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RESEARCH

EFFECTIVENESS OF EXTRACORPOREAL SHOCK WAVE THERAPY TO TREAT PRIMARY MEDIAL KNEE OSTEOARTHRITIS WITH AND WITHOUT BONE MARROW EDEMA IN ELDERLY PATIENTS

Abstract

Introduction: This study aimed to evaluate the clinical and radiographic effectiveness of extracorporeal shock wave therapy to treat primary medial knee osteoarthritis with and without bone marrow edema in elderly patients.

Materials and Method: Elderly patients with right knee osteoarthritis and bone marrow edema confirmed by magnetic resonance imaging were allocated to the first group (n=40), whereas patients without bone marrow edema were randomly allocated to either the second (n=40) or third (n=40) groups. The patients were treated twice weekly with a total of 10 sessions of extracorporeal shock wave therapy (Groups 1 and 2) or were left untreated with sham extracorporeal shock wave (Group 3).

Results: The comparison of the patients' Visual Analogue Scale, Western Ontario and McMaster Universities Osteoarthritis Index and Lequesne scores before treatment and at 6 months and 1 year after treatment revealed significant score reductions in the first and second groups ($p<0.05$). One year after treatment, the medial joint space was preserved in Groups 1 and 2 ($p<0.05$), whereas the medial joint width protection was more prominent in Group 1 ($p<0.05$) than in Groups 2 and 3.

Conclusion: In elderly patients with knee osteoarthritis, extracorporeal shock wave therapy led to functional and radiologic improvements and pain relief without substantial complications. The improvement remained at the 1 year follow-up and was higher in patients with bone marrow edema. Further studies are required to investigate its potential as a disease-modifying physical agent, particularly for treating elderly patients with knee osteoarthritis with bone marrow edema.

Keywords: Aged; Osteoarthritis, knee; Extracorporeal shock wave therapy

ARAŞTIRMA

YAŞLI HASTALARDA KEMİK İLİĞİ ÖDEMLİ VE ÖDEMSİZ MEDİAL DİZ OSTEOARTRİTİNİN TEDAVİSİNDE EKSTRAKORPOREAL ŞOK DALGA TEDAVİSİNİN ETKİNLİĞİ

Öz

Giriş: Bu çalışmada, yaşlı hastalarda, kemik iliği ödemi olan ve olmayan primer medial diz osteoartritini tedavi etmede ekstrakorporeal şok dalga tedavisinin klinik ve radyografik etkinliğinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Sağ diz osteartriti olan ve magnetik rezonans görüntüleme ile dizde kemik iliği ödemi teyit edilen yaşlı hastalar birinci gruba (n=40), kemik iliği ödemi olmayan hastalar ise randomize olarak ikinci gruba (n=40) veya üçüncü gruba (n=40) ayrıldı. Hastalar haftada iki kez toplam 10 seans ekstrakorporeal şok dalga tedavisi (Grup 1 ve 2) ile tedavi edildi ya da sham ekstrakorporeal şok dalga ile tedavi edilmedi (Grup 3).

Bulgular: Hastaların Vizuel Analog Skala, Western Ontario ve McMaster Üniversiteleri Osteoartrit İndeksi ve Lequesne skorlarının tedaviden önce ve tedaviden 6 ay ve 1 yıl sonra karşılaştırılması, birinci ve ikinci gruplarda bu skorlarda anlamlı derecede azalma olduğunu gösterdi ($p<0.05$). Tedaviden bir yıl sonra, medial eklem genişliği grup 1 ve 2'de ($p<0.05$) korunurken, medial eklem genişliğinin korunması Grup 1'de ($p<0.05$) Grup 2 ve 3'e göre daha belirgindi ($p<0.05$).

Sonuç: Diz osteoartritli yaşlı hastalarda, ekstrakorporeal şok dalga tedavisi önemli komplikasyonlar oluşturmaksızın fonksiyonel ve radyolojik iyileşmelere ve ağrı giderilmesine neden oldu. İyileşme, 1 yıllık izlemde devam etti ve kemik iliği ödemli diz osteoartriti hastalarında daha yüksekti. Özellikle kemik iliği ödemli yaşlı diz osteoartriti hastaların tedavisinde, ekstrakorporeal şok dalga tedavisinin bir hastalık modifiye edici fiziksel ajan olarak potansiyelini araştırmak için, daha fazla çalışmaya gereksinim vardır.

