ORIGINAL ARTICLE

Focused extracorporeal shockwave therapy (f-ESWT) for knee osteoarthritis: a double-blind randomized clinical trial

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ABSTRACT

Objective: To assess the efficacy of focused extracorporeal shockwave therapy (f-ESWT) when compared to sham for pain and disability in patients with knee osteoarthritis (OA). **Methods:** Randomized, parallel, double-blind, sham-controlled clinical trial. Patients with primary knee OA were given a set of exercises (hamstring stretching and quadriceps strengthening) and randomized into f-ESWT or sham (sham probe). All patients were submitted to 4 weekly sessions of 7,000 pulses, and in the f-ESWT group energy was up to 0.15mJ/mm2. Primary outcome was visual analog scale (VAS) for pain at 1 month. Secondary outcomes were WOMAC, TUG, Lequesne's index and OMERACT-OARSI responder index at 1 and 3 months; as well as VAS at 3 months and adverse events (AEs). Both patients and outcome assessors were blinded. Mann-Whitney U test and Fisher's exact test were used with alpha=5% and power=80% in an intention-to-treat analysis. Continuous outcomes were reported as mean± standard deviation. **Results:** 18 patients were included (9 in each group), aging 60.6±8.7, with 33.3% males. There was no significant difference at baseline across groups in any variables. Active f-ESWT was not superior to sham f-ESWT at 1 month: VAS=-2.97±3.18 and -2.68±2.33cm, respectively, p=0.96. TUG at 1 month had significant differences: 9.09±2.30 and 11.01±2.85sec, p=0.01. No serious AEs were observed. **Conclusions:** Active f-ESWT was not superior to sham f-ESWT for knee OA. This RCT was underpowered to detect differences in this study. New RCTs should use WOMAC A (pain subscale) as primary outcome and recruit at least 92 patients.

Keywords: High-Energy Shock Waves, Osteoarthritis, Knee, Disability Evaluation

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INTRODUCTION

Osteoarthrosis (OA) is the musculoskeletal pathology with the greatest burden of pain and functionality in the world.[1] Treatment management consists of non-pharmacological modalities such as personal re-education such as weight loss and strengthening training, as well as analgesics and nonsteroidal anti-inflammatory drugs.[2] However, patients generally maintain the debilitating pain and may benefit from different treatments, such as extracorporeal shock wave therapy (ESWT).

ESWT is a sequence of high intensity, short duration, and rapid accelerating[3] acoustic pulses that can be used to treat different musculoskeletal conditions.[4-10] Shock waves are acoustic pulses observed in explosive events in nature (e.g. lightning, eruptions of volcanoes) and can be generated when an aircraft breaks the sound barrier.[11] Medical use of ESWT began in 1980 for lithotripsy, and in the 1990s it began to be used for musculoskeletal disorders.[11] ESWT creates a micro-trauma which induces angiogenesis,[12-16] potentially reducing inflammation and improving the quality of cartilage.[9,17-20] It decreases nerve conduction velocity, which could explain the immediate antinociceptive effect.[21-24] However, the exact mechanism of action on the pain is still uncertain.

There are two main types of ESWT: radial and focal. Radial ESWT (r-ESWT) has a shorter pulse duration and its maximum energy is delivered to the skin. Focal ESWT (f-ESWT) provides maximum energy in a focused area 4-6 cm below the skin.[11] Due to a greater energy dispersion at greater depths with r-ESWT, we believe that f-ESWT is more effective at treatment of pathologies such as knee OA. A recent randomized controlled trial comparing r-ESWT with placebo for knee OA did not show efficacy,[25] whereas another with f-ESWT managed to demonstrate its success for treating OA.[26] Therefore, we hypothesized that f-ESWT is superior to sham f-ESWT for reducing pain and disability of patients with knee OA.

OBJECTIVE

The objective of this study is to evaluate the efficacy of focal extracorporeal shockwave therapy (f-ESWT) compared to sham f-ESWT for reducing pain and disability of patients with knee osteoarthritis.

METHODS

A double-blind, sham controlled randomized clinical trial was conducted from May to October of 2016 at the *Instituto de Medicina Física e Reabilitação (IMREA) - Hospital das Clínicas da Universidade de São Paulo*. The study protocol was approved by the Institutional Ethics Review Board (approval number 54013616.1.0000.0068) and was conducted under the Helsinki Declaration guidelines.

The patients were recruited based on the medical records of the IMREA of those with the M17 code of the International Classification of Diseases (ICD-10), and those who met the inclusion criteria were included in the study (Figure 1). The approved protocol was designed to include patients with OA classification Kellgren & Lawrence (KL) II and III, nevertheless, during the study recruitment, the authors decided to include patients with classification KL-I, after an amendment.

