ORIGINAL REPORT

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RADIAL EXTRACORPOREAL SHOCK WAVE THERAPY FOR DISABLING PAIN DUE TO SEVERE PRIMARY KNEE OSTEOARTHRITIS

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Objective: To assess the efficacy and safety of radial extracorporeal shock wave therapy (rESWT) for disabling pain due to primary knee osteoarthritis.

Design: Randomized, placebo-controlled trial (level of evidence, 1).

Subjects: A total of 105 women with disabling pain due to primary knee osteoarthritis lasting for a mean of 103 months (range 3–480 months).

Methods: Patients received either rESWT (3 sessions, each one week apart, 2,000 rESWT impulses per session, positive energy flux density 0.10–0.16 mJ/mm²) or placebo treatment. Primary outcome measure was pain on movement 3 months after the final treatment session. Secondary outcomes were pain, stiffness and limitations in physical function on the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index and the level of tolerance to pressure over muscles, tendons, ligaments and skin at both the treated and the untreated side at 1 week and 3 months follow-up examinations.

Results: Compared with placebo treatment, rESWT led to a statistically significant improvement only in mean WOMAC scores for pain and a few of the pressure measurements.

Conclusion: rESWT, as performed in the present study, is not efficient for treating patients with disabling pain due to primary knee osteoarthritis. Published data indicate that substantially higher energy flux densities are necessary for treatment success in this condition.

Key words: extracorporeal shock wave therapy; knee osteoarthritis; radial extracorporeal shock wave therapy; rehabilitation.

Osteoarthritis (OA) is the most common cause of pain and disability worldwide (1), especially in the elderly population (2, 3). Women are affected more frequently than men (4), and the hip and knee joints are most commonly affected (5). Despite its high prevalence and negative impact on quality of life of affected individuals, there is no cure for OA (2, 3). Therapeutic measures aim to relieve painful symptoms and maximize functional capacity and quality of life, while minimizing adverse effects from drugs and invasive interventions (6). Patients worldwide with knee OA reporting severe disabling and refractory pain are usually referred for a total or partial arthroplasty (7, 8).

Total knee replacement has been shown in a recent study to result in greater pain relief and functional improvement after 12 months than non-surgical treatment involving exercise, education, dietary advice, use of insoles and pain medication (8). However, total knee replacement was associated with a higher number of serious adverse events than the non-surgical treatment (8). Thus, and since total knee replacement may not be possible due to the patient's medical condition, or the limited availability and/or expense of the procedure, there is a need for alternatives to surgery for the treatment of knee OA. Extracorporeal shock wave therapy (ESWT) is one of the best investigated treatment modalities for various musculoskeletal conditions (for reviews see, e.g. 9–12). Extracorporeal shock waves are acoustic high-pressure waves generated by electrohydraulic, electromagnetic, piezoelectric or ballistic/radial methods (11–16). Experimental studies in animal models have indicated that ESWT may be effective in treating disabling pain due to primary OA (17–20). This was corroborated by 2 randomized controlled trials (RCTs) in which ESWT was used successfully to alleviate pain in patients with knee OA (21, 22). However, these RCTs varied considerably with respect to the applied shock wave energy (the total applied energy flux density varied between 120 and 4,000 mJ/mm²). Furthermore, none of these RCTs adhered to the Consolidated Standards of Reporting Trials (CONSORT) Statement, which is an evidence-based, minimum set of recommendations for reporting RCTs (23) (for example, in none of these RCTs was a power analysis reported). Thus, it is not known whether ESWT is an effective and safe treatment for disabling pain due to severe primary knee OA.

The present RCT evaluated the efficacy of a radial ESWT (rESWT) protocol (3 sessions, each 1 week apart, 2,000 impulses each, positive energy flux density (positive EFD) 0.10–0.16 mJ/mm²) in reducing

pain and improving knee function in patients with disabling pain due to severe primary knee OA. This rESWT protocol represents the mean number of rESWT sessions, the mean interval between sessions, the mean number of impulses per session, and the mean positive EFD applied in 23 RCTs on rESWT for tendon and other pathologies of the musculoskeletal system with positive outcome (i.e. rESWT statistically significantly better than either placebo or alternative treatment modalities) (12). Based on the outcome of the aforementioned RCTs (21, 22), in which ESWT was successfully used to alleviate pain in patients with knee OA, we hypothesized that the outcome of the rESWT protocol in the current study would be superior to placebo treatment.
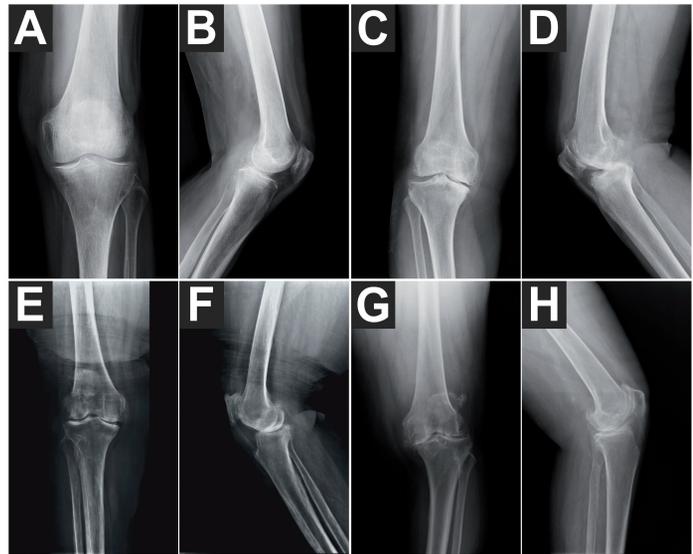