Anahtar sözcükler: Yaşlı; Diz osteoartriti; Ekstrakorporeal şok dalga tedavisi

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INTRODUCTION

Knee osteoarthritis (OA) is a common and debilitating form of arthritis that affects the entire joint tissues, including bone, synovium and cartilage, leading to progressive joint degeneration in the elderly (1). Bone marrow edema (BME) consists of highly painful fluid accumulation in the extracellular bone marrow spaces, which usually spreads into the subchondral region of the joint (1). In knee OA, the cartilage pathology may be accompanied by alterations of the subchondral bone and marrow space (1). Previous MRI studies have indicated a relationship between BME and knee OA-related structural deterioration, particularly osteoarthritic cartilage degradation (2). Moreover, in knee OA, bone marrow lesions are predictive of worsening of the radiographic joint space narrowing (JSN) (2,3), and BME has been associated with clinical symptoms, such as pain and disease progression, assessed in terms of JSN (3,4).

Extracorporeal shock waves are acoustic waves generated by electromagnetic, electrohydraulic or piezoelectric methods (5), and extracorporeal shock wave therapy (ESWT) may promote reparative processes of the cartilage and bone via angiogenic (neovascularisation), anti-edema, anti-inflammatory and trophic effects (6-10). ESWT was previously shown to effectively treat pain and BME in patients with hip and knee OA (7,10) and is considered a powerful non-pharmacological tool to normalise the vascular and metabolic impairments of hip BME (6,7). Previous studies have also shown ESWT-induced functional improvement, pain reduction and normalisation of MRI features (resolving BME) in patients with knee OA (10).

Herein, we hypothesised that BME positively affects the clinical activity of ESWT in elderly patients with knee OA. To our knowledge, no previous clinical trials have compared the effectiveness of ESWT to improve radiographic JSN in patients with knee OA with and without BME. Therefore, the current study aimed to perform a prospective clinical trial to compare and evaluate the clinical and radiographic effectiveness of ESWT to treat primary knee OA with and without BME in elderly patients.

MATERIALS AND METHOD

This study enrolled elderly patients (aged 65–75 years) with primary medial tibiofemoral knee OA who presented at the Physical Medicine and Rehabilitation outpatient clinic of our University Medical Faculty Hospital and underwent MRI examination and weight-bearing fixed-flexion knee radiography between 11th November, 2014 and 3rd September, 2016. The study protocol was approved by the Medical Clinical Ethical Committee of our University.

The patient selection was based on the following inclusion criteria: a) radiological and clinical diagnosis of primary medial tibiofemoral knee OA, according to the ACR criteria; b) age range between 65 and 75 years; c) knee pain lasting a minimum of 6 months; d) bilateral stage 2 or 3 OA according to the KL radiological stage; and e) ability to independently continue follow-up and provide informed consent for the study.

Patient exclusion was based on the following criteria: a) secondary knee OA; b) use of oral or intramuscular corticosteroids or any intraarticular injections within the previous 6 months; c) knee arthritis due to inflammatory joint disease; d) undergoing physical therapy during the previous year; e) history of malignancy, knee surgery or knee trauma; f) presence of other diseases that cause pain in the lower extremities (neuropathy, herpes zoster, restless legs syndrome, fibromyalgia, hemiparesis, etc.); g) mental status disorder, neurological or vestibular diseases (Parkinson's, Alzheimer's, polyneuropathy, etc.) and poor overall health status (heart failure, chronic obstructive pulmonary disease, cancer, etc.).

Age, sex, complaints, physical examination findings and laboratory and radiological examination results [KL stage, medial joint space width (JSW) and BME presence in the MRI] of each patient were collected into a special form. The patients' history, including bone diseases, rheumatoid arthritis, trauma, seronegative spondyloarthropathies and other diseases that could lead to secondary gonarthrosis, was collected.

From the 189 patients with primary medial knee OA assessed at the outpatient clinic, 40 patients were allocated to each treatment group following the initial assessment. Patients with primary medial knee OA and MRI-confirmed BME [51 of 189 patients (26.98%) had MRI-proven BME] in the right knee joint were allocated to the first group (TENS + ESWT-treated group, n=40). TENS was applied to the patients' right knee before ESWT treatment to prevent treatment-related pain. TENS was applied for 30 min at a 80-Hz frequency prior to each ESWT session. The existing of BME was accepted as extending 5–40 mm diameter BME lesion into the subchondral area in the medial tibial and/or medial femoral plateau on MRI T2-weighted sequences.