Patients who met the eligibility criteria (Chart 1) were assessed at IMREA and submitted to a knee radiography for KL classification of the knee with the highest pain level. The eligible patients were instructed to keep current medications and avoid further treatments during the study.

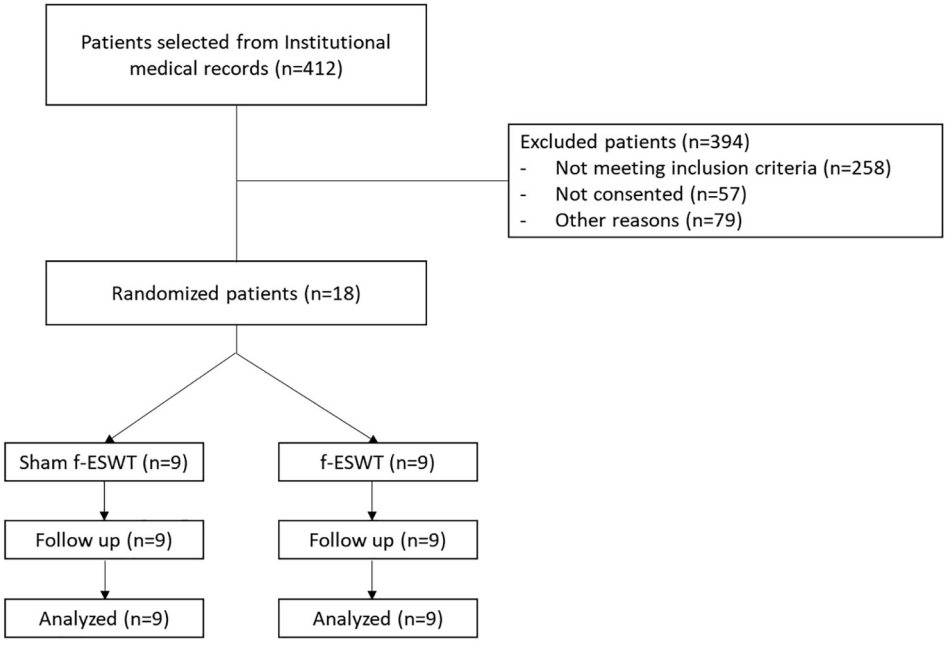

Figure 1. Inclusion and analysis flow chart

Randomization and treatment allocation

Patients were randomized at a 1:1 proportion with a computer-generated list of random numbers by the site http://www.randomization.com. The patient's allocation was sealed in an opaque envelope, held by a member of our research center. Moments before the intervention, the investigator responsible for the f-ESWT application received the envelope and connected the active or sham probe to the equipment. This researcher had no contact with other researchers or subjects other than during the procedure itself. The patients, the other researchers, and statisticians were blinded to treatment allocation.

Intervention

Both treatment groups were instructed to perform two sets of exercises at home: hamstring stretching and isometric quadriceps femoris strengthening at least once a day. Analgesics were prescribed as needed (dipyrone 1g every 6 hours or acetaminophen 500mg at 8 hours). Patients were advised to keep a diary for exercise adherence and use of analgesics.

F-ESWT was administered with a Duolith SD1 Ultra (Storz Medical, Switzerland) by two

Chart 1. Eligibility criteria

Inclusion Criteria
1. Osteoarthritis diagnosis, according to the American College of Rheumatology
2. Age >45 and <80 years
3. High-school educational level
4. Pain ≥ 4 at Visual Analogue Scale (VAS) for more than 3 months
5. Kellgren-Lawrence classification 1-3
6. Availability for attending the visits and the follow up assessments
7. Ability to comprehend the Informed Consent Form
Exclusion Criteria
1. Lumbar spinal stenosis or history or actual radiculopathy
2. Presence of signs or symptoms of neurological diseases
3. Fibromyalgia or generalized pain
4. Incapacity to walk (gait)
5. Previous knee surgery
6. Secondary causes of osteoarthritis (e.g. inflammatory or trauma)
7. Use of quinolones or statins in the previous year
8. Instable psychiatric diseases
9. Intra-articular injections 6 months prior to inclusion
10. Presence of skin lesion, infection or tumor at the application site of the f-ESWT

researchers (GTS and AKK) in the knee with greater pain measured by VAS at baseline.

The device produces a focal area of shock waves in the shape of an ellipse, having its center at 5 cm deep and measuring 2 cm in length on its long axis, where cavitation and energy release efficiently produce biological responses.

The sham probe was identical to the active probe, but this was filled with foam, so that shock waves were not transmitted. The shape, color, weight, touch, and sound of both probes could not be differentiated by the patient.