Fig. 1. Standard anterior-posterior (A, C, E, G) and lateral (B, D, F, H) radiographs of representative patients with disabling pain due to severe primary knee osteoarthritis (OA) enrolled in the present study. All patients were female. (A, B) 73-year-old, left knee, pain for 10 months, visual analogue scale (VAS) score = 9.9, Kellgren-Lawrence (KL) grade = 2, no knee deformity. (C, D) 60-year-old, right knee, pain for 60 months, VAS score = 9.5, KL grade = 4, genu varum. (E, F) 74-year-old, right knee, pain for 12 months, VAS score = 5.8, KL grade = 2–3, no knee deformity. (G, H) 72-year-old, left knee, pain for 24 months, VAS score = 5.0, KL grade = 4, genu varum. Note that there was no correlation between the individual VAS score on the one hand and the individual KL grade and the presence or absence of knee deformities on the other hand. The final figure was constructed using Corel Photo-Paint X6 and Corel Draw X6 (both versions 16.1.0.843; Corel, Ottawa, Canada). Only minor adjustments of contrast and brightness were made, without altering the appearance of the original materials.

METHODS

Patients

A total of 237 female patients with disabling pain due to severe primary knee OA were assessed between May 2010 and October 2012 for eligibility for enrollment in the present study. Patients of any race and ethnicity were eligible to participate. Some patients were from the waiting list for total knee replacement at the Department of Orthopedics and Traumatology, University of São Paulo School of Medicine, São Paulo, Brazil. Other patients were from the community of São Paulo and referred to the Institute of Physical Medicine and Rehabilitation, University of São Paulo School of Medicine. Thus, the patients assessed for eligibility for enrollment in the present study were representative of the citizens of São Paulo, Brazil. Patients were diagnosed based on their medical history and physical examination at the Department of Orthopedics and Traumatology and the Institute of Physical and Rehabilitation Medicine at the University of São Paulo School of Medicine. Radiographs showed signs of knee OA according to Kellgren & Lawrence (24) grades 2–4 as well as knee deformities. However, individual Kellgren & Lawrence (24) grades were not used to make decisions about eligibility for enrollment in the present study because of the known discordance between pain and radiographic severity in knee OA (25), which was also found in the present study (Fig. 1). The same reasoning applied to the presence or absence of knee deformities (Fig. 1). All patients had undergone 2 or more types of conservative treatment (medications, anti-inflammatory drugs, physical therapy, stretching, acupuncture, orthotics, and others) without success. Patients were considered for participation in the present study according to the inclusion and exclusion criteria summarized in Table I.

Ethics statement

Patients were allowed to withdraw their free and informed consent to participate in the present study at any time. The study was approved by the Ethics Committee for Analysis of Research Projects (CAPPesq), Hospital of Clinics, University of São Paulo Medical School, São Paulo, Brazil (CAPPesq 0130/10) and was carried out in accordance with the World Medical Association Declaration of Helsinki (26). The study has been registered with ClinicalTrials.gov (identifier NCT02197962).

Randomization

Before randomization, 132 of the 237 patients assessed for eligibility chose to withdraw, declined to sign the consent form, or were excluded because they did not meet the inclusion criteria. After having obtained written informed consent from each of the remaining 105 patients, they were randomly assigned to receive either rESWT (*n* = 52) or placebo treatment (*n* = 53). Randomization was performed by a person who was not involved in the study, at the Institute of Physical and Rehabilitation Medicine at the University of São Paulo School of Medicine (São Paulo, Brazil), using a computerized random number generator. The randomization numbers were placed in sealed opaque envelopes, thus concealing allocation from both patients and therapists until treatment started.

The characteristics of the included patients at baseline are shown in Table II. These patients had disabling pain for between 3 and 480 months (25th percentile 48 months, median 72 months, 75th percentile 132 months).

Treatment

The intervention group received rESWT with the radial shock wave device, Swiss DolorClast (EMS Electro Medical Systems, Nyon, Switzerland) using the "radial" (blue) handpiece. Each patient received 3 sessions of rESWT, 1 week apart, 2,000 impulses per session, to the most painful area determined by palpa-

Table I. Inclusion and exclusion criteria for patients with primary knee osteoarthritis (OA) enrolled in the present study

Inclusion criteria

Clinical and radiological diagnosis of primary knee OA

Intensity of pain: visual analogue scale equal to 5 or greater

Failure of 2 or more types of previous conservative treatment (medications, anti-inflammatory drugs, physical therapy, stretching, acupuncture, orthotics and others)

Age over 59 years (i.e. 60 years or older)

Availability to attend the hospital during the treatment and follow-up examinations

Exclusion criteria

Major clinical manifestations in other lower limb joints (hip and ankle) as well as spinal

Clinical signs of neuropathy, including radiculopathies and peripheral neuropathies

Systemic inflammatory diseases (rheumatoid arthritis, Reiter's arthritis, ankylosing spondylitis, generalized polyarthritis, neoplasms)

Associated metabolic or endocrine diseases

Fibromyalgia

Serious psychiatric disorders requiring psychiatric care

Steroid injections during the last 48 h before treatment*

Infection or tumour at the site of therapy application*

Serious blood dyscrasia*

Blood-clotting disorders (including local thrombosis)*

Treatment with oral anticoagulants*

Treatment with extracorporeal shock waves in the past

*Contraindications for radial extracorporeal shock wave therapy (rESWT)

tion. The air pressure of the device was adjusted to the maximum discomfort the individual patient could tolerate, resulting in individual air pressures of between 2.5 and 4.0 bar and, thus, positive EFD of between 0.10 and 0.16 mJ/mm². Impulses were applied at a frequency of 8 Hz. Local anaesthesia or analgesic drugs were not applied during the rESWT sessions. The decision to omit the use of local anaesthesia was based on 2 RCTs that demonstrated that application of local anaesthesia to the area of treatment adversely affects the outcome of ESWT (27, 28).