Following application of the exclusion criteria, 11 patients were excluded from the first group. Patients with primary medial knee OA without MRI-proven BME [138 of 189 patients (73.02%)] in the right knee were randomly allocated to either the second (TENS + ESWT-treated, n=40) or third (only TENS + sham ESWT, n=40) group. Following application of the exclusion criteria, 58 of 138 patients were excluded from the second and third groups.

The treatment and evaluation were performed only for the patients' right knee. For patients in the first and second groups, ESWT was applied to the medial femur and tibia condyles while the knee was kept at a 90° flexion. An ESWT device from the Medical Italia brand (SN: EK1238092) was used, and the dose was set according to the generally accepted therapeutic dose for tendinopathy (11).

ESWT was applied with 2,500 pulses at a pressure of 3 bar and a frequency of 12 Hz. Two weekly sessions were performed [one session (Tuesday) for the medial femur condyle and one session (Thursday) for the medial tibial condyle] for 5 weeks, resulting in a total of 10 ESWT sessions within 5 weeks. Sham ESWT was applied to the third group, according to a similar schedule. To enhance the sham design, with every shock wave, the ESWT machine made a noise, and minimal energy pulses were generated.

The selected patients were interviewed and evaluated by a single investigator who was blinded to the treatment group. Information about the outcome measures was written on specific follow-up forms. All evaluations were conducted prior to treatment (PT) and at 6 months and 1 year after the end of treatment (AT). The following outcome measures were evaluated:

JSN, the primary outcome measure, was assessed for structural progression using bilateral weight-bearing, standing, mild flexion (20°–30° flexed knees with 10° rotated feet), posterior–anterior radiographs of the knees. Medial JSW (mm) in the medial tibiofemoral compartment was electronically measured using the hospital's Picture Archiving Communication System (PACS). JSW was defined as the maximum height of the radiolucent area of the medial tibio–femoral articular surfaces between the radiopaque margins in the mid-portion of the medial compartment of the treated right knees. All measurements were made by the same investigator to avoid interobserver variation. JSN was calculated as JSW at 6 months and 1 year minus the pre-treatment JSW. Other primary outcome measures included the Western Ontario and McMaster Universities Index (WOMAC) and scores of pain (P), stiffness (S) and function (F) subscales. Validity and reliability analyses of the Turkish version of WOMAC were conducted. The variable names were pain (WomacP), stiffness (WomacS), function (WomacF) and total score (WomacTS). A standard 10-cm visual analogue scale (VAS) chart was used to assess pain severity during the night, at rest and during movement. The VAS score corresponded to the mean of those three scores. The Lequesne index assesses pain, discomfort, maximum walking distance and daily life activities, determines the functional status and is frequently used for OA. The total score was used for the present study. Moreover, the medial JSW was evaluated using PACS, as described above.

Statistical analysis

All statistical analyses were performed using the SPSS software, and $p< 0.05$ was considered statistically significant. Categorical variables were expressed as numbers, whereas continuous variables were expressed as mean±standard deviation. Between-group comparisons of sex and radiographic

stage were evaluated using the chi-square test. Within-group pre- and post-treatment comparisons were performed using paired *t*-tests. Bonferroni corrected ANOVA was performed to compare treatment effects between groups.

RESULTS

Three patients from the first group, two from the second group and five from the third group were lost to follow-up and were thus excluded from the study. ESWT caused only minor bruising or transient soft tissue swelling. No clinically device-related systemic or neuromuscular adverse effects were observed; thus, no patient was excluded due to side effects. The three groups did not differ significantly in terms of age, sex, body mass index, symptom duration and KL knee OA stage (stage 2/3) (Table 1).

Table 1. Age, sex and knee OA KL stage distribution accross treatment groups. Group1, (primary medial knee OA with BME in the joint) ESWT treatment group; group 2, (primary medial knee OA without BME in the joint) ESWT treatment group; group 3, (primary knee OA without BME in the joint) sham ESWT group.

