioration than that of the tibial and patellar articular cartilage in early stage knee osteoarthritis: a cross-sectional study. Osteoarthritis Cartilage 2014;22:1583-9.
27. Mosher TJ, Dardzinski BJ. Cartilage MRI T2 relaxation time mapping: overview and applications. Semin Musculoskelet Radiol 2004;8: 355-68.
28. Trattnig S, Mamisch TC, Welsch GH, et al. Quantitative T2 mapping of matrix-associated autologous chondrocyte transplantation at 3 Tesla: an in vivo cross-sectional study. Invest Radiol 2007;42:442-8.
29. Munukka M, Waller B, Rantalainen T, et al. Efficacy of progressive aquatic resistance training for tibiofemoral cartilage in postmenopausal women with mild knee osteoarthritis: a randomised controlled trial. Osteoarthritis Cartilage 2016;24:1708-17.
30. Wang CJ, Wang FS, Yang KD, et al. Shock wave therapy induces neovascularization at the tendon-bone junction. A study in rabbits. J Orthop Res 2003;21:984-9.
31. Wang CJ, Wang FS, Yang KD. Biological effects of extracorporeal shockwave in bone healing: a study in rabbits. Arch Orthop Trauma Surg 2008;128:879-84.
32. Zhao Z, Ji H, Jing R, et al. Extracorporeal shock-wave therapy reduces progression of knee osteoarthritis in rabbits by reducing nitric oxide level and chondrocyte apoptosis. Arch Orthop Trauma Surg 2012;132: 1547-53.
33. Takahashi N, Wada Y, Ohtori S, Saisu T, Moriya H. Application of shock waves to rat skin decreases calcitonin gene-related peptide immunoreactivity in dorsal root ganglion neurons. Auton Neurosci 2003;107:81-4.
34. Fricova J, Rokyta R. The effects of extracorporeal shock wave therapy on pain patients. Neuro Endocrinol Lett 2015;36:161-4.