The control group received placebo treatment in an identical manner to the rESWT treatments described above, except for the fact that no EFD was applied. This was achieved by using a placebo handpiece that looked, felt and sounded identical to the "radial" (blue) handpiece of the Swiss DolorClast device, but did not emit radial shock waves (a similar placebo handpiece was used in (29)).

Both groups received a post-application home treatment programme for 3 consecutive days after each treatment session, consisting of surface heat on the skin areas exposed to rESWT or sham-rESWT for 20 min. If necessary, paracetamol (500 mg every 6 h), or a similar medicine in case of allergy, was prescribed for 3 consecutive days after each treatment session.

Treatments were performed at the Institute of Physical and Rehabilitation Medicine, University of São Paulo School of Medicine. Thus, at first glance the intervention was undertaken in a specialist centre that was not representative of the hospitals and clinics that most of the source population would attend. However, all treatments were performed on an outpatient basis and, thus, representative of that in use in the source population.

Outcome measures

Clinical assessments included assessment of pain on movement and physical function. The primary outcome measure was pain on movement, measured using a 10-cm visual analogue scale (VAS) (30), with 0 indicating no pain and 10 maximum pain. Secondary outcomes were pain, stiffness and limitations in physical function on the WOMAC Index (31) on both the treated and the untreated side. Evaluation was performed at baseline, and 1 week (W1) and 3 months (M3) after the final treatment session.

The WOMAC Index assesses the symptoms of OA and is a validated, disease-specific, self-reporting questionnaire referring to the 48 h before assessment (31). The index consists of 5 questions for severity of knee pain, 2 for stiffness, and 17 for limitations in physical function. In the present study a modified WOMAC score was calculated, ranging from 0 (best) to 4 (worst) for each criterion (i.e. severity of knee pain, stiffness, and limitations in physical function).

A further evaluation criterion was the level of tolerance to pressure (32, 33) in the following muscles: vastus medialis, vastus lateralis, rectus femoris, gracilis, adductor longus, tibialis anterior, peroneus longus, quadratus lumborum, iliopsoas, and popliteus; pes anserinus and the patellar tendon, the medial joint line, supraspinous ligaments from L1 to S1 and the territory of the dermatomes of L1 to S2. These measurements were performed using a Fischer algometer (Pain Treatment, Great Neck, NY, USA).

Treatment success was defined as individual improvement in the primary outcome measure (VAS score for pain on movement) by >50% compared with baseline.

Complications, adverse effects and complaints during treatment were documented.

Blinding

Both patients and the study investigators were blinded for the entire duration of the study. Specifically, the patients were not aware whether they received rESWT or placebo treatment, and the study investigators did not have access to the patients' treatment records, including patient allocation or the allocation sequence, until all patients had completed the 3-month follow-up examination.

As in case of all studies on ESWT listed in the open-access Physiotherapy Evidence Database (PEDro) (12), the therapists who applied the treatments were not blinded. To prevent any bias, they interacted with the study participants strictly in a standardized way

Table II. Characteristics of included patients at baseline (intention-to-treat population)

Variable	rESWT (*n* = 52)	Placebo (*n* = 53)
Age, years, mean (SD)	70.0 (6.5)	72.4 (6.5)
Woman, *n* (%)	52 (100)	53 (100)
Affected side, left, *n* (%)	29 (55.8)	24 (45.3)
Duration of pain before treatment, months, mean (SD)	92.4 (77.4)	113.7 (99.0)
VAS score, median (range)	7.3 (2–10)	7.8 (4.8–10)
WOMAC score for pain on the treated side, median (range)	2.4 (0–3.8)	2.2 (0–3.6)
WOMAC score for pain on the untreated side, median (range)	1.2 (0–3.4)	1.5 (0–3.4)
WOMAC score for stiffness on the treated side, median (range)	2.2 (0–4.0)	2.1 (0–4.0)
WOMAC score for stiffness on the untreated side, median (range)	1.3 (0–4.0)	1.4 (0–4.0)
WOMAC score for limitations in physical function on the treated side, median (range)	2.6 (0.9–4.0)	2.4 (0–3.8)
WOMAC score for limitations in physical function on the untreated side, median (range)	1.4 (0–3.9)	1.8 (0–3.5)

SD: standard deviation; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; rESWT: radial extracorporeal shock wave therapy.

irrespective of treatment allocation, preventing any behaviour that could have indicated to the patients whether they received rESWT or placebo treatment. This was further supported by the fact that the look, handling and sound of the rESWT device were identical in both rESWT and placebo treatments, and all rESWT or placebo treatment sessions took approximately 10 min. Furthermore, only patients who had not received ESWT treatments previously were enrolled in the present study, and the names of other patients in the study were not disclosed. Thus, patients could not determine whether they were in the rESWT or the placebo group based on slight pain and discomfort experienced during treatment (which is inherent to rESWT; c.f., e.g. (11)).

Drop-outs and loss to follow-up

The patient flow in the present study according to CONSORT (23) is shown in Fig. 2. Of the 237 patients assessed for eligibility, 105 were randomly allocated to rESWT (*n*=52) or placebo treatment (*n*=53), respectively. All patients received treatment as allocated. Six out of the 52 patients in the rESWT group and 6 out of the 53 patients in the placebo group were lost to follow up, resulting in full analysis of, respectively, 46/52 (88.5%; rESWT) and 47/53 (88.7%; placebo) of the patients who were randomized.

Power analysis

Based on anecdotal evidence from colleagues and our own preliminary data we expected treatment success (i.e. individual reduction of the VAS score by >50% compared with baseline) in 65% of the patients to be treated with rESWT, and in 30% of the patients to be treated with placebo. Considering a 2-sided significance level of 95%, power of 0.9 and equal samples, the power analysis retrieved a minimum number of, respectively, 43 (according to (34)) or 41(according to (35)) per group to be enrolled in the present study. Power analysis was performed with the online tool, Open Source Epidemiologic Statistics for Public Health (36).