Every patient undertook 7,000 pulses of f-ESWT, either sham or active, once a week for four weeks under the following fashion:

- Dorsal decubitus position: A) extended knee: 3,000 pulses in the anteromedial quadrant (covering the medial tibial plateau, the anteromedial portion of the femoral condyle, patella and painful areas), with slow movements of the probe. Up to the first 500 pulses, we used an adaptation phase of 0.10mJ/mm^2, progressing up to 0.12-0.15mJ/mm^2, for better tolerability. B) maximum knee flexion: 2000 pulses in the femoral trochlea, intercondylar fossa or painful areas, starting at 0.07mJ/mm^2 up to 0.15mJ/mm^2 or greater tolerable energy.
- Ventral decubitus position: with extended knee, 2,000 pulses were applied in the posteromedial quadrant (medial tibial plateau, medial femoral condyle or painful areas) at 0.15mJ/mm^2.

The follow up assessments were conducted 1 and 3 months after the last f-ESWT session.

Outcomes

The primary outcome of this study was the change in pain from baseline to the 1 month follow up, measured by a 10-centimeter visual analogue scale (VAS).

The secondary outcomes were pain at 1 month follow up assessed by the Western Ontario e McMaster University Osteoarthritis Index (WOMAC) and at 3 months assessed by VAS and WOMAC; Lequesne Index and Timed Up and Go (TUG) at 1 and 3 months; and OMERACT-OARSI response (for VAS, WOMAC, and Lequesne) at 1 and 3 months. The WOMAC was divided in subscales: A (pain), B (rigidity), and C (disability).

Statistical Analysis

The analysis was conducted with Stata 13 (Stata Corp., 2013. Stata Statistical Software: Version 13. College Station, TX: Stata Corp LP). Intention-to-treat analysis was performed, and the missing data was addressed with the last observation carried forward (LOCF) approach. Only 2 observations (TUG and VAS at 3 months) of a single patient were missing.

Continuous varibles were reported as mean and standard deviation (SD), and analyzed using the Mann-Whitney U-test. The binomial outcomes were analyzed by Fisher's exact test.

The sample size was calculated according to Zhao et al.[10] We estimated the size of the largest effect once Zhao et al used ESWT radial and highest standard deviation (SD). Therefore, estimating a minimum difference of VAS at 1 month of 2.5 cm, SD = 3.5 and dropout rate of 12.5%, we recruited 18 patients. Statistical power of 80% and alpha of 5% were used in all analyzes.

RESULTS

The baseline data of both treatment groups were not statistically different (Table 1). No superiority of active f-ESWT over sham f-ESWT was found in our sample for the primary outcome in any time point (Table 2). However, the TUG was significantly different between both groups one month after the end of the treatment, as the active treatment group presented better time in this evaluation (9.09 vs 11.01sec, p = 0.01). There was no differences in adherence to the physical exercises nor in use of analgesics (Tables 3 and 4).

There was no Serious Adverse Events (SAE) along the study (Table 5). A patient from the active treatment group had emotional distress, and from sham treatment group, one patient had popliteal cyst, and another patient underwent severe increase of pain one month after the treatment and was eventually diagnosed with rheumatoid arthritis. All patients concluded the four sessions and an Intention to Treat analysis was conducted.

DISCUSSION

To our knowledge, this is the first double-blind, sham controlled, randomized clinical trial to test f-ESWT for knee osteoarthritis. However, there was no superiority of the active treatment group when compared to the sham treatment group one or three months after the treatment.

Some factors may have diluted the effect size of our study compared to Zhao et al.[10] Firstly, Zhao et al. did not report exercise therapy for any group. In our study, both

Table 1. Baseline characteristics (mean±SD, except for KL)

	Active f-ESWT (N=9)	Sham f-ESWT (N=9)	Total (N=18)	p-value
Age, years	59.63 ± 11.11	61.55 ± 5.80	60.59 ± 8.66	0.45
Male (%)	5 (55.5)	1 (11.1)	6/18 (33.33)	0.13
Time since diagnosis, months	7.28 ± 5.92	10.00 ± 11.54	8.64 ± 9.01	
BMI, kg/m²	28.42 ± 4.74	29.83 ± 2.67	29.13 ± 3.80	0.45
VAS	6.54 ± 2.20	6.54± 2.40	6.54 ± 2.24	1.00
WOMAC A	5.89±2.57	7.0±2.6	6.44±2.57	0.45
WOMAC B	3.55±1.94	4.2±2.6	3.88±2.27	0.56
WOMAC C	31.77±10.92	33.2±14	32.5±12.18	0.75
Lequesne	12.33±3.86	13.22±3.75	12.77±3.72	0.69
KL	I: 2 II: 3 III: 4	I: 0 II: 4 III: 5	I: 2 II: 7 III: 9	N/A