	Group 1 (with BME in the joint) (n=37) ESWT treatment (mean±sd)	Group 2 (without BME in the joint) (n=38) ESWT treatment (mean±sd)	Group 3 (without BME in the joint) (n=35) Sham ESWT (mean±sd)	p
Age (year)	69.74±3.91	70.48±4.18	69.65±4.49	>0.05
BMI (kg/m²)	27.12±5.09	26.91±4.67	26.89±4.85	>0.05
Sex (F/M)	24/13	24/14	22/13	>0.05
Kellgren–Lawrence stage (stage 2/3)	16/21	18/20	16/19	>0.05
Symptom (knee pain) duration (months)	38.64±14.47	40.72±15.14	39.43±12.34	>0.05

VAS PT-VAS 6. Month AT: At both 6 months and 1 year after treatment, the VAS scores were significantly lower in the first and second groups compared with those before treatment; the decrease in the VAS scores was greater in the first group than in the second group ($p<0.05$) (Table 2).

Pre- and post-treatment comparisons revealed that the WOMAC pain, stiffness and function subscales and total scores (WOMAC P, S, F and TS PT-WOMAC P, S, F and TS 6.Month AT) and the Lequesne scores underwent significant reductions in the first and second groups ($p<0.05$); the decrease in these scores was greater in the first group than in the second group ($p<0.05$) (Table 2).

Changes in the medial joint width (JSN) before treatment and at 6 months and 1 year after treatment: The medial joint space was more preserved in groups 1 and 2 than in group 3 ($p<0.05$). One year after treatment, the medial joint width protection was more prominent in group 1 ($p<0.05$) (Table 3).

Table 2. Between-group comparisons for VAS, WOMAC (total [TS], pain [P], stiffness [S], function [F] subscales) and Lequesne scores and score changes prior to treatment (PT) and at 6 months (Significance P1) and 1 year after treatment (AT-Significance P2).

Outcome measures	Group1 (with BME in the joint) (n=37) ESWT treatment (Mean±sd)	Group2 (without BME in the joint) (n=38) ESWT treatment (Mean±sd)	Group3 (without BME in the joint) (n=35) Sham ESWT treatment (Mean±sd)	P1	P2
VAS PT	6.66±1.58	6.42±1.76	6.35±1.28		
VAS 6th month AT	4.58±1.47	5.16±1.34	5.43±1.22		
VAS 1 year AT	4.87±1.78	5.27±1.53	5.98±1.91		
VAS Change- 6thmonth AT	1.64±1.15	1.31±1.71	1.28±0.91	<0.05	
VAS Change-1 year AT	1.47±1.34	1.14±1.44	1.10±1.02		<0.05
LQ PT	10.31±2.77	10.58±2.51	10.49±2.58		
LQ 6. month AT	8.17±2.88	9.31±2.52	9.96±2.45		
LQ 1 year AT	8.33±2.67	9.43±2.27	10.02±2.14		
LQ Change – 6th month AT	1.73±0.89	1.25±1.29	0.57±1.01	<0.05	
LQ Change -1 year AT	1.69±1.12	1.14±1.37	0.37±0.83		<0.05
WomacTS- PT	40.63±7.04	40.33±6.28	42.30±7.55		
Womac TS- 6th month AT	37.61±5.36	37.08±7.04	40.33±7.51		
Womac TS- 1 year AT	38.12±4.87	38.43±7.65	40.54±6.97		
WOMAC TS Change- 6th month AT	4.35±2.82	3.21±2.98	1.95±2.19	<0.05	
WOMAC TS Change-1 year AT	3.97±3.01	2.78±2.54	1.15±2.14		<0.05
WomacP- PT	12.38±2.34	12.01±2.72	12.19±3.03		
WomacP 6th month AT	9.57±3.85	9.27±5.15	11.93±3.06		
WomacP 1 year AT	9.69±4.12	9.82±4.42	11.56±4.76		
WomacP Change-6th month AT	2.59±1.78	2.32±1.66	0.38±1.05	<0.05	
WomacP Change- 1 year AT	2.23±1.52	1.98±1.77	0.68±1.43		<0.05
WomacS- PT	4.35±1.25	4.24±1.36	4.31±1.48		
WomacS 6th month AT	3.71±0.88	3.90±0.95	4.27±1.42		
WomacS 1 year AT	3.93±1.14	4.02±1.22	4.25±1.18		
WomacS Change-6th month AT	0.61±0.74	0.36±1.04	0.09±0.56	<0.05	
WomacS Change-1 year AT	0.54±0.81	0.32±0.92	0.14±0.48		<0.05
WomacF-PT	24.68±3.58	24.97±4.08	24.77±4.95		
WomacF 6. month AT	18.34±3.79	20.61±4.06	24.27±5.87		
WomacF 1 year AT	20.65±4.14	22.75±5.43	24.46±5.12		
WomacF Change-6th month AT	5.32±2.05	3.43±3.11	0.50±3.33	<0.05	
WomacF Change- 1 year AT	5.32±2.05	3.43±3.11	0.50±3.33		<0.05

Table 3. Changes in the medial joint width (joint space narrowing) before treatment and at 6 months and 1 year after treatment. Different lower case refers to statistically difference between groups.