Statistical analysis

Statistical analysis was performed on an intention-to-treat basis using the last observation carried forward approach (37). Mean and standard error of the mean (SEM) were calculated for all investigated variables.

Differences at baseline between the patients treated with rESWT and those treated with placebo were tested with Student's unpaired *t*-test in case of the mean age of the patients, Mann–Whitney test in case of the mean duration of pain before treatment, VAS score, and WOMAC scores for pain, rigidity and limitations in physical function, and Fisher's exact test in case of the affected side.

Treatment-related differences in mean VAS scores and mean levels of tolerance to pressure over the supraspinous ligaments between the patients treated with rESWT and those treated with placebo were tested with repeated measures analysis of variance (ANOVA), with the different times (BL, W1, M3) as within-subject factor, and the treatment (rEWST, placebo) as between-subject factor.

Treatment-related differences in mean WOMAC scores for pain, rigidity and limitations in physical function, as well as mean levels of tolerance to pressure over muscles, tendons and skin between the patients treated with rESWT and those treated with placebo were tested with 2-way repeated measures ANOVA, with the different times (BL, W1, M3) and the side (treated, untreated) as within-subject factors, and the treatment (rEWST, placebo) as between-subject factor.

Treatment success (i.e. number of patients with individual improvement in the VAS score by more than 50% at W1 and M3) was tested with Fisher's exact test.

In all analyses an effect was considered statistically significant if its associated p-value was smaller than 0.05. Calculations were performed using SPSS (Version 23 for Windows; IBM, Armonk, NY, USA).

RESULTS

Baseline characteristics and demographic data of the patients

With the numbers available, the patients in the intention-to-treat population treated with rESWT were not significantly different statistically from the patients treated with placebo with respect to the sex distribution, mean age, affected side, duration of pain before treatment, mean overall VAS score, and mean WOMAC scores for pain, stiffness and limitations in physical function at both the treated and the untreated sides.
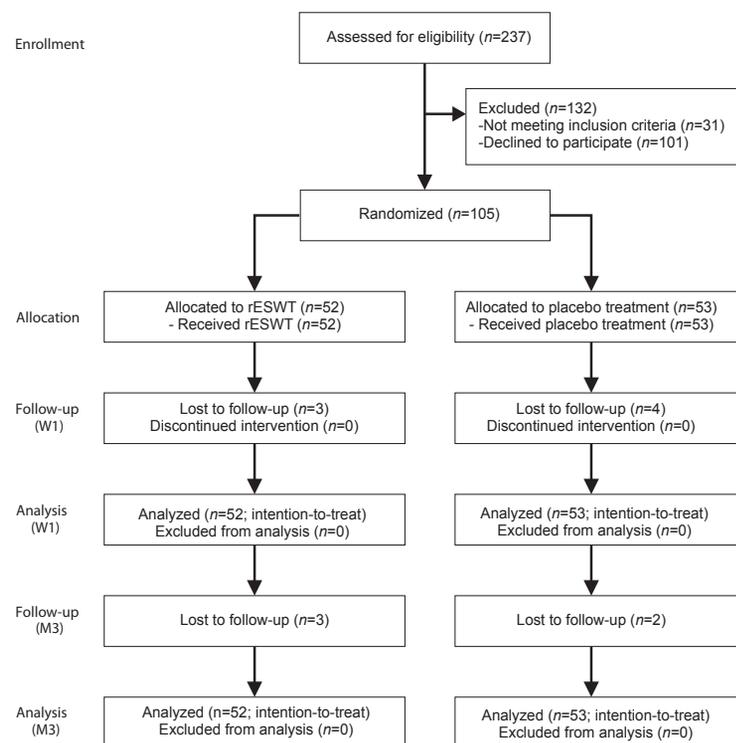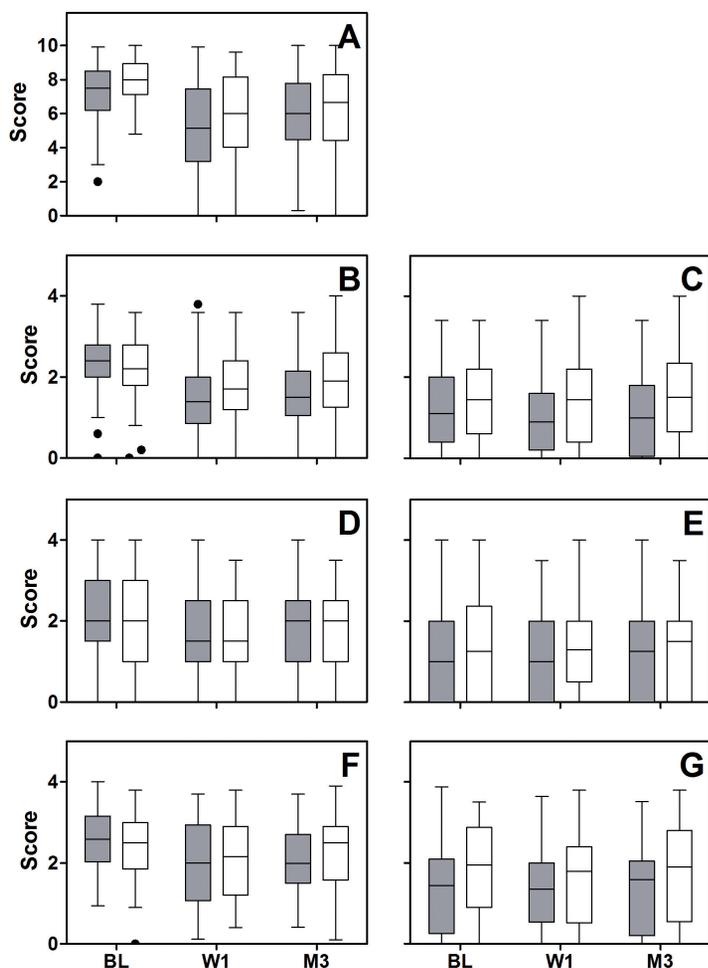

Fig. 2. Study participants according to the Consolidated Standards of Reporting Trials (CONSORT) Statement (23).