SD, standard deviation; KL, Kellgren-Lawrence classification; f-ESWT, focused extracorporeal shockwave therapy; BMI, body mass index; VAS, visual analogue scale for pain; WOMAC, Western Ontario McMaster Osteoarthritis Index

Table 2. Change from baseline to 1 and 3 months after the end of the treatment compared to baseline, except for TUG and WOMAC (mean SD)

	1 month			3 months		
	Active f-ESWT	Sham f-ESWT	p-value	Active f-ESWT	Sham f-ESWT	p-value
VAS	-2.97 (3.18)	-2.68 (2.33)	0.96	-2.25 (3.71)	-2.85 (2.99)	0.50
WOMAC A	-3.33 (2.23)	-1.77 (2.94)	0.15	-1.55 (2.18)	-1.22 (2.86)	0.89
WOMAC B	-1.44 (1.66)	-1.22 (1.20)	0.81	-12.22 (10.09)	-7.33 (11.12)	0.85
WOMAC C	-17.77 (11.60)	-8.77 (7.36)	0.08	-6.11 (5.01)	-3.72 (3.09)	0.35
Lequesne	-6.11(5.01)	-3.72 (3.09)	0.35	-4.38 (5.20)	-3.55 (3.47)	0.79
TUG	9.09 (2.30)	11.01 (2.85)	0.01	9.45 (2.71)	10.49 (2.55)	0.10
OMERACT-OARSI	4	4	1.00	5	4	1.00

SD, standard deviation; TUG, Timed Up and Go; WOMAC (A, B, and C), Western Ontario McMaster Osteoarthritis Index, (pain, rigidity, and disability respectively) ;

Table 3. Adherence to physical exercises (number of patients)

	Active f-ESWT (n=9)	Sham f-ESWT (n=9)	p-value
1 month	7	8	0.99
3 months	5	7	0.62

Table 4. Use of analgesics (number of patients)

	Active f-ESWT (n=9)	Sham f-ESWT (n=9)	p-value
1 month	2	2	0.99
3 months	3	2	0.99

Table 5. Adverse events (number of patients)

	Active f-ESWT (n=9)	Sham f-ESWT (n=9)
Total Adverse events	2	1
Treatment-related adverse events	0	2
Serious adverse events	0	0

groups adhered to exercise therapy (Table 3). A recent meta-analysis suggests a moderate effect of ground exercises on knee OA for both pain and disability (effect size of 0.49 and 0.52, respectively).[27] Also, it is possible that patients in the knee study by Zhao et al.[10] were not adequately blind. The ESWT equipment produces a sound on each pulse emitted and their equipment was set at 0mJ/mm² for the placebo group, thus making no sound. In our study, the equipment emitted a regular sound, however the energy was not transmitted to the patient given the probe was false. Finally, since most patients had bilateral knee pain and only one side was treated, f-ESWT may have been underestimated.

A recent study published by Lee et al.[26] showed superiority of f-ESWT over placebo. However, it presents several possible sources of bias: open label testing without allocation or concealment of allocation, no description of sample size estimation or the statistical power of their analysis.

We recommend that future randomized controlled trials use WOMAC A (pain subscale) as the primary outcome, with a sample size of at least 92 patients with unilateral knee pain.

Study limitations

The sample size estimation was based on previous unsuitable estimates. We based our calculation on a study of radial ESWT without co-intervention. A post-hoc calculation showed that our study was subjected to a low statistical power of 4%. However, p values for WOMAC A and C (pain and disability) at 1 month reached 0.15 and 0.08, respectively, and TUG was significantly lower in the active f-ESWT treatment group at month 1. The poor response of the overall VAS may have resulted from: not being task specific (ie walking); only one treated knee; increase of functionality until they reach baseline pain level. We consider that choosing WOMAC A as the primary outcome may be preferable.

Central sensitization was not addressed in our study. It could potentially decrease the effect size of our intervention, since patients with central sensitization present more extensive and intense pain.[28,29] Due to the small sample size, we did not perform a subgroup analysis by KL. We cannot exclude that different classifications would respond differently to this treatment.

Demanding secondary educational level may have hindered our recruitment rate, as we are in a country with low schooling standards. However, we wanted the subjects to completely understand questionnaires such as the WOMAC and Lequesne index.

CONCLUSION

We observed that active f-ESWT was not superior to sham f-ESWT for treating knee OA and that this randomized clinical trial was insufficient to detect. New trials should use WOMAC A as the primary outcome and recruit at least 92 patients with pain.

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