Evaluation time	Group1 (with BME in the joint) (n=37) ESWT treatment Joint Space Narrowing (mm) mean (95% confidence interval)	Group2 (without BME in the joint) (n=38) ESWT treatment Joint Space Narrowing (mm) mean (95% confidence interval)	Group3 (without BME in the joint) (n=35) only TENS treatment Joint Space Narrowing (mm) mean (95% confidence interval)	p
6 months after treatment	0.043 (−0.062 to 0.104)a	0.039 (−0.071 to 0.081)a	−0.053 (−0.142 to 0.017)b	<0.05
1 year after treatment	0.032 (−0.072 to 0.143)a	−0.011 (−0.057 to 0.044)b	−0.081 (−0.182 to −0.013)c	<0.05

DISCUSSION

The present study showed a positive effect of ESWT on the treatment of elderly patients with knee OA with and without BME during ten session treatment. The effect was maintained at a 1-year follow-up. These findings also suggest that ESWT modulates pathological processes such as BME, which are responsible for the progression of knee OA. Further studies are required to investigate its potential as a disease-modifying physical agent, particularly for the treatment of knee OA with and without BME. Previous clinical trials have shown the effectiveness of ESWT to treat avascular necrosis and pain via reducing bone edema (10-17). A few studies have also showed the effectiveness of ESWT to treat hip BME (7,8), and a recent study showed that ESWT is highly effective for pain relief and functional improvement in knee OA with BME (10).

The pathological course of OA involves crucial subchondral bone changes, including local BME under the damaged articular cartilage. Some studies demonstrated that BME is clearly associated with pain and rapid cartilage damage. Previous studies have also shown that the detection of BME on knee MRIs predicted the rate of radiographic changes in JSW, a risk factor for structural deterioration as well as the progression of knee OA (2,3). Additionally, BME is an indirect sign of knee OA-related cartilage damage (1). The mechanisms by which ESWT acts on BME and regenerates tissues in knee OA are not fully understood, and it is possible that they involve a neoangiogenic effect and anti-inflammatory action, including nitroxide and other molecular pathways (endothelial nitric oxide synthase, vascular endothelial growth factor, BMP-2, etc.) as well as a stimulation effect on osteoblasts and periosteal cells, a reduction effect on the production of pro-osteoclastogenic factors and the differentiation of mesenchymal stem cells to chondrogenic and osteogenic cells (7,8,13-21). Based on animal studies, other potential mechanisms are the following: decreased cartilage degradation, improved subchondral bone remodelling and reduced chondrocyte apoptosis (18-22).

Our trial showed that ESWT leads to functional and radiologic improvement as well as pain relief without substantial complications in knee OA with

and without BME. In the present study, focused ESWT was used. In line with our study, other previous studies showed successful treatment of knee OA using radial or focused ESWT (23-25). Radial and focused ESWT have comparable efficacy to treat musculoskeletal disorders, except deep nonunions (25). Our findings are also consistent with a recently published trial by Kang et al. (10) indicating that ESWT is an effective, non-invasive treatment of painful BME, along with its rapid normalisation of the MRI appearance, in patients with knee OA.

This study has several limitations. First, the mechanisms, standard doses, number of sessions and indications of ESWT in knee OA are not clearly determined. Second, there was no randomised control group with BME. Thirdly, only radiographic JSN was investigated; control MRI to confirm BME resolution was not performed.

In conclusion, the current study showed that ESWT led to functional and radiologic improvement and pain relief without substantial complications in knee OA with and without BME. Those improvements were maintained at the 1-year follow-up. These findings also suggest that ESWT modulates the pathological processes underlying the progression of knee OA, such as BME, and further studies are required to investigate its potential as a disease-modifying physical agent, particularly for treating elderly patients with knee OA with BME.

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