Fig. 3. Tukey box-plots of: (A) visual analogue scale (VAS) scores; (B, C) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores for pain; (D, E) WOMAC scores for rigidity; (F, G) WOMAC scores for limitations in physical function, obtained with intention-to-treat analysis at baseline (BL), 1 week after the final treatment session (W1) and 3 months after the final treatment session (M3) of the patients treated with radial extracorporeal shock wave therapy (rESWT) (grey boxes) or placebo (open boxes). (B, D and F) WOMAC scores obtained on the treated side; (C, E and G) WOMAC scores obtained on the untreated (contralateral) side.

WOMAC scores for pain, stiffness and limitations in physical function on the treated side

rESWT reduced the mean WOMAC score for pain on the treated side by 36.5% at W1, and by 32.2% at M3 (Fig. 3B). The corresponding numbers for placebo treatment were 19.2% at W1 and 11.8% at M3 (Fig. 3B). This difference between rESWT and placebo treatment was statistically significant (p-values are summarized in Table III). The mean WOMAC scores for stiffness and limitations in physical function were not statistically significantly different between rESWT and placebo treatment (Fig. 3D, F).

WOMAC scores for pain, stiffness and limitations in physical function on the untreated side

The mean WOMAC scores for pain, stiffness, and limitations in physical function on the untreated side were statistically significantly lower than the corresponding scores on the treated side (p-values are summarized in Table III) and showed only small changes during follow-up after rESWT or placebo treatment (Fig. 3C, E, G).

Tolerance to pressure

Slight, but statistically significant, differences between the patients treated with rESWT and those treated with placebo were only found in the iliopsoas muscle (p-values are summarized in Table III). The other measurements showed no statistically significant differences between rESWT and placebo treatment. Overall, differences between the patients treated with rESWT and those treated with placebo were small.

Complications

No complications were observed.

VAS score

rESWT reduced the mean VAS score by 29.7% (or 2.2 absolute score points) from baseline to 1 week after the final treatment session (W1), and by 21.2% (or 1.6 absolute score points) from baseline to 3 months after the final treatment session (M3) (Fig. 3A). However, similar changes in mean VAS score were also found after placebo treatment (W1: reduction by 25.0% or 1.9 absolute score points; M3: reduction by 22.4% or 1.7 absolute score points) (Fig. 3A). No statistically significant difference was found between rESWT and placebo treatment (p-values are summarized in Table III).

Both rESWT and placebo treatment resulted in similar relative numbers of patients with treatment success (defined as individual reduction in VAS score by >50% compared with baseline) (W1: 25.0% (13/52) after rESWT and 20.8% (11/53) after placebo treatment; M3: 23.1% (12/52) after rESWT and 20.8% (11/53) after placebo treatment). No statistically significant difference was found between rESWT and placebo treatment (W1: $p=0.648$; M3: $p=0.817$).

Table III. Statistical analysis of the visual analogue scale (VAS) score, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores for pain, rigidity and limitations in physical function, and the level of tolerance to pressure over muscles, tendons, ligaments and skin using a Fischer algometer

Variable	T	F	F×T	S	S×T	F×S	F×S×T
VAS score	0.132	**<0.001**	0.689	–	–	–	–
WOMAC score for pain	0.038	**<0.001**	**0.010**	**<0.001**	0.146	**<0.001**	0.386
WOMAC score for rigidity	0.786	**0.012**	0.724	**<0.001**	0.071	0.173	0.584
WOMAC score for limit physical functioning	0.263	**<0.001**	0.514	**<0.001**	**0.034**	**<0.001**	0.061
Algometer – vastus medialis muscle	0.734	0.146	0.698	0.079	**0.031**	**0.004**	0.613
Algometer – vastus lateralis muscle	0.481	0.192	0.131	0.098	0.240	0.371	0.998
Algometer – rectus femoris muscle	0.967	0.623	0.752	0.217	0.430	0.899	0.153
Algometer – gracilis muscle	0.984	0.378	0.692	0.146	0.736	0.550	0.681
Algometer – adductor longus muscle	0.999	0.287	0.514	0.284	**0.011**	0.393	0.779
Algometer – tibialis anterior muscle	0.623	**0.005**	0.073	0.228	0.085	0.792	0.811
Algometer – quadratus lumborum muscle	0.569	0.194	0.700	0.258	0.922	**0.026**	0.408
Algometer – iliopsoas muscle	0.400	0.404	**0.026**	0.757	0.835	0.982	0.053
Algometer – popliteus muscle	0.896	**0.018**	0.763	0.172	0.952	0.118	0.367
Algometer – patellar tendon	0.522	**0.009**	0.679	0.351	0.701	0.249	0.138
Algometer – supraspinous ligament L1/L2	0.838	0.297	0.208	–	–	–	–
Algometer – supraspinous ligament L2/L3	0.857	0.276	0.132	–	–	–	–
Algometer – supraspinous ligament L3/L4	0.823	0.107	0.822	–	–	–	–
Algometer – supraspinous ligament L4/L5	0.931	0.219	0.420	–	–	–	–
Algometer – supraspinous ligament L5/S1	0.741	**0.013**	0.387	–	–	–	–
Algometer – supraspinous ligament S1/S2	0.525	**0.013**	0.716	–	–	–	–
Algometer – dermatome L1	0.851	0.414	0.084	0.209	0.970	0.535	**0.047**
Algometer – dermatome L2	0.489	0.244	0.098	0.539	**0.037**	0.422	0.809
Algometer – dermatome L3	0.340	**0.039**	0.115	0.526	0.674	0.627	0.150
Algometer – dermatome L4	0.777	0.417	0.317	0.866	0.330	0.176	0.957
Algometer – dermatome L5	0.582	0.111	0.094	0.254	0.795	0.422	0.553
Algometer – dermatome S1	0.590	**0.014**	0.535	0.374	0.810	0.757	0.485
Algometer – dermatome S2	0.655	0.947	0.499	**0.031**	0.217	**0.021**	0.604

T: treatment (radial extracorporeal shock wave therapy (rESWT) or placebo); F: follow-up (examination at baseline, 1 week after the final treatment and 3 months after the final treatment); S: side (affected/treated or unaffected/untreated). *p*-values <0.05 are shown in bold.

DISCUSSION

The findings of the present study can be summarized as follows: rESWT, as applied here (3 sessions, each 1 week apart, 2000 impulses each, positive EFD 0.10–0.16 mJ/mm2) was not superior to placebo treatment (except for an improved mean WOMAC score for pain in the treated side and some of the pressure measurements obtained with a Fischer algometer). Thus, rESWT, as performed in the present study, was not superior to placebo.

In order to identify the factors that may have caused the negative outcome of the present study we compared our rESWT protocol with other ESWT protocols that were applied successfully in RCTs on ESWT for alleviating pain in patients with knee OA (21, 22) (Table IV). Initially, it appears that differences in the mean duration of pain before ESWT (92.4 months in our study; between 3 and 19.3 months in the other studies) could have caused the difference in outcome. However, the duration of pain before rESWT varied between 3 and 480 months in our study and had no impact on the individual change in the VAS score after rESWT (data not shown). In fact, the data summarized in Table IV do not allow us to determine why the present study failed to demonstrate any superiority of rESWT over placebo, when other studies using fESWT (21) or rEWST (22) were successful in alleviating pain in patients with knee OA. However, the results of the study by Kim et al. (21) should be interpreted cautiously, as the lower of the 2 total energy flux densities (EFDs) applied in this study (i.e. 120 mJ/mm²) was approximately 10 times less than the mean total EFD applied in 66 RCTs on fESWT for tendon and other pathologies of the musculoskeletal system with positive outcome (12), but was approximately 33 times

Table IV. Details of published studies on extracorporeal shock wave therapy for knee osteoarthritis

Study	R	T	N-P	D	P-BL	P-M3	N-S	I-S	N-I	EFD	E	M
Kim et al. 2015 (21)	21	Focused	30	19.3	6.1	1.6	3	1	1,000	0.04	120	1
Kim et al. 2015 (21)	21	Focused	30	16.7	5.9	1.9	3	1	1,000	0.093	279	2.3
Zhao et al. 2013 (22)	22	Radial	34	>3*	7.6	3.8	4	1	4,000	0.25	4,000	33
Present study		Radial	52	92.4	7.3	5.8	3	1	2,000	0.10–0.16	600–960	5–8

ªZhao et al. (22) reported that the patients had knee pain for only 3 months before treatment.
R: reference number; T: type of extracorporeal shock waves; N-P: number of patients treated with extracorporeal shock wave therapy (ESWT); D: mean duration of pain before ESWT (weeks). P-BL: mean pain level (visual analogue scale (VAS) score) at baseline; P-M3: mean pain level (VAS score) 3 months after the treatment; N-S: number of ESWT sessions; I-S: interval between the ESWT sessions (weeks); N-I: number of extracorporeal shock waves per session; EDF: energy flux density of the applied extracorporeal shock waves (mJ/mm²); E: total energy flux density (mJ/mm²); M: multiple of the total energy flux density compared with the lower energy flux density used in Kim et al.'s study (21).

less than the total positive EFD used by Zhao et al. (22) for treating knee OA with rESWT. Nevertheless, Kim et al.'s results (21) were supposedly better than the results obtained by Zhao et al. (22), let alone the results of the present study. On the other hand, several studies demonstrated that the effects of ESWT on the musculoskeletal system are dose-dependent, i.e. "more is better" (c.f., e.g. 38–40), and fESWT is not better than rESWT (or vice versa) when treating pathologies of the musculoskeletal system (12) except of deep non-unions. It is therefore highly desirable to repeat Kim et al.'s study on an independent sample of patients, including a placebo group (which was not done in the study by Kim et al. (21), but was in the study by Zhao et al. (22) and the present study). When comparing only Zhao et al.'s study (22) with the present one, the best explanation for the different outcome is that Zhao et al. (22) used radial extracorporeal shock waves with a higher positive EFD and a more than 4 times higher total positive EFD than the present study.

It should be noted that Chen et al. (41) used fESWT for treating patients with knee OA and a sesamoid bone in the popliteus muscle (popliteal cyamella). However, the authors focused the extracorporeal shock waves on the sesamoid bones with the aim to treat them similarly to the treatment of calcific tendinopathy. Thus, this study by Chen et al. (41) cannot be compared with the studies summarized in Table IV (including the present one).

The molecular and cellular mechanisms of ESWT mediating pain relief in knee OA are virtually unknown. Ochiai et al. (42) showed in a rat model of knee OA that, compared with control animals, the number of neurones immunopositive (ip) for calcitonin gene-related peptide (CGRP) was increased in those dorsal root ganglia (DRG) innervating the knee, and application of extracorporeal shock waves reduced the number of these CGRP-ip neurones to control levels. This is in line with the results of Hausdorf et al. (43), who found that application of extracorporeal shock waves to the distal femur of rabbits diminished the number of substance P-ip neurones in dorsal root ganglia L5. Substance P and CGRP are important neuropeptides in nociceptive processes (reviewed in (44)) and contribute to the nociceptive input from joints in different types of spinal cord neurones. Depletion of substance P from the small, unmyelinated C-fibres is considered a major player in mediating pain relief by ESWT (45). Other potential mechanisms mediating pain relief in knee OA by ESWT that have been proposed in the literature based on animal experiments are improved subchondral bone remodelling and decreased cartilage degradation (18, 19), as well as reduced progression of knee OA due to decreased levels of nitric oxide and reduced chondrocyte apoptosis (20). However, it appears unlikely that these mechanisms play a major role in human knee OA with disabling pain for several years. More relevant are data from Frisbie et al. (46), who experimentally induced OA in the middle carpal joints of horses without lameness, exposed them to ESWT 2 weeks after induction of OA, performed clinical assessments of the degree of lameness every 2 weeks and weekly synovial fluid analyses, and euthanized the horses 70 days after induction of OA for histological examinations of cartilage and synovial membrane specimens at necropsy. These authors found that the degree of lameness in horses treated with ESWT improved significantly, compared with the degree of lameness in placebo-treated horses. However, no disease-modifying effects were evident in results for synovial fluid, synovial membranes, or cartilage from the horses treated with ESWT (46). In summary, further studies are required to identify the molecular and cellular mechanisms of ESWT mediating pain relief in knee OA.

The present study is an audit of prospectively collected data, and therefore has inherent limitations. First, there was no blinding of the physician who administered the therapy; however, this was also the case in all studies on ESWT listed in the PEDro database (12). Secondly, the final follow-up examination was performed at 3 months, i.e. relatively soon after the treatment; however, the negative outcome 3 months after the final treatment would not have justified an additional follow-up examination at a later time-point. Thirdly, the small number of patients could potentially confound the clinical results; however, to our knowledge the present study on ESWT for knee OA was the one with the largest number of patients performed so far. Fourthly, we did not perform magnetic resonance imaging (MRI) and did not rule out bone marrow oedema and synovitis of the knee, because bone marrow oedema of the knee occurs secondary to a myriad of causes (47). Furthermore, diagnosis of bone marrow oedema or synovitis of the knee would not have had any impact on inclusion or exclusion of patients into the present study. In this regard it is important to note that it is unknown whether rESWT may have any impact on bone marrow oedema. For focused shock waves applied at a substantially higher energy flux density than used in the present study, one study (48) showed that, in patients with chronic plantar fasciopathy, the presence of calcaneal bone marrow oedema on pre-therapeutic MRI is a good predictive variable for a satisfactory clinical outcome of ESWT. However, it is important to note that there are substantial differences in the pathogenesis of plantar fasciopathy and knee OA and, thus, there may also be different mechanisms of action of ESWT in these different conditions. Furthermore, the clinical symptoms, physical findings and

radiological examinations used to define knee OA in the present study are generally accepted and considered appropriate for this condition (21, 22, 24).

In conclusion, rESWT, as applied in the present study, is not efficient for treating patients with disabling pain due to severe primary knee OA. Data from Zhao et al. (22) show that in order to achieve treatment success this indication requires substantially higher total positive EFDs than were applied in the present study. Further RCTs are warranted to determine whether this can be achieved with more impulses (e.g. 5 treatment sessions with 5,000 impulses per session and a positive EFD of 0.16 mJ/mm^2) or whether radial shock waves with positive EFD higher than 0.16 mJ/mm^2 must be applied (as was done in (22)). The "Power+" (red) handpiece of the Swiss DolorClast can deliver radial shock waves with positive EFD of up to 0.4 mJ/mm^2. In any case, such studies should have both subjective and objective endpoints.

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REFERENCES

1. World report on disability 2011 [cited 2016 Jan 1]. Geneva: World Health Organization. Available from: www.who.int/disabilities/world_report/2011/report.pdf.
2. Felson DT. Clinical practice. Osteoarthritis of the knee. N Engl J Med 2006; 354: 841–848.
3. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum 2012; 64: 1697–1707.
4. Salaffi F, Ciapetti A, Carotti M. The sources of pain in osteoarthritis: a pathophysiological review. Reumatismo 2014; 66: 57–71.
5. Fransen M, Agaliotis M, Bridgett L, Mackey MG. Hip and knee pain: role of occupational factors. Best Pract Res Clin Rheumatol 2011; 25: 81–101.
6. Lluch Girbés E, Nijs J, Torres-Cueco R, López Cubas C. Pain treatment for patients with osteoarthritis and central sensitization. Phys Ther 2013; 93: 842–851.
7. Carr AJ, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, et al. Knee replacement. Lancet 2012; 379: 1331–1340.
8. Skou ST, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Simonsen O, et al. A randomized, controlled trial of total knee replacement. N Engl J Med 2015; 373: 1597–1606.
9. Speed C. A systematic review of shockwave therapies in soft tissue conditions: focusing on the evidence. Br J Sports Med 2014; 48: 1538–1542.
10. Mani-Babu S, Morrissey D, Waugh C, Screen H, Barton C. The effectiveness of extracorporeal shock wave therapy in lower limb tendinopathy: a systematic review. Am J Sports Med 2015; 43: 752–761.
11. Schmitz C, Császár NB, Rompe JD, Chaves H, Furia JP. Treatment of chronic plantar fasciopathy with extracorporeal shock waves (review). J Orthop Surg Res 2013; 8: 31.
12. Schmitz C, Császár NB, Milz S, Schieker M, Maffulli N, Rompe JD, et al. Efficacy and safety of extracorporeal shock wave therapy for orthopedic conditions: a systematic review on studies listed in the PEDro database. Br Med Bull 2015; 116: 115–138.
13. Ueberle F. Shock wave technology. In: Siebert W, Buch M, editor. Extracorporeal shock waves in orthopaedics, 1st edition. Berlin: Springer; 1998, p. 59–87.
14. Ogden JA, Tóth-Kischkat A, Schultheiss R. Principles of shock wave therapy. Clin Orthop Rel Res 2001; 387: 8–17.
15. Rompe JD, Furia J, Weil L, Maffulli N. Shock wave therapy for chronic plantar fasciopathy. Br Med Bull 2007; 81–82: 183–208.
16. Császár NB, Angstman NB, Milz S, Sprecher CM, Kobel P, Farhat M, et al. Radial shock wave devices generate cavitation. PLoS One 2015; 10: e0140541.
17. 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: 449–454.
18. Wang CJ, Weng LH, Ko JY, Sun YC, Yang YJ, Wang FS. Extracorporeal shockwave therapy shows chondroprotective effects in osteoarthritic rat knee. Arch Orthop Trauma Surg 2011; 131: 1153–1158.
19. 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.
20. Zhao Z, Ji H, Jing R, Liu C, Wang M, Zhai L, 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: 1547–1553.
21. Kim JH, Kim JY, Choi CM, Lee JK, Kee HS, Jung KI, et al. The dose-related effects of extracorporeal shock wave therapy for knee osteoarthritis. Ann Rehabil Med 2015; 39: 616–623.
22. 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: 661–666.
23. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. PLoS Med 2010; 7: e1000251.
24. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957; 16: 494–502.
25. Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, et al. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. Arthritis Rheum 2013; 65: 363–372.
26. Fuson RL, Sherman M, Van Vleet J, Wendt T. The conduct of orthopaedic clinical trials. J Bone Joint Surg Am 1997; 79: 1089–1098.
27. Rompe JD, Meurer A, Nafe B, Hofmann A, Gerdesmeyer L. Repetitive low energy shock wave application without local anesthesia is more efficient than repetitive low-energy shock wave application with local anesthesia in the treatment of chronic plantar fasciitis. J Orthop Res 2005; 23: 931–941.
28. Labek G, Auersperg V, Ziernhöld M, Poulios N, Böhler N. Einfluss von Lokalanasthesie und Energieflussdichte bei niederenergetischer extrakorporaler Stosswellentherapie der chronischen Plantaren Fasziitis – Eine prospektivrandomisierte klinische Studie. Z Orthop Ihre Grenzgeb 2005; 143: 240–246.
29. Gerdesmeyer L, Frey C, Vester J, Maier M, Weil L Jr, Weil L Sr, 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: 2100–2109.

30. Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. Pain 1983; 16: 87–101.

31. 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: 2413–2415.

32. Imamura M, Imamura ST, Kaziyama HH, Targino RA, Hsing WT, de Souza LP, et al. Impact of nervous system hyperalgesia on pain, disability, and quality of life in patients with knee osteoarthritis: a controlled analysis. Arthritis Rheum 2008; 59: 1424–1431.

33. Skou ST, Roos EM, Simonsen O, Laursen MB, Rathleff MS, Arendt-Nielsen L, Rasmussen S. The effects of total knee replacement and non-surgical treatment on pain sensitization and clinical pain. Eur J Pain 2016; 20: 1612-1621.

34. Kelsey JL, Whittemore AS, Evans AS, Thompson WD. Methods in Observational Epidemiology. New York, Oxford University Press, 1996.

35. Fleiss JL, Levin B, Paik MC. Statistical methods for rates and proportions, 3rd edition. New Jersey: Wiley; 2003.

36. Open Source Epidemiologic statistics for public health. [cited 2016 Apr 20]. Available from: www.openepi.com.

37. European Medicine Agency. Guideline on missing data in confirmatory clinical trials, 2010 [cited 2016 Apr 20]. Available from: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf.

38. Chow IHW, Cheing GLY. Comparison of different energy densities of extracorporeal shock wave therapy (ESWT) for the management of chronic heel pain. Clin Rehabil 2007; 21: 131–141.

39. Loew M, Daecke W, Kusnierczak D, Rahmanzadeh M, Ewerbeck V. Shock-wave therapy is effective for chronic calcifying tendinitis of the shoulder. J Bone Joint Surg Br 1999; 81: 863–867.

40. Angstman NB, Kiessling MC, Frank HG, Schmitz C. High interindividual variability in dose-dependent reduction in speed of movement after exposing C. elegans to shock waves. Front Behav Neurosci 2015; 9: 12.

41. Chen TW, Lin CW, Lee CL, Chen CH, Chen YJ, Lin TY, et al. The efficacy of shock wave therapy in patients with knee osteoarthritis and popliteal cyamella. Kaohsiung J Med Sci 2014; 30: 362–370.

42. Ochiai N, Ohtori S, Sasho T, Nakagawa K, Takahashi K, Takahashi N, et al. Extracorporeal shock wave therapy improves motor dysfunction and pain originating from knee osteoarthritis in rats. Osteoarthritis Cartilage 2007; 15: 1093–1096.

43. Hausdorf J, Lemmens MA, Kaplan S, Marangoz C, Milz S, Odaci E, et al. Extracorporeal shockwave application to the distal femur of rabbits diminishes the number of neurons immunoreactive for substance P in dorsal root ganglia L5. Brain Res 2008; 1207: 96–101.

44. Snijdelaar DG, Dirksen R, Slappendel R, Crul BJ. Substance P. Eur J Pain 2000; 4: 121–135.

45. Maier M, Averbeck B, Milz S, Refior HJ, Schmitz C. Substance P and prostaglandin E2 release after shock wave application to the rabbit femur. Clin Orthop Relat Res 2003; 406: 237–245.

46. 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: 449–454.

47. Collins J, Beutel B, Bosco J, Strauss E, Youm T, Jazrawi L. Bone marrow edema: chronic bone marrow lesions of the knee and the association with osteoarthritis. Bull Hosp Jt Dis 2016; 74: 24–36.

48. Maier M, Steinborn M, Schmitz C, Stäbler A, Köhler S, Pfahler M, et al. Extracorporeal shock wave application for chronic plantar fasciitis associated with heel spurs: prediction of outcome by magnetic resonance imaging. J Rheumatol 2000; 27: 2455–